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(54) **Title**: POLYNUCLEOTIDES ENCODING METHYLMALONYL-CoA MUTASE

(57) **Abstract**: The disclosure relates to polynucleotides comprising an open reading frame of linked nucleosides encoding human methylmalonyl-CoA mutase precursor, human methylmalonyl-CoA mutase (MCM) mature form, or functional fragments thereof. In some embodiments, the disclosure includes methods of treating methylmalonic acidemia in a subject in need thereof comprising administering an mRNA encoding an MCM polypeptide.

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POLYNUCLEOTIDES ENCODING METHYLMALONYL-CoA MUTASE

BACKGROUND OF THE DISCLOSURE

[0001] The reference to prior art in this specification is not and should not be taken as an acknowledgment or any form of suggestion that the referenced prior art forms part of the common general knowledge in Australia or in any other country.

[0002] Methylmalonic acidemia (MMA) is a metabolic disorder characterized by the abnormal buildup of the metabolic byproduct methylmalonic acid in patients. MMA causes developmental delay, intellectual disability, kidney disease, coma, or even death. MMA is also referred to as methylmalonic aciduria. It has an estimated incidence of 1 in 50,000 to 100,000. Current treatment for MMA is primarily via dietary control to limit the usage of metabolic pathways that lead to methylmalonic acid formation. In serious cases, kidney and liver transplants have also been performed to provide a new reservoir of cells that can properly metabolize and remove the methylmalonic acid. However, none of these treatments completely or reliably controls the disorder. As such there is a need for improved therapy to treat MMA.

[0003] The principal gene associated with MMA is methylmalonyl-CoA mutase (NM_000255; NP_000246; also referred to as MCM or MUT). MCM is a metabolic enzyme (E.C. 5.4.99.2) that plays a critical role in the catabolism of various amino acids, fatty acids, and cholesterol. MCM's biological function is to isomerize L-methylmalonyl-CoA into succinyl-CoA, a Krebs cycle intermediate. MCM localizes to the mitochondria of cells, exists as a homodimer in its native form and is adenosylcobalamin-dependent. The precursor form of human MCM is 750 amino acids, while its mature form is 718 amino acids – a 32 amino acid leader sequence is cleaved off by mitochondrial importation and processing machinery. This leader sequence is variously referred to as MCM's mitochondrial targeting peptide, mitochondrial targeting sequence, or mitochondrial transit peptide.

[0004] A complete or partial loss of MCM function leads to buildup of abnormal metabolites and metabolic intermediates upstream of MCM, such as methylmalonic acid, propionyl-carnitine, acetyl-carnitine, propionyl-CoA, D-methylmalonyl-CoA and L-methylmalonyl-CoA. For example, loss of MCM has been reported to lead to a 1000-fold increase in the methylmalonic acid. Nonetheless, there is no currently available therapeutic to treat MMA.

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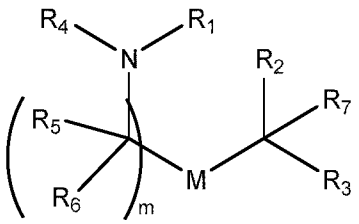
SUMMARY OF THE DISCLOSURE

[0005] The present disclosure provides methods of treating methylmalonic acidemia in a subject, the methods comprising administering to the subject an effective amount of a polynucleotide comprising an mRNA encoding an MCM polypeptide, wherein the administration alleviates the symptoms of methylmalonic acidemia in the subject. The present disclosure also provides compositions comprising a polynucleotide sequence encoding an MCM polypeptide. In some embodiments, the compositions include a delivery agent.

[0006] In some embodiments, the composition comprises a polynucleotide that comprises an open reading frame (ORF) encoding an MCM polypeptide and a delivery agent, wherein the delivery agent comprises a compound having the formula (I)



(I),

or a salt or stereoisomer thereof, wherein

R_1 is selected from the group consisting of C_{5-20} alkyl, C_{5-20} alkenyl, -R*YR", -YR", and –R"M'R';

R_2 and R_3 are independently selected from the group consisting of H, C_{1-14} alkyl, C_{2-14} alkenyl, -R*YR", -YR", and –R*OR", or R_2 and R_3, together with the atom to which they are attached, form a heterocycle or carbocycle;

R_4 is selected from the group consisting of a C_{3-6} carbocycle, $-(CH_2)_nQ$, $-(CH_2)_nCHQR$,

-CHQR, $-CQ(R)_2$, and unsubstituted C_{1-6} alkyl, where Q is selected from a carbocycle, heterocycle,

-OR, $-O(CH_2)_nN(R)_2$, -C(O)OR, -OC(O)R, $-CX_3$, $-CX_2H$, $-CXH_2$, -CN, $-N(R)_2$, $-C(O)N(R)_2$, $-N(R)C(O)R$, $-N(R)S(O)_2R$, $-N(R)C(O)N(R)_2$, $-N(R)C(S)N(R)_2$, and $-C(R)N(R)_2C(O)OR$, and each n is independently selected from 1, 2, 3, 4, and 5;

each R_5 is independently selected from the group consisting of C_{1-3} alkyl, C_{2-3} alkenyl, and H;

each R_6 is independently selected from the group consisting of C_{1-3} alkyl, C_{2-3} alkenyl, and H;

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M and M' are independently selected from –C(O)O-, -OC(O)-, -C(O)N(R')-, -N(R')C(O)-, -C(O)-, -C(S)-, -C(S)S-, -SC(S)-, -CH(OH)-, -P(O)(OR')O-, -$S(O)_2$-, an aryl group, and a heteroaryl group;

R_7 is selected from the group consisting of C_{1-3} alkyl, C_{2-3} alkenyl, and H;

each R is independently selected from the group consisting of C_{1-3} alkyl, C_{2-3} alkenyl, and H;

each R' is independently selected from the group consisting of C_{1-18} alkyl, C_{2-18} alkenyl, -R*YR", -YR", and H;

each R" is independently selected from the group consisting of C_{3-14} alkyl and C_{3-14} alkenyl;

each R* is independently selected from the group consisting of C_{1-12} alkyl and C_{2-12} alkenyl;

each Y is independently a C_{3-6} carbocycle;

each X is independently selected from the group consisting of F, Cl, Br, and I; and

m is selected from 5, 6, 7, 8, 9, 10, 11, 12, and 13; and

provided when R_4 is $–(CH_2)_nQ$, $-(CH_2)_nCHQR$, –CHQR, or $–CQ(R)_2$, then (i) Q is not $–N(R)_2$ when n is 1, 2, 3, 4 or 5, or (ii) Q is not 5, 6, or 7-membered heterocycloalkyl when n is 1 or 2.

[0007] In some embodiments, the delivery agent further comprises a phospholipid, a structural lipid, a PEG lipid, or any combination thereof.

[0008] In some embodiments, the polynucleotides comprise an ORF having significant sequence similarity to a polynucleotide selected from the group of SEQ ID NOs: 1-207, 732-765, and 772, wherein the ORF encodes an MCM polypeptide. In some embodiments, the polynucleotides comprise an ORF having significant sequence similarity to a polynucleotide selected from the group of SEQ ID NOs: 151, 152, 153, 154, 732, 733, and 734 (**FIGS. 9-15**), wherein the ORF encodes an MCM polypeptide. In some embodiments, the polynucleotide comprises an ORF having significant sequence similarity to SEQ ID NO: 734 (**FIG. 11**) , wherein the ORF encodes an MCM polypeptide.

[0009] In some embodiments, the disclosure is directed to a polynucleotide comprising an ORF having at least 99% or 100% sequence identity to nucleotide 97 to nucleotide 2250 of SEQ ID NO: 734, wherein the ORF encodes an MCM polypeptide.

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[0010] In some embodiments, the disclosure is directed to a polynucleotide comprising an ORF sequence having at least 98%, at least 99%, or 100% sequence identity to nucleotide 97 to nucleotide 2250 of SEQ ID NO: 732, wherein the ORF encodes an MCM polypeptide.

[0011] In some embodiments, the disclosure is directed to a polynucleotide comprising an ORF having at least 92%, at least 93%, at least 94%, at least 95%, at least 96%, at least 97%, at least 98%, at least 99%, or 100% sequence identity to a sequence selected from the group consisting of nucleotides 97 to nucleotides 2250 of SEQ ID NOs: 182, 733, and 741, wherein the ORF encodes an MCM polypeptide.

[0012] In some embodiments, the disclosure is directed to a polynucleotide comprising an ORF having at least 91%, at least 92%, at least 93%, at least 94%, at least 95%, at least 96%, at least 97%, at least 98%, at least 99%, or 100% sequence identity to a sequence selected from the group consisting of nucleotides 97 to nucleotides 2250 of SEQ ID NOs: 735, 736, 738, 743, 744, 748, 749, 750, 754, 755, 758, 762, and 765, wherein the ORF encodes an MCM polypeptide.

[0013] In some embodiments, the disclosure is directed to a polynucleotide comprising an ORF sequence having at least 90%, at least 91%, at least 92%, at least 93%, at least 94%, at least 95%, at least 96%, at least 97%, at least 98%, at least 99%, or 100% sequence identity to a sequence selected from the group consisting of nucleotides 97 to nucleotides 2250 of SEQ ID NOs: 180, 187, 737, 739, 740, 742, 745, 746, 747, 751, 752, 753, 757, 759, 760, 761, 763, and 764, wherein the ORF encodes an MCM polypeptide.

[0014] In some embodiments, the disclosure is directed to a polynucleotide comprising an ORF having at least 89%, at least 90%, at least 91%, at least 92%, at least 93%, at least 94%, at least 95%, at least 96%, at least 97%, at least 98%, at least 99%, or 100% sequence identity to a sequence selected from the group consisting of nucleotides 97 to nucleotides 2250 of SEQ ID NO: 181 and 756, wherein the ORF encodes an MCM polypeptide.

[0015] In some embodiments, the disclosure is directed to a polynucleotide comprising an ORF having at least 88%, at least 89%, at least 90%, at least 91%, at least 92%, at least 93%, at least 94%, at least 95%, at least 96%, at least 97%, at least 98%, at least 99%, or 100% sequence identity to a sequence selected from the group consisting of nucleotides 97 to nucleotides 2250 of SEQ ID NO: 154, 165, 171, 173, and 175, wherein the ORF encodes an MCM polypeptide.

[0016] In some embodiments, the disclosure is directed to a polynucleotide comprising an ORF having at least 87%, at least 88%, at least 89%, at least 90%, at least 91%, at least 92%, at least 93%, at least 94%, at least 95%, at least 96%, at least 97%, at least 98%, at least 99%, or

100% sequence identity to a sequence selected from the group consisting of nucleotides 97 to nucleotides 2250 of SEQ ID NO: 151, 152, 153, 163, 164, 166, 167, 168, 169, 170, 172, 177, 178, 179, 195, and 204, wherein the ORF encodes an MCM polypeptide.

[0017] In some embodiments, the disclosure is directed to a polynucleotide comprising an ORF having at least 86%, at least 87%, at least 88%, at least 89%, at least 90%, at least 91%, at least 92%, at least 93%, at least 94%, at least 95%, at least 96%, at least 97%, at least 98%, at least 99%, or 100% sequence identity to a sequence selected from the group consisting of nucleotides 97 to nucleotides 2250 of SEQ ID NOs: 156, 157, 158, 159, 160, 161, 162, 174 and 176, wherein the ORF encodes an MCM polypeptide.

[0018] In some embodiments, the disclosure is directed to a polynucleotide comprising an ORF having at least 85%, at least 86%, at least 87%, at least 88%, at least 89%, at least 90%, at least 91%, at least 92%, at least 93%, at least 94%, at least 95%, at least 96%, at least 97%, at least 98%, at least 99%, or 100% sequence identity to a sequence selected from the group consisting of nucleotides 97 to nucleotides 2250 of SEQ ID NOs: 155 and 203, wherein the ORF encodes an MCM polypeptide.

[0019] In some embodiments, the disclosure is directed to a polynucleotide comprising an ORF having at least 82%, at least 83%, at least 84%, at least 85%, at least 86%, at least 87%, at least 88%, at least 89%, at least 90%, at least 91%, at least 92%, at least 93%, at least 94%, at least 95%, at least 96%, at least 97%, at least 98%, at least 99%, or 100% sequence identity to a sequence selected from the group consisting of nucleotides 97 to nucleotides 2250 of SEQ ID NOs: 64, 66, 71, 91, and 128, wherein the ORF encodes an MCM polypeptide.

[0020] In some embodiments, the disclosure is directed to a polynucleotide comprising an ORF having at least 81%, at least 82%, at least 83%, at least 84%, at least 85%, at least 86%, at least 87%, at least 88%, at least 89%, at least 90%, at least 91%, at least 92%, at least 93%, at least 94%, at least 95%, at least 96%, at least 97%, at least 98%, at least 99%, or 100% sequence identity to a sequence selected from the group consisting of nucleotides 97 to nucleotides 2250 of SEQ ID NOs: 9, 11, 18, 19, 21, 22, 23, 24, 32, 33, 37, 39, 40, 44, 45, 47, 50, 51, 52, 55, 57, 61, 65, 70, 79, 84, 86, 88, 90, 92, 98, 100, 115, 117, 126, 129, 135, 136, 137, 144, 148, 150, 184, 190, 191, and 206, wherein the ORF encodes an MCM polypeptide.

[0021] In some embodiments, the disclosure is directed to a polynucleotide comprising an ORF having at least 80%, at least 81%, at least 82%, at least 83%, at least 84%, at least 85%, at least 86%, at least 87%, at least 88%, at least 89%, at least 90%, at least 91%, at least 92%, at

least 93%, at least 94%, at least 95%, at least 96%, at least 97%, at least 98%, at least 99%, or 100% sequence identity to a sequence selected from the group consisting of nucleotides 97 to nucleotides 2250 of SEQ ID NOs: 3, 5, 6, 8, 10, 12, 14, 16, 17, 20, 27, 28, 29, 31, 34, 35, 36, 38, 41, 42, 43, 46, 48, 49, 53, 54, 56, 58, 60, 63, 68, 69, 74, 77, 78, 80, 83, 85, 87, 93, 95, 96, 97, 99, 102, 103, 104, 105, 107, 110, 112, 113, 114, 116, 119, 120, 122, 123, 124, 125, 127, 131, 132, 133, 134, 138, 139, 140, 141, 142, 143, 147, 149, 183, 186, 188, 189, 192, 193, 194, 196, 197, 198, 199, 200, 201, 202, 205, and 207, wherein the ORF encodes an MCM polypeptide.

[0022] In some embodiments, the disclosure is directed to a polynucleotide comprising an ORF having at least 79%, at least 80%, at least 81%, at least 82%, at least 83%, at least 84%, at least 85%, at least 86%, at least 87%, at least 88%, at least 89%, at least 90%, at least 91%, at least 92%, at least 93%, at least 94%, at least 95%, at least 96%, at least 97%, at least 98%, at least 99%, or 100% sequence identity to a sequence selected from the group consisting of nucleotides 97 to nucleotides 2250 of SEQ ID NOs: 1, 2, 4, 7, 13, 15, 25, 26, 30, 59, 62, 67, 72, 73, 75, 76, 81, 82, 89, 94, 101, 106, 108, 109, 111, 118, 121, 130, 145, 146, and 185, wherein the ORF encodes an MCM polypeptide.

[0023] In some embodiments, the polynucleotides further comprise a nucleotide sequence encoding a transit peptide, *e.g.*, mitochondrial transit peptide. The mitochondrial transit peptide can be any peptide that facilitates the transport of MCM to mitochondria or localization of MCM in mitochondria. In some embodiments, the polynucleotide comprises a nucleotide sequence encoding a mitochondrial transit peptide selected from the group listed in **Table 1** (SEQ ID NOs: 251 to 265). In some embodiments, the polynucleotide comprises a nucleotide sequence encoding a mitochondrial transit peptide selected from the group consisting of SEQ ID NOs: 270 to 719.

[0024] In some embodiments, the disclosure is directed to a polynucleotide comprising an ORF having at least 99% or 100% sequence identity to nucleotide 1 to nucleotide 2250 of SEQ ID NO: 734, wherein the ORF encodes an MCM polypeptide.

[0025] In some embodiments, the disclosure is directed to a polynucleotide comprising an ORF having at least 98%, at least 99%, or 100% sequence identity to nucleotide 1 to nucleotide 2250 of SEQ ID NO: 732, wherein the ORF encodes an MCM polypeptide.

[0026] In some embodiments, the disclosure is directed to a polynucleotide comprising an ORF having at least 92%, at least 93%, at least 94%, at least 95%, at least 96%, at least 97%, at least 98%, at least 99%, or 100% sequence identity to a sequence selected from the group

consisting of nucleotides 1 to nucleotides 2250 of SEQ ID NO: 182 and 733, wherein the ORF encodes an MCM polypeptide.

[0027] In some embodiments, the disclosure is directed to a polynucleotide comprising an ORF having at least 91%, at least 92%, at least 93%, at least 94%, at least 95%, at least 96%, at least 97%, at least 98%, at least 99%, or 100% sequence identity to a sequence selected from the group consisting of nucleotides 1 to nucleotides 2250 of SEQ ID NOs: 735, 741, 743, 744, 748, 758, 762, and 765, wherein the ORF encodes an MCM polypeptide.

[0028] In some embodiments, the disclosure is directed to a polynucleotide comprising an ORF having at least 90%, at least 91%, at least 92%, at least 93%, at least 94%, at least 95%, at least 96%, at least 97%, at least 98%, at least 99%, or 100% sequence identity to a sequence selected from the group consisting of nucleotides 1 to nucleotides 2250 of SEQ ID NOs: 180, 181 , 736, 738, 739, 740, 742, 746, 747, 749, 750, 751, 752, 753, 754, 755, 757, 759, 760, 761, and 763, wherein the ORF encodes an MCM polypeptide.

[0029] In some embodiments, the disclosure is directed to a polynucleotide comprising an ORF having at least 89%, at least 90%, at least 91%, at least 92%, at least 93%, at least 94%, at least 95%, at least 96%, at least 97%, at least 98%, at least 99%, or 100% sequence identity to a sequence selected from the group consisting of nucleotides 1 to nucleotides 2250 of SEQ ID NO: 745, 756, and 764, wherein the ORF encodes an MCM polypeptide.

[0030] In some embodiments, the disclosure is directed to a polynucleotide comprising an ORF having at least 88%, at least 89%, at least 90%, at least 91%, at least 92%, at least 93%, at least 94%, at least 95%, at least 96%, at least 97%, at least 98%, at least 99%, or 100% sequence identity to a sequence selected from the group consisting of nucleotides 1 to nucleotides 2250 of SEQ ID NO: 154, 165, 171, 173, and 175, wherein the ORF encodes an MCM polypeptide.

[0031] In some embodiments, the disclosure is directed to a polynucleotide comprising an ORF having at least 87%, at least 88%, at least 89%, at least 90%, at least 91%, at least 92%, at least 93%, at least 94%, at least 95%, at least 96%, at least 97%, at least 98%, at least 99%, or 100% sequence identity to a sequence selected from the group consisting of nucleotides 1 to nucleotides 2250 of SEQ ID NO: 151, 152, 153, 163, 166, 167, 168, 169, 170, 172, 177, 178, 179, 187, and 204, wherein the ORF encodes an MCM polypeptide.

[0032] In some embodiments, the disclosure is directed to a polynucleotide comprising an ORF having at least 86%, at least 87%, at least 88%, at least 89%, at least 90%, at least 91%, at least 92%, at least 93%, at least 94%, at least 95%, at least 96%, at least 97%, at least 98%, at

least 99%, or 100% sequence identity to a sequence selected from the group consisting of nucleotides 1 to nucleotides 2250 of SEQ ID NO: 156, 157, 158, 159, 160, 162, 164, 174, 176, 195, and 737, wherein the ORF encodes an MCM polypeptide.

[0033] In some embodiments, the disclosure is directed to a polynucleotide comprising an ORF having at least 85%, at least 86%, at least 87%, at least 88%, at least 89%, at least 90%, at least 91%, at least 92%, at least 93%, at least 94%, at least 95%, at least 96%, at least 97%, at least 98%, at least 99%, or 100% sequence identity to a sequence selected from the group consisting of nucleotides 1 to nucleotides 2250 of SEQ ID NOs: 155, 161, and 203, wherein the ORF encodes an MCM polypeptide.

[0034] In some embodiments, the disclosure is directed to a polynucleotide comprising an ORF having at least 82%, at least 83%, at least 84%, at least 85%, at least 86%, at least 87%, at least 88%, at least 89%, at least 90%, at least 91%, at least 92%, at least 93%, at least 94%, at least 95%, at least 96%, at least 97%, at least 98%, at least 99%, or 100% sequence identity to a sequence selected from the group consisting of nucleotides 1 to nucleotides 2250 of SEQ ID NOs: 71 and 128, wherein the ORF encodes an MCM polypeptide.

[0035] In some embodiments, the disclosure is directed to a polynucleotide comprising an ORF having at least 81%, at least 82%, at least 83%, at least 84%, at least 85%, at least 86%, at least 87%, at least 88%, at least 89%, at least 90%, at least 91%, at least 92%, at least 93%, at least 94%, at least 95%, at least 96%, at least 97%, at least 98%, at least 99%, or 100% sequence identity to a sequence selected from the group consisting of nucleotides 1 to nucleotides 2250 of SEQ ID NOs: 4, 6, 8, 9, 11, 19, 22, 23, 24, 32, 33, 37, 40, 44, 45, 47, 51, 61, 64, 65, 66, 79, 84, 86, 90, 91, 92, 100, 101, 112, 115, 117, 126, 129, 135, 136, 146, 148, 184, 190, and 191, wherein the ORF encodes an MCM polypeptide.

[0036] In some embodiments, the disclosure is directed to a polynucleotide comprising an ORF having at least 80%, at least 81%, at least 82%, at least 83%, at least 84%, at least 85%, at least 86%, at least 87%, at least 88%, at least 89%, at least 90%, at least 91%, at least 92%, at least 93%, at least 94%, at least 95%, at least 96%, at least 97%, at least 98%, at least 99%, or 100% sequence identity to a sequence selected from the group consisting of nucleotides 1 to nucleotides 2250 of SEQ ID NOs: 2, 3, 5, 7, 10, 12, 13, 14, 15, 16, 18, 20, 21, 26, 27, 28, 29, 31, 34, 36, 38, 39, 41, 42, 43, 46, 48, 49, 52, 53, 54, 55, 56, 57, 58, 59, 60, 62, 68, 69, 70, 72, 73, 74, 76, 77, 80, 83, 85, 88, 95, 96, 97, 98, 102, 104, 105, 106, 107, 108, 109, 110, 113, 114, 120, 121, 122, 123, 124, 127, 131, 132, 133, 134, 137, 138, 139, 140, 141, 142, 144, 145, 147, 149, 150,

186, 188, 189, 192, 193, 194, 196, 198, 199, 200, 202, 205, 206, and 207, wherein the ORF encodes an MCM polypeptide.

[0037] In some embodiments, the disclosure is directed to a polynucleotide comprising an ORF having at least 79%, at least 80%, at least 81%, at least 82%, at least 83%, at least 84%, at least 85%, at least 86%, at least 87%, at least 88%, at least 89%, at least 90%, at least 91%, at least 92%, at least 93%, at least 94%, at least 95%, at least 96%, at least 97%, at least 98%, at least 99%, or 100% sequence identity to a sequence selected from the group consisting of nucleotides 1 to nucleotides 2250 of SEQ ID NOs: 1, 17, 25, 30, 35, 50, 63, 67, 75, 78, 81, 82, 87, 89, 93, 94, 99, 103, 111, 116, 118, 119, 125, 130, 143, 183, 185, 197, and 201, wherein the ORF encodes an MCM polypeptide.

[0038] In some embodiments, the disclosure is directed to polynucleotides that encode functional MCMs or fragments thereof. In some embodiments, the disclosure provides polynucleotides that encode functional human MCMs (SEQ ID NO: 208, SEQ ID NO: 209, SEQ ID NO: 210, SEQ ID NO: 211, SEQ ID NO: 212, and SEQ ID NO: 213). In some embodiments, the disclosure provides polynucleotides that encode functional MCM polypeptides having at least one point mutation in the MCM sequence, while still retaining MCM enzymatic activity. In some embodiments, the encoded MCM polypeptide comprises one or more of the point mutations V69, T499, H532, A598, and V671, as defined by the polypeptide sequences in SEQ ID NO: 209, SEQ ID NO: 210, SEQ ID NO: 211, SEQ ID NO: 212, and SEQ ID NO: 213, respectively. In some embodiments, the polynucleotides are fully or partially modified (*e.g.*, chemically and/or structurally) in a manner as to avoid the deficiencies of other molecules of the art. The polynucleotides of the disclosure can be synthesized as an IVT polynucleotide, chimeric polynucleotide or a circular polynucleotide and such embodiments are contemplated.

[0039] In some embodiments, the polynucleotide is a DNA or RNA that comprises at least one chemically modified nucleoside. In some embodiments, the at least one chemically modified nucleoside is selected from any of those described herein.

[0040] In some embodiments, the polynucleotide further comprises or encodes a 5' UTR. In other embodiments, the polynucleotide further comprises or encodes a 3' UTR. In some embodiments, the UTR comprises or encodes a miRNA (*e.g.*, miR-142-3p, miR-142-5p, miR-126-3p, and/or miR-126-5p). In some embodiments, the polynucleotide further comprises a 5' terminal cap. In some embodiments, the polynucleotide further comprises or encodes a 3' polyA tail.

[0041] In some embodiments, the polynucleotide is RNA, *e.g.*, mRNA. In some embodiments, the mRNA comprises the sequences listed in SEQ ID NOs: 766-771.

[0042] In some embodiments, the polynucleotide is an RNA polynucleotide that is formulated in a lipid nanoparticle (LNP) carrier.

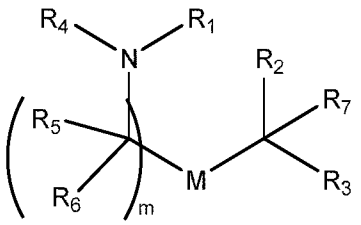
[0043] The disclosure is also directed to a method of treating methylmalonic acidemia in a subject, the method comprising administering to the subject an effective amount of a polynucleotide comprising an mRNA encoding an MCM polypeptide, wherein the administration alleviates the symptoms of methylmalonic acidemia in the subject. In some embodiments, the polynucleotide useful for the disclosure is any one of the polynucleotides encoding an MCM polypeptide described herein or is formulated as any one of the compositions described herein.

[0044] In some embodiments, the disclosure includes a method of reducing the level of a metabolite associated with methylmalonic acidemia in a subject in need thereof, the method comprising administering to the subject an effective amount of a polynucleotide comprising an mRNA encoding an MCM polypeptide. In some embodiments, the polynucleotide is a polynucleotide described elsewhere herein, or is formulated as a composition described herein. In certain embodiments, the polynucleotide reduces the level of methylmalonic acid present in the subject after the administration by at least about 10%, at least about 20%, at least about 30%, at least about 40%, at least about 50%, at least about 60%, at least about 70%, at least about 80%, at least about 90%, or about 100%. In other embodiments, after the administration, the polynucleotide reduces the level of propionyl-carnitine present in the subject by at least about 10%, at least about 20%, at least about 30%, at least about 40%, at least about 50%, at least about 60%, at least about 70%, at least about 80%, at least about 90%, or about 100%. In yet other embodiments, the polynucleotide reduces the level of acetyl-carnitine present in the subject after the administration by at least about 10%, at least about 20%, at least about 30%, at least about 40%, at least about 50%, at least about 60%, at least about 70%, at least about 80%, at least about 90%, or about 100%. In certain embodiments, one or more metabolites associated with methylmalonic acidemia are reduced after the administration within one day, within two days, within three days, within four days, within five days, within seven days, within one week, within two weeks, within three weeks, or within one month of the administration of the polynucleotide.

[0045] The details of various embodiments of the disclosure are set forth in the description below. Other features, objects, and advantages of the disclosure will be apparent from the description and the drawings, and from the claims.

EMBODIMENTS

[0046] E1. A composition comprising a polynucleotide that comprises an open reading frame (ORF) encoding an MCM polypeptide and a delivery agent, wherein the delivery agent comprises a compound having the formula (I)



(I),

or a salt or stereoisomer thereof, wherein

R_1 is selected from the group consisting of C_{5-20} alkyl, C_{5-20} alkenyl, -R*YR", -YR", and –R"M'R';

R_2 and R_3 are independently selected from the group consisting of H, C_{1-14} alkyl, C_{2-14} alkenyl, -R*YR", -YR", and –R*OR", or R_2 and R_3, together with the atom to which they are attached, form a heterocycle or carbocycle;

R_4 is selected from the group consisting of a C_{3-6} carbocycle, $-(CH_2)_nQ$, $-(CH_2)_nCHQR$,

-CHQR, $-CQ(R)_2$, and unsubstituted C_{1-6} alkyl, where Q is selected from a carbocycle, heterocycle,

-OR, $-O(CH_2)_nN(R)_2$, -C(O)OR, -OC(O)R, $-CX_3$, $-CX_2H$, $-CXH_2$, -CN, $-N(R)_2$, $-C(O)N(R)_2$, $-N(R)C(O)R$, $-N(R)S(O)_2R$, $-N(R)C(O)N(R)_2$, $-N(R)C(S)N(R)_2$, and $-C(R)N(R)_2C(O)OR$, and each n is independently selected from 1, 2, 3, 4, and 5;

each R_5 is independently selected from the group consisting of C_{1-3} alkyl, C_{2-3} alkenyl, and H;

each R_6 is independently selected from the group consisting of C_{1-3} alkyl, C_{2-3} alkenyl, and H;

M and M' are independently selected from –C(O)O-, -OC(O)-, -C(O)N(R')-, -N(R')C(O)-, -C(O)-, -C(S)-, -C(S)S-, -SC(S)-, -CH(OH)-, -P(O)(OR')O-, -$S(O)_2$-, an aryl group, and a heteroaryl group;

R_7 is selected from the group consisting of C_{1-3} alkyl, C_{2-3} alkenyl, and H;

each R is independently selected from the group consisting of C_{1-3} alkyl, C_{2-3} alkenyl, and H;

each R' is independently selected from the group consisting of C_{1-18} alkyl, C_{2-18} alkenyl, -R*YR", -YR", and H;

each R" is independently selected from the group consisting of C_{3-14} alkyl and C_{3-14} alkenyl;

each R* is independently selected from the group consisting of C_{1-12} alkyl and C_{2-12} alkenyl;

each Y is independently a C_{3-6} carbocycle;

each X is independently selected from the group consisting of F, Cl, Br, and I; and

m is selected from 5, 6, 7, 8, 9, 10, 11, 12, and 13; and

provided when R_4 is $–(CH_2)_nQ$, $-(CH_2)_nCHQR$, –CHQR, or $–CQ(R)_2$, then (i) Q is not $–N(R)_2$ when n is 1, 2, 3, 4 or 5, or (ii) Q is not 5, 6, or 7-membered heterocycloalkyl when n is 1 or 2.

[0047] E2. The composition of embodiment 1, wherein the ORF has at least 80%, at least 85%, at least 86%, at least 87%, at least 88%, at least 89%, at least 90%, at least 91%, at least 92%, at least 93%, at least 94%, at least 95%, at least 96%, at least 97%, at least 98%, at least 99%, or 100% sequence identity to a sequence selected from the group consisting of nucleotides 97 to nucleotides 2250 of SEQ ID NOs: 1 to 207, 732 to 765, and 772.

[0048] E3. The composition of embodiment 1 or 2, wherein the ORF has

(i) at least 99% or 100% sequence identity to nucleotide 97 to nucleotide 2250 of SEQ ID NO: 734,

(ii) at least 98%, at least 99%, or 100% sequence identity to nucleotide 97 to nucleotide 2250 of SEQ ID NO: 732,

(iii) at least 92%, at least 93%, at least 94%, at least 95%, at least 96%, at least 97%, at least 98%, at least 99%, or 100% sequence identity to a sequence selected from the group consisting of nucleotides 97 to nucleotides 2250 of SEQ ID NOs: 182, 733, and 741;

(iv) at least 91%, at least 92%, at least 93%, at least 94%, at least 95%, at least 96%, at least 97%, at least 98%, at least 99%, or 100% sequence identity to a sequence selected from the group consisting of nucleotides 97 to nucleotides 2250 of SEQ ID NOs: 735, 736, 738, 743, 744, 748, 749, 750, 754, 755, 758, 762, and 765;

(v) at least 90%, at least 91%, at least 92%, at least 93%, at least 94%, at least 95%, at least 96%, at least 97%, at least 98%, at least 99%, or 100% sequence identity to a sequence selected from the group consisting of nucleotides 97 to nucleotides 2250 of SEQ ID NOs: 180, 187, 737, 739, 740, 742, 745, 746, 747, 751, 752, 753, 757, 759, 760, 761, 763, and 764;

(vi) at least 89%, at least 90%, at least 91%, at least 92%, at least 93%, at least 94%, at least 95%, at least 96%, at least 97%, at least 98%, at least 99%, or 100% sequence identity to a sequence selected from the group consisting of nucleotides 97 to nucleotides 2250 of SEQ ID NOs: 181 and 756;

(vii) at least 88%, at least 89%, at least 90%, at least 91%, at least 92%, at least 93%, at least 94%, at least 95%, at least 96%, at least 97%, at least 98%, at least 99%, or 100% sequence identity to a sequence selected from the group consisting of nucleotides 97 to nucleotides 2250 of SEQ ID NO: 154, 165, 171, 173, and 175;

(viii) at least 87%, at least 88%, at least 89%, at least 90%, at least 91%, at least 92%, at least 93%, at least 94%, at least 95%, at least 96%, at least 97%, at least 98%, at least 99%, or 100% sequence identity to a sequence selected from the group consisting of nucleotides 97 to nucleotides 2250 of SEQ ID NO: 151, 152, 153, 163, 164, 166, 167, 168, 169, 170, 172, 177, 178, 179, 195, and 204;

(ix) at least 86%, at least 87%, at least 88%, at least 89%, at least 90%, at least 91%, at least 92%, at least 93%, at least 94%, at least 95%, at least 96%, at least 97%, at least 98%, at least 99%, or 100% sequence identity to a sequence selected from the group consisting of nucleotides 97 to nucleotides 2250 of SEQ ID NOs: 156, 157, 158, 159, 160, 161, 162, 174 and 176;

(x) at least 85%, at least 86%, at least 87%, at least 88%, at least 89%, at least 90%, at least 91%, at least 92%, at least 93%, at least 94%, at least 95%, at least 96%, at least 97%, at least 98%, at least 99%, or 100% sequence identity to a sequence selected from the group consisting of nucleotides 97 to nucleotides 2250 of SEQ ID NOs: 155 and 203;

(xi) at least 82%, at least 83%, at least 84%, at least 85%, at least 86%, at least 87%, at least 88%, at least 89%, at least 90%, at least 91%, at least 92%, at least 93%, at least 94%, at

least 95%, at least 96%, at least 97%, at least 98%, at least 99%, or 100% sequence identity to a sequence selected from the group consisting of nucleotides 97 to nucleotides 2250 of SEQ ID NOs: 64, 66, 71, 91, and 128;

(xii) at least 81%, at least 82%, at least 83%, at least 84%, at least 85%, at least 86%, at least 87%, at least 88%, at least 89%, at least 90%, at least 91%, at least 92%, at least 93%, at least 94%, at least 95%, at least 96%, at least 97%, at least 98%, at least 99%, or 100% sequence identity to a sequence selected from the group consisting of nucleotides 97 to nucleotides 2250 of SEQ ID NOs: 9, 11, 18, 19, 21, 22, 23, 24, 32, 33, 37, 39, 40, 44, 45, 47, 50, 51, 52, 55, 57, 61, 65, 70, 79, 84, 86, 88, 90, 92, 98, 100, 115, 117, 126, 129, 135, 136, 137, 144, 148, 150, 184, 190, 191, and 206;

(xiii) at least 80%, at least 81%, at least 82%, at least 83%, at least 84%, at least 85%, at least 86%, at least 87%, at least 88%, at least 89%, at least 90%, at least 91%, at least 92%, at least 93%, at least 94%, at least 95%, at least 96%, at least 97%, at least 98%, at least 99%, or 100% sequence identity to a sequence selected from the group consisting of nucleotides 97 to nucleotides 2250 of SEQ ID NOs: 3, 5, 6, 8, 10, 12, 14, 16, 17, 20, 27, 28, 29, 31, 34, 35, 36, 38, 41, 42, 43, 46, 48, 49, 53, 54, 56, 58, 60, 63, 68, 69, 74, 77, 78, 80, 83, 85, 87, 93, 95, 96, 97, 99, 102, 103, 104, 105, 107, 110, 112, 113, 114, 116, 119, 120, 122, 123, 124, 125, 127, 131, 132, 133, 134, 138, 139, 140, 141, 142, 143, 147, 149, 183, 186, 188, 189, 192, 193, 194, 196, 197, 198, 199, 200, 201, 202, 205, and 207; or

(xiv) at least 79%, at least 80%, at least 81%, at least 82%, at least 83%, at least 84%, at least 85%, at least 86%, at least 87%, at least 88%, at least 89%, at least 90%, at least 91%, at least 92%, at least 93%, at least 94%, at least 95%, at least 96%, at least 97%, at least 98%, at least 99%, or 100% sequence identity to a sequence selected from the group consisting of nucleotides 97 to nucleotides 2250 of SEQ ID NOs: 1, 2, 4, 7, 13, 15, 25, 26, 30, 59, 62, 67, 72, 73, 75, 76, 81, 82, 89, 94, 101, 106, 108, 109, 111, 118, 121, 130, 145, 146, and 185.

[0049] E4. The composition of any one of embodiments 1 to 3, wherein the ORF further comprises a nucleic acid sequence encoding a transit peptide.

[0050] E5. The composition of embodiment 4, wherein the transit peptide comprises a mitochondrial transit peptide.

[0051] E6. The composition of embodiment 5, wherein the mitochondrial transit peptide is derived from a protein selected from the group consisting of SEQ ID NOs: 251 to 265 and 270 to 719.

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[0052] E7. The composition of any one of embodiments 4 to 6, wherein the nucleic acid sequence encoding a transit peptide has at least about 70%, at least about 80%, at least about 90%, at least about 95%, at least about 96%, at least about 97%, at least about 98%, at least about 99%, or about 100% sequence identity to a sequence selected from the group consisting of nucleotides 1 to 96 of SEQ ID NOs: 1 to 207, 732 to 765, and 772.

[0053] E8. The composition of any one of embodiments 1 to 7, wherein the ORF has

(i) at least 99% or 100% sequence identity to nucleotide 1 to nucleotide 2250 of SEQ ID NO: 734;

(ii) at least 98%, at least 99%, or 100% sequence identity to nucleotide 1 to nucleotide 2250 of SEQ ID NO: 732;

(iii) at least 92%, at least 93%, at least 94%, at least 95%, at least 96%, at least 97%, at least 98%, at least 99%, or 100% sequence identity to a sequence selected from the group consisting of nucleotides 1 to nucleotides 2250 of SEQ ID NOs: 182 and 733;

(iv) at least 91%, at least 92%, at least 93%, at least 94%, at least 95%, at least 96%, at least 97%, at least 98%, at least 99%, or 100% sequence identity to a sequence selected from the group consisting of nucleotides 1 to nucleotides 2250 of SEQ ID NOs: 735, 741, 743, 744, 748, 758, 762, and 765;

(v) at least 90%, at least 91%, at least 92%, at least 93%, at least 94%, at least 95%, at least 96%, at least 97%, at least 98%, at least 99%, or 100% sequence identity to a sequence selected from the group consisting of nucleotides 1 to nucleotides 2250 of SEQ ID NOs: 180, 181, 736, 738, 739, 740, 742, 746, 747, 749, 750, 751, 752, 753, 754, 755, 757, 759, 760, 761, and 763;

(vi) at least 89%, at least 90%, at least 91%, at least 92%, at least 93%, at least 94%, at least 95%, at least 96%, at least 97%, at least 98%, at least 99%, or 100% sequence identity to a sequence selected from the group consisting of nucleotides 1 to nucleotides 2250 of SEQ ID NO: 745, 756, and 764;

(vii) at least 88%, at least 89%, at least 90%, at least 91%, at least 92%, at least 93%, at least 94%, at least 95%, at least 96%, at least 97%, at least 98%, at least 99%, or 100% sequence identity to a sequence selected from the group consisting of nucleotides 1 to nucleotides 2250 of SEQ ID NO: 154, 165, 171, 173, and 175;

(viii) at least 87%, at least 88%, at least 89%, at least 90%, at least 91%, at least 92%, at least 93%, at least 94%, at least 95%, at least 96%, at least 97%, at least 98%, at least 99%, or 100% sequence identity to a sequence selected from the group consisting of nucleotides 1 to nucleotides 2250 of SEQ ID NO: 151, 152, 153, 163, 166, 167, 168, 169, 170, 172, 177, 178, 179, 187, and 204;

(ix) at least 86%, at least 87%, at least 88%, at least 89%, at least 90%, at least 91%, at least 92%, at least 93%, at least 94%, at least 95%, at least 96%, at least 97%, at least 98%, at least 99%, or 100% sequence identity to a sequence selected from the group consisting of nucleotides 1 to nucleotides 2250 of SEQ ID NO: 156, 157, 158, 159, 160, 162, 164, 174, 176, 195, and 737;

(x) at least 85%, at least 86%, at least 87%, at least 88%, at least 89%, at least 90%, at least 91%, at least 92%, at least 93%, at least 94%, at least 95%, at least 96%, at least 97%, at least 98%, at least 99%, or 100% sequence identity to a sequence selected from the group consisting of nucleotides 1 to nucleotides 2250 of SEQ ID NOs: 155, 161, and 203;

(xi) at least 82%, at least 83%, at least 84%, at least 85%, at least 86%, at least 87%, at least 88%, at least 89%, at least 90%, at least 91%, at least 92%, at least 93%, at least 94%, at least 95%, at least 96%, at least 97%, at least 98%, at least 99%, or 100% sequence identity to a sequence selected from the group consisting of nucleotides 1 to nucleotides 2250 of SEQ ID NOs: 71 and 128;

(xii) at least 81%, at least 82%, at least 83%, at least 84%, at least 85%, at least 86%, at least 87%, at least 88%, at least 89%, at least 90%, at least 91%, at least 92%, at least 93%, at least 94%, at least 95%, at least 96%, at least 97%, at least 98%, at least 99%, or 100% sequence identity to a sequence selected from the group consisting of nucleotides 1 to nucleotides 2250 of SEQ ID NOs: 4, 6, 8, 9, 11, 19, 22, 23, 24, 32, 33, 37, 40, 44, 45, 47, 51, 61, 64, 65, 66, 79, 84, 86, 90, 91, 92, 100, 101, 112, 115, 117, 126, 129, 135, 136, 146, 148, 184, 190, and 191;

(xiii) at least 80%, at least 81%, at least 82%, at least 83%, at least 84%, at least 85%, at least 86%, at least 87%, at least 88%, at least 89%, at least 90%, at least 91%, at least 92%, at least 93%, at least 94%, at least 95%, at least 96%, at least 97%, at least 98%, at least 99%, or 100% sequence identity to a sequence selected from the group consisting of nucleotides 1 to nucleotides 2250 of SEQ ID NOs: 2, 3, 5, 7, 10, 12, 13, 14, 15, 16, 18, 20, 21, 26, 27, 28, 29, 31, 34, 36, 38, 39, 41, 42, 43, 46, 48, 49, 52, 53, 54, 55, 56, 57, 58, 59, 60, 62, 68, 69, 70, 72, 73, 74, 76, 77, 80, 83, 85, 88, 95, 96, 97, 98, 102, 104, 105, 106, 107, 108, 109, 110, 113, 114, 120, 121,

122, 123, 124, 127, 131, 132, 133, 134, 137, 138, 139, 140, 141, 142, 144, 145, 147, 149, 150, 186, 188, 189, 192, 193, 194, 196, 198, 199, 200, 202, 205, 206, and 207; or

(xiv) at least 79%, at least 80%, at least 81%, at least 82%, at least 83%, at least 84%, at least 85%, at least 86%, at least 87%, at least 88%, at least 89%, at least 90%, at least 91%, at least 92%, at least 93%, at least 94%, at least 95%, at least 96%, at least 97%, at least 98%, at least 99%, or 100% sequence identity to a sequence selected from the group consisting of nucleotides 1 to nucleotides 2250 of SEQ ID NOs: 1, 17, 25, 30, 35, 50, 63, 67, 75, 78, 81, 82, 87, 89, 93, 94, 99, 103, 111, 116, 118, 119, 125, 130, 143, 183, 185, 197, and 201.

[0054] E9. The composition of any one of embodiments 1 to 8, wherein the MCM polypeptide comprises an amino acid sequence at least about 95%, at least about 96%, at least about 97%, at least about 98%, at least about 99%, or about 100% identical to SEQ ID NO: 208, and wherein the MCM polypeptide retains methylmalonyl-CoA mutase activity.

[0055] E10. The composition of embodiment 9, wherein the MCM polypeptide comprises SEQ ID NO: 209.

[0056] E11. The composition of embodiment 9, wherein the MCM polypeptide comprises SEQ ID NO: 210.

[0057] E12. The composition of embodiment 9, wherein the MCM polypeptide comprises SEQ ID NO: 211.

[0058] E13. The composition of embodiment 9, wherein the MCM polypeptide comprises SEQ ID NO: 212.

[0059] E14. The composition of embodiment 9, wherein the MCM polypeptide comprises SEQ ID NO: 213.

[0060] E15. The composition of any one of embodiments 1-14, wherein the polynucleotide comprises at least one chemically modified nucleobase, sugar, backbone, or any combination thereof.

[0061] E16. The composition of embodiment 15, wherein the at least one chemically modified nucleobase is selected from the group consisting of pseudouracil (ψ), N1-methylpseudouracil (m1ψ), 2-thiouracil (s2U), 4'-thiouracil, 5-methylcytosine, 5-methyluracil, and any combination thereof.

[0062] E17. The composition of embodiment 16, wherein the at least one chemically modified nucleoside is 5-methoxyuracil.

[0063] E18. The composition of any one of embodiments 1-17, wherein the nucleosides in the polynucleotide sequence are chemically modified by at least 10%, at least 20%, at least 30%, at least 40%, at least 50%, at least 60%, at least 70%, at least 80%, at least 90%, at least 95%, at least 99%, or 100%.

[0064] E19. The composition of any one of embodiments 15-18, wherein the chemically modified nucleosides in the polynucleotide sequence are selected from the group consisting of uridine, adenine, cytosine, guanine, and any combination thereof.

[0065] E20. The composition of any one of embodiments 1-19, wherein the uridine nucleosides in the polynucleotide sequence are chemically modified by at least 10%, at least 20%, at least 30%, at least 40%, at least 50%, at least 60%, at least 70%, at least 80%, at least 90%, at least 95%, at least 99%, or 100%.

[0066] E21. The composition of any one of embodiments 1-20, wherein the adenine nucleosides in the polynucleotide sequence are chemically modified by at least 10%, at least 20%, at least 30%, at least 40%, at least 50%, at least 60%, at least 70%, at least 80%, at least 90%, at least 95%, at least 99%, or 100%.

[0067] E22. The composition of any one of embodiments 1-21, wherein the cytosine nucleosides in the polynucleotide sequence are chemically modified by at least at least 10%, at least 20%, at least 30%, at least 40%, at least 50%, at least 60%, at least 70%, at least 80%, at least 90%, at least 95%, at least 99%, or 100%.

[0068] E23. The composition of any one of embodiments 1-22, wherein the guanine nucleosides in the polynucleotide sequence are chemically modified by at least at least 10%, at least 20%, at least 30%, at least 40%, at least 50%, at least 60%, at least 70%, at least 80%, at least 90%, at least 95%, at least 99%, or 100%.

[0069] E24. The composition of any one of embodiments 1-23, wherein the polynucleotide further comprises a 5' UTR.

[0070] E25. The composition of embodiment 24, wherein the 5' UTR comprises a nucleic acid sequence at least 90%, 95%, 96%, 97%, 98%, 99%, or 100% identical to a sequence selected from SEQ ID NOs: 215-231, 266, and 725-731.

[0071] E26. The composition of any one of embodiments 1 to 25, wherein the polynucleotide further comprises a miRNA binding site.

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[0072] E27. The composition of embodiment 26, wherein the miRNA binding site comprises one or more polynucleotide sequences selected SEQ ID NOs: 720, 721, 722, 723, and 724.

[0073] E28. The composition of embodiment 26, wherein the miRNA binding site binds to miR-142 or miR-126.

[0074] E29. The composition of embodiment 26, wherein the miRNA binding site binds to miR-142-3p, miR-142-5p, miR-126-3p, or miR-126-5p.

[0075] E30. The composition of embodiment 24, wherein the 5'UTR comprises a sequence selected from SEQ ID NOs: 725, 726, 727, 728, 729, 730, and 731.

[0076] E31. The composition of any one of embodiments 24-30, wherein the 5' UTR is sequence optimized.

[0077] E32. The composition of any one of embodiments 1-31, wherein the polynucleotide further comprises a 3' UTR.

[0078] E33. The composition of embodiment 32, wherein the 3' UTR comprises a nucleic acid sequence at least 90%, 95%, 96%, 97%, 98%, 99%, or 100% identical to a sequence selected from SEQ ID NO: 232-248 and 267.

[0079] E34. The composition of embodiment 32 or 33, wherein the 3' UTR is codon optimized.

[0080] E35. The composition of any one of embodiments 1-34, wherein the polynucleotide further comprises a 5' terminal cap.

[0081] E36. The composition of embodiment 35, wherein the 5' terminal cap is a Cap0, Cap1, ARCA, inosine, N1-methyl-guanosine, 2'fluoro-guanosine, 7-deaza-guanosine, 8-oxo-guanosine, 2-amino-guanosine, LNA-guanosine, 2-azidoguanosine, Cap2, Cap4, 5' methylG cap, or an analog thereof.

[0082] E37. The composition of any one of embodiments 1-36, wheren the polynucleotide further comprises a 3' polyA tail.

[0083] E38. The composition of any one of embodiments 1-37, wherein the polynucleotide is RNA.

[0084] E39. The composition of embodiment 38, wherein the RNA is mRNA.

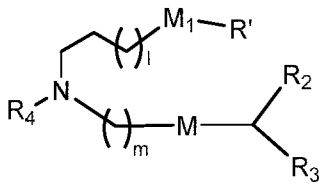
[0085] E40. The composition of any one of embodiments 1-39, wherein the polynucleotide is *in vitro* transcribed (IVT).

[0086] E41. The composition of any one of embodiments 1-40, wherein the polynucleotide is chimeric.

[0087] E42. The composition of any one of embodiments 1-41, wherein the polynucleotide is circular.

[0088] E43. The composition of any one of embodiments 1-42, wherein the polynucleotide is purified by strong anion exchange HPLC, weak anion exchange HPLC, reverse phase HPLC (RP-HPLC), and hydrophobic interaction HPLC (HIC-HPLC), liquid chromatography-mass spectrometry (LCMS), capillary electrophoresis (CE) and capillary gel electrophoresis (CGE).

[0089] E44. The composition of any one of embodiments 1-43, wherein the compound is of Formula (IA):



(IA),

or a salt or stereoisomer thereof, wherein

l is selected from 1, 2, 3, 4, and 5;

m is selected from 5, 6, 7, 8, and 9;

M_1 is a bond or M';

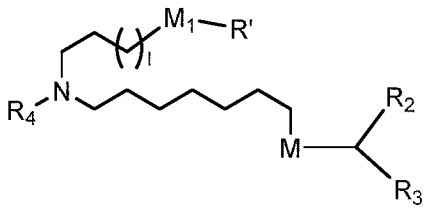
R_4 is unsubstituted C_{1-3} alkyl, or $-(CH_2)_nQ$, in which n is 1, 2, 3, 4, or 5 and Q is OH, $-NHC(S)N(R)_2$, or $-NHC(O)N(R)_2$;

M and M' are independently selected from C(O)O , OC(O) , C(O)N(R') , P(O)(OR')O, an aryl group, and a heteroaryl group; and

R_2 and R_3 are independently selected from the group consisting of H, C_{1-14} alkyl, and C_{2-14} alkenyl.

[0090] E45. The composition of any one of embodiments 1 to 44, wherein m is 5, 7, or 9.

[0091] E46. The composition of any one of embodiments 1 to 45, wherein the compound is of Formula (II):



(II),

or a salt or stereoisomer thereof, wherein

l is selected from 1, 2, 3, 4, and 5;

M_1 is a bond or M';

R_4 is unsubstituted C_{1-3} alkyl, or $-(CH_2)_nQ$, in which n is 2, 3, or 4 and Q is OH, -NHC(S)N$(R)_2$, or –NHC(O)N$(R)_2$;

M and M' are independently selected from – C(O)O, OC(O), C(O)N(R'), P(O)(OR')O, an aryl group, and a heteroaryl group; and

R_2 and R_3 are independently selected from the group consisting of H, C_{1-14} alkyl, and C_{2-14} alkenyl.

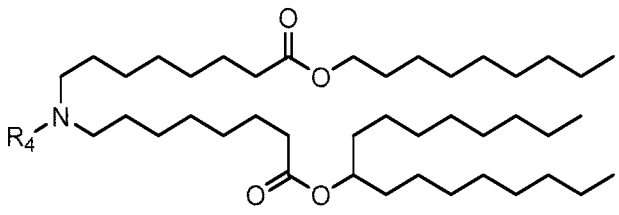
[0092] E47. The composition of any one of embodiments 44 to 46, wherein M_1 is M'.

[0093] E48. The composition of embodiment 47, wherein M and M' are independently –C(O)O- or –OC(O)-.

[0094] E49. The composition of any one of embodiments 44 to 48, wherein l is 1, 3, or 5.

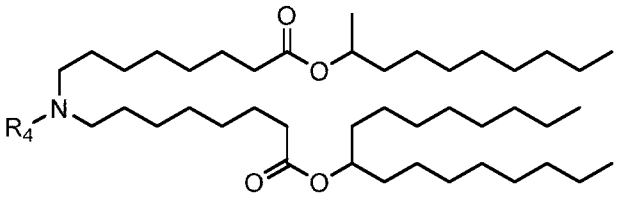
[0095] E50. The composition of any one of embodiments 1 to 43, wherein the compound is selected from the group consisting of Compound 1 to Compound 147, salts and stereoisomers thereof, and any combination thereof.

[0096] E51. The composition of any one of embodiments 1 to 43, wherein the compound is of the Formula (IIa),



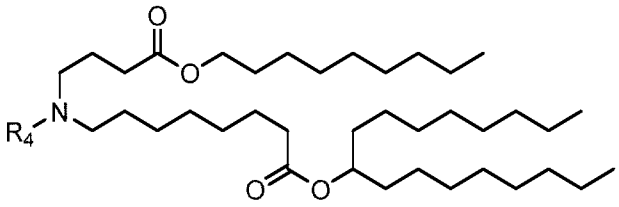
(Iia), or a salt or stereoisomer thereof.

[0097] E52. The composition of any one of embodiments 1 to 43, wherein the compound is of the Formula (IIb),

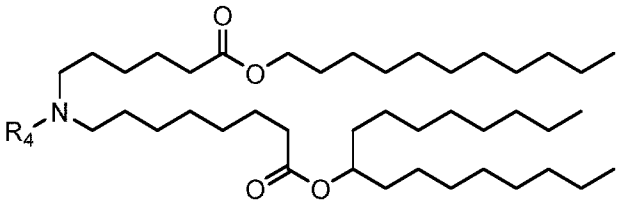


(IIb), or a salt or stereoisomer thereof.

[0098] E53. The composition of any one of embodiments 1 to 43, wherein the compound is of the Formula (IIc) or (IIe),



(IIc),

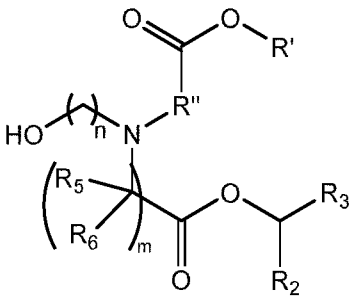


(IIe),

or a salt or stereoisomer thereof.

[0099] E54. The composition of any one of embodiments 51 to 53, wherein R_4 is selected from $-(CH_2)_nQ$ and $-(CH_2)_nCHQR$.

[0100] E55. The composition of any one of embodiments 1 to 43, wherein the compound is of the Formula (IId),



(IId), or a salt or stereoisomer thereof,

wherein R_2 and R_3 are independently selected from the group consisting of C_{5-14} alkyl and C_{5-14} alkenyl, n is selected from 2, 3, and 4, and R', R'', R_5, R_6 and m are as defined in embodiment 1.

[0101] E56. The composition of embodiment 55, wherein R_2 is C_8 alkyl.

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[0102] E57. The composition of embodiment 56, wherein R_3 is C_5 alkyl, C_6 alkyl, C_7 alkyl, C_8 alkyl, or C_9 alkyl.

[0103] E58. The composition of any one of embodiments 55 to 57, wherein m is 5, 7, or 9.

[0104] E59. The composition of any one of embodiments 55 to 58, wherein each R_5 is H.

[0105] E60. The composition of embodiment 59, wherein each R_6 is H.

[0106] E61. The composition of any one of embodiments 1 to 60, wherein the composition is a nanoparticle composition.

[0107] E62. The composition of embodiment 61, wherein the delivery agent further comprises a phospholipid.

[0108] E63. The composition of embodiment 62, wherein the phospholipid is selected from the group consisting of 1,2-dilinoleoyl-sn-glycero-3-phosphocholine (DLPC), 1,2-dimyristoyl-sn-glycero-phosphocholine (DMPC), 1,2-dioleoyl-sn-glycero-3-phosphocholine (DOPC), 1,2-dipalmitoyl-sn-glycero-3-phosphocholine (DPPC), 1,2-distearoyl-sn-glycero-3-phosphocholine (DSPC), 1,2-diundecanoyl-sn-glycero-phosphocholine (DUPC), 1-palmitoyl-2-oleoyl-sn-glycero-3-phosphocholine (POPC), 1,2-di-O-octadecenyl-*sn*-glycero-3-phosphocholine (18:0 Diether PC), 1-oleoyl-2-cholesterylhemisuccinoyl-*sn*-glycero-3-phosphocholine (OChemsPC), 1-hexadecyl-sn-glycero-3-phosphocholine (C16 Lyso PC), 1,2-dilinolenoyl-sn-glycero-3-phosphocholine, 1,2-diarachidonoyl-sn-glycero-3-phosphocholine, 1,2-didocosahexaenoyl-sn-glycero-3-phosphocholine, 1,2-dioleoyl-sn-glycero-3-phosphoethanolamine (DOPE), 1,2-diphytanoyl-sn-glycero-3-phosphoethanolamine (ME 16:0 PE), 1,2-distearoyl-sn-glycero-3-phosphoethanolamine, 1,2-dilinoleoyl-sn-glycero-3-phosphoethanolamine, 1,2-dilinolenoyl-sn-glycero-3-phosphoethanolamine, 1,2-diarachidonoyl-sn-glycero-3-phosphoethanolamine, 1,2-didocosahexaenoyl-sn-glycero-3-phosphoethanolamine,

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1,2-dioleoyl-sn-glycero-3-phospho-rac-(1-glycerol) sodium salt (DOPG), sphingomyelin, and any mixtures thereof.

[0109] E64. The composition of any one of embodiments 1 to 63, wherein the delivery agent further comprises a structural lipid.

[0110] E65. The composition of embodiment 64, wherein the structural lipid is selected from the group consisting of cholesterol, fecosterol, sitosterol, ergosterol, campesterol, stigmasterol, brassicasterol, tomatidine, ursolic acid, alpha-tocopherol, and any mixtures thereof.

[0111] E66. The composition of any one of embodiments 1 to 65, wherein the delivery agent further comprises a PEG lipid.

[0112] E67. The composition of embodiment 66, wherein the PEG lipid is selected from the group consisting of a PEG-modified phosphatidylethanolamine, a PEG-modified phosphatidic acid, a PEG-modified ceramide, a PEG-modified dialkylamine, a PEG-modified diacylglycerol, a PEG-modified dialkylglycerol, and any mixtures thereof.

[0113] E68. The composition of any one of embodiments 1 to 67, wherein the delivery agent further comprises an ionizable lipid selected from the group consisting of 3-(didodecylamino)-N1,N1,4-tridodecyl-1-piperazineethanamine (KL10), N1-[2-(didodecylamino)ethyl]-N1,N4,N4-tridodecyl-1,4-piperazinediethanamine (KL22), 14,25-ditridecyl-15,18,21,24-tetraaza-octatriacontane (KL25), 1,2-dilinoleyloxy-N,N-dimethylaminopropane (DLin-DMA), 2,2-dilinoleyl-4-dimethylaminomethyl-[1,3]-dioxolane (DLin-K-DMA), heptatriaconta-6,9,28,31-tetraen-19-yl 4-(dimethylamino)butanoate (DLin-MC3-DMA), 2,2-dilinoleyl-4-(2-dimethylaminoethyl)-[1,3]-dioxolane (DLin-KC2-DMA), 1,2-dioleyloxy-N,N-dimethylaminopropane (DODMA), 2-({8-[(3β)-cholest-5-en-3-yloxy]octyl}oxy)-N,N-dimethyl-3-[(9Z,12Z)-octadeca-9,12-dien-1-yl oxy]propan-1-amine (Octyl-CLinDMA), (2R)-2-({8-[(3β)-cholest-5-en-3-yloxy]octyl}oxy)-N,N-dimethyl-3-[(9Z,12Z)-octadeca-9,12-die n-1-yloxy]propan-1-amine (Octyl-CLinDMA (2R)), and (2S)-2-({8-[(3β)-cholest-5-en-3-yloxy]octyl}oxy)-N,N-dimethyl-3-[(9Z,12Z)-octadeca-9,12-dien -1-yloxy]propan-1-amine (Octyl-CLinDMA (2S)).

[0114] E69. The composition of any one of embodiments 1 to 68, wherein the delivery agent further comprises a phospholipid, a structural lipid, a PEG lipid, or any combination thereof.

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[0115] E70. The composition of any one of embodiments 1-69, wherein the composition is formulated for *in vivo* delivery.

[0116] E71. The composition of embodiment 70 which is formulated for intramuscular, subcutaneous, or intradermal delivery.

[0117] E72. The composition of any one of embodiments 1-71 which increases cellular expression of MCM.

[0118] E73. The composition of embodiment 72, wherein the cellular expression of MCM is increased by at least 20%, at least 25%, at least 30%, at least 35%, at least 40%, at least 45%, or at least 50%.

[0119] E74. A method of administering the composition of any one of embodiments 1-73, wherein the administration alleviates the symptoms of methylmalonic acidemia in the subject.

[0120] E75. The method of embodiment 74, wherein the administration results in a reduction of the level of a metabolite associated with methylmalonic acidemia in a subject in need thereof.

[0121] E76. The method of embodiment 74 or 75, further comprising measuring the level of the metabolite in the subject or in a sample obtained from the subject before and/or after the administering.

[0122] E77. The method of embodiment 76, wherein the sample is taken from the subject's blood, urine, cerebrospinal fluid, or any combination thereof.

[0123] E78. The method of any of embodiments 74 to 77, wherein the administration reduces the level of methylmalonic acid present in the subject by at least about 10%, at least about 20%, at least about 30%, at least about 40%, at least about 50%, at least about 60%, at least about 70%, at least about 80%, at least about 90%, or about 100%.

[0124] E79. The method of any of embodiments 74 to 78, wherein the polynucleotide reduces the level of propionyl-carnitine present in the subject by at least about 10%, at least about 20%, at least about 30%, at least about 40%, at least about 50%, at least about 60%, at least about 70%, at least about 80%, at least about 90%, or about 100%.

[0125] E80. The method of any of embodiments 74 to 79, wherein the polynucleotide reduces the level of acetyl-carnitine present in the subject by at least about 10%, at least about 20%, at least about 30%, at least about 40%, at least about 50%, at least about 60%, at least about 70%, at least about 80%, at least about 90%, or about 100%.

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[0126] E81. The method of any one of embodiments 74 to 80, wherein one or more metabolites associated with methylmalonic acidemia are reduced within one day, within two days, within three days, within four days, within five days, within seven days, within one week, within two weeks, within three weeks, or within one month of the administration of the polynucleotide.

[0127] E82. A method of treating methylmalonic acidemia in a subject in need thereof, the method comprising administering to the subject an effective amount of a polynucleotide comprising an mRNA that comprises an ORF encoding an MCM polypeptide, wherein the administration alleviates the symptoms of methylmalonic acidemia in the subject.

[0128] E83. The method of embodiment 82, wherein the polynucleotide comprises the polynucleotide in the composition of any one of embodiments 1 to 73.

[0129] E84. The method of embodiment 82 or 83, wherein the administration reduces the level of a metabolite associated with methylmalonic acidemia in a subject in need thereof.

[0130] E85. The method of any one of embodiments 82-84, further comprising measuring the level of the metabolite in the subject or in a sample obtained from the subject before and/or after the administering.

[0131] E86. The method of embodiment 85, wherein the sample is taken from the subject's blood, urine, cerebrospinal fluid, or any combination thereof.

[0132] E87. The method of any of embodiments 82 to 86, wherein the polynucleotide reduces the level of methylmalonic acid present in the subject by at least about 10%, at least about 20%, at least about 30%, at least about 40%, at least about 50%, at least about 60%, at least about 70%, at least about 80%, at least about 90%, or about 100%.

[0133] E88. The method of any of embodiments 82 to 87, wherein the polynucleotide reduces the level of propionyl-carnitine present in the subject by at least about 10%, at least about 20%, at least about 30%, at least about 40%, at least about 50%, at least about 60%, at least about 70%, at least about 80%, at least about 90%, or about 100%.

[0134] E89. The method of any of embodiments 82 to 88, wherein the polynucleotide reduces the level of acetyl-carnitine present in the subject by at least about 10%, at least about 20%, at least about 30%, at least about 40%, at least about 50%, at least about 60%, at least about 70%, at least about 80%, at least about 90%, or about 100%.

[0135] E90. The method of any one of embodiments 82 to 89, wherein one or more metabolites associated with methylmalonic acidemia are reduced within one day, within two

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days, within three days, within four days, within five days, within seven days, within one week, within two weeks, within three weeks, or within one month of the administration of the polynucleotide.

[0136] E91. The method of any one of embodiments 82 to 90, wherein the nucleotide is administered as a nanoparticle composition.

[0137] E92. The method of embodiment 91, wherein the composition further comprises a delivery agent.

[0138] E93. The method of embodiment 92, wherein the delivery agent comprises a phospholipid.

[0139] E94. The method of embodiment 93, wherein the phospholipid is selected from the group consisting of 1,2-dilinoleoyl-sn-glycero-3-phosphocholine (DLPC), 1,2-dimyristoyl-sn-glycero-phosphocholine (DMPC), 1,2-dioleoyl-sn-glycero-3-phosphocholine (DOPC), 1,2-dipalmitoyl-sn-glycero-3-phosphocholine (DPPC), 1,2-distearoyl-sn-glycero-3-phosphocholine (DSPC), 1,2-diundecanoyl-sn-glycero-phosphocholine (DUPC), 1-palmitoyl-2-oleoyl-sn-glycero-3-phosphocholine (POPC), 1,2-di-O-octadecenyl-*sn*-glycero-3-phosphocholine (18:0 Diether PC), 1-oleoyl-2-cholesterylhemisuccinoyl-*sn*-glycero-3-phosphocholine (OChemsPC), 1-hexadecyl-sn-glycero-3-phosphocholine (C16 Lyso PC), 1,2-dilinolenoyl-sn-glycero-3-phosphocholine, 1,2-diarachidonoyl-sn-glycero-3-phosphocholine, 1,2-didocosahexaenoyl-sn-glycero-3-phosphocholine, 1,2-dioleoyl-sn-glycero-3-phosphoethanolamine (DOPE), 1,2-diphytanoyl-sn-glycero-3-phosphoethanolamine (ME 16:0 PE), 1,2-distearoyl-sn-glycero-3-phosphoethanolamine, 1,2-dilinoleoyl-sn-glycero-3-phosphoethanolamine, 1,2-dilinolenoyl-sn-glycero-3-phosphoethanolamine, 1,2-diarachidonoyl-sn-glycero-3-phosphoethanolamine, 1,2-didocosahexaenoyl-sn-glycero-3-phosphoethanolamine, 1,2-dioleoyl-sn-glycero-3-phospho-rac-(1-glycerol) sodium salt (DOPG), sphingomyelin, and any mixtures thereof.

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[0140] E95. The method of any one of embodiments 92 to 94, wherein the delivery agent further comprises a structural lipid.

[0141] E96. The method of embodiment 95, wherein the structural lipid is selected from the group consisting of cholesterol, fecosterol, sitosterol, ergosterol, campesterol, stigmasterol, brassicasterol, tomatidine, ursolic acid, alpha-tocopherol, and any mixtures thereof.

[0142] E97. The method of any one of embodiments 92 to 96, wherein the delivery agent further comprises a PEG lipid.

[0143] E98. The method of embodiment 97, wherein the PEG lipid is selected from the group consisting of a PEG-modified phosphatidylethanolamine, a PEG-modified phosphatidic acid, a PEG-modified ceramide, a PEG-modified dialkylamine, a PEG-modified diacylglycerol, a PEG-modified dialkylglycerol, and any mixtures thereof.

[0144] E99. The method of any one of embodiments 92 to 98, wherein the delivery agent further comprises an ionizable lipid selected from the group consisting of 3-(didodecylamino)-N1,N1,4-tridodecyl-1-piperazineethanamine (KL10), N1-[2-(didodecylamino)ethyl]-N1,N4,N4-tridodecyl-1,4-piperazinediethanamine (KL22), 14,25-ditridecyl-15,18,21,24-tetraaza-octatriacontane (KL25), 1,2-dilinoleyloxy-N,N-dimethylaminopropane (DLin-DMA), 2,2-dilinoleyl-4-dimethylaminomethyl-[1,3]-dioxolane (DLin-K-DMA), heptatriaconta-6,9,28,31-tetraen-19-yl 4-(dimethylamino)butanoate (DLin-MC3-DMA), 2,2-dilinoleyl-4-(2-dimethylaminoethyl)-[1,3]-dioxolane (DLin-KC2-DMA), 1,2-dioleyloxy-N,N-dimethylaminopropane (DODMA), 2-({8-[(3β)-cholest-5-en-3-yloxy]octyl}oxy)-N,N-dimethyl-3-[(9Z,12Z)-octadeca-9,12-dien-1-yl oxy]propan-1-amine (Octyl-CLinDMA), (2R)-2-({8-[(3β)-cholest-5-en-3-yloxy]octyl}oxy)-N,N-dimethyl-3-[(9Z,12Z)-octadeca-9,12-die n-1-yloxy]propan-1-amine (Octyl-CLinDMA (2R)), and (2S)-2-({8-[(3β)-cholest-5-en-3-yloxy]octyl}oxy)-N,N-dimethyl-3-[(9Z,12Z)-octadeca-9,12-dien -1-yloxy]propan-1-amine (Octyl-CLinDMA (2S)).

[0145] E100. The method of any one of embodiments 92 to 99, wherein the delivery agent further comprises a phospholipid, a structural lipid, a PEG lipid, or any combination thereof.

[0146] E101. The method of any one of embodiments 92-100, wherein the composition is formulated for *in vivo* delivery.

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[0147] E102. The method of embodiment 101 which is formulated for intramuscular, subcutaneous, or intradermal delivery.

[0148] E103. The method of any one of embodiments 82-102 which increases cellular expression of MCM.

[0149] E104. The method of embodiment 103, wherein the cellular expression of MCM is increased by at least 20%, at least 25%, at least 30%, at least 35%, at least 40%, at least 45%, or at least 50%.

[0150] E105. The method of any one of embodiments 74 to 104, wherein the polynucleotide is administered at a dose of 0.1 mg/kg to 1.0 mg/kg, 0.1 mg/kg to 10 mg/kg, 0.1 mg/kg to 2 mg/kg, 0.1 mg/kg to 5 mg/kg, 1 mg/kg to 5 mg/kg, or 1 mg/kg to 3 mg/kg.

[0151] E106. The method of any one of embodiments 74 to 105, wherein the plasma MMA level after the administration is reduced at least 70%, at least 75%, at least 80%, at least 85%, at least 90%, or at least 95% compared to the plasma MMA level prior to the administration.

[0152] E107. The method of embodiment 106, wherein the plasma MMA level is reduced about 75% to 85% compared to the plasma MMA level prior to the administration.

[0153] E108. The method of any one of embodiments 74 to 107, wherein the plasma MMA level after the administration is lower than about 5 μmol/L, about 4.5 μmol/L, about 4 μmol/L, about 3.5 μmol/L, about 3 μmol/L, about 2.5 μmol/L, about 2 μmol/L, about 1.5 μmol/L, about 1 μmol/L, about 0.9 μmol/L, about 0.8 μmol/L, about 0.7 μmol/L, about 0.6 μmol/L, about 0.5 μmol/L, about 0.4 μmol/L, about 0.3 μmol/L, or 0.27 μmol/L.

[0154] E109. The method of embodiments 74 to 108, wherein the urinary MMA level is less than 2000 mmol/mol creatinine, less than 1900 mmol/mol creatinine, less than 1800 mmol/mol creatinine, less than 1700 mmol/mol creatinine, less than 1600 mmol/mol creatinine, less than 1500 mmol/mol creatinine, less than 1400 mmol/mol creatinine, less than 1300 mmol/mol creatinine, less than 1200 mmol/mol creatinine, less than 1100 mmol/mol creatinine, less than 1000 mmol/mol creatinine, 900 mmol/mol creatinine, 800 mmol/mol creatinine, 700 mmol/mol creatinine, 600 mmol/mol creatinine, 500 mmol/mol creatinine, 400 mmol/mol creatinine, 300 mmol/mol creatinine, 200 mmol/mol creatinine, 100 mmol/mol creatinine, 90 mmol/mol creatinine, 80 mmol/mol creatinine, 70 mmol/mol creatinine, 60 mmol/mol creatinine, 50 mmol/mol creatinine, 40 mmol/mol creatinine, 30 mmol/mol creatinine, 20 mmol/mol creatinine, 10 mmol/mol creatinine, 9 mmol/mol creatinine, 8 mmol/mol creatinine, 7 mmol/mol

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creatinine, 6 mmol/mol creatinine,5 mmol/mol creatinine, 4 mmol/mol creatinine, 3 mmol/mol creatinine, 2 mmol/mol creatinine, or 1 mmol/mol creatinine.

BRIEF DESCRIPTION OF THE DRAWINGS

[0155] **FIG. 1** is a Western blot analysis of endogenous methylmalonyl-CoA mutase expression in a mouse liver mitochondrial extract, mouse cells (Hepa1-6), and human cells (HepG2, SNU423, and HeLa). The upper band (thin arrow) shows Mouse α–Methymalonyl-CoA mutase, and the lower band (thick arrow) shows Rabbit α–Citrate synthetase.

[0156] **FIGS. 2A-2C** show immunofluorescence analyses of the localization of endogenous methylmalonyl-CoA mutase in HeLa cells. **FIG. 2A** shows the location of mitochondria using Mitotracker and the nucleus using DAPI. **FIG. 2B** shows the immunostaining of hMCM protein using a murine monoclonal anti-MCM antibody and the location of the nucleus using DAPI. **FIG. 2C** shows the merged picture of **FIGS. 2A** and **2B**.

[0157] **FIG. 3** is a Western blot analysis comparing methylmalonyl-CoA mutase expression in (i) HeLa cells transfected with a control GFP expression construct, (ii) HeLa cells transfected with a construct for expressing methylmalonyl-CoA mutase, and (iii) a mouse liver mitochondrial extract.

[0158] **FIG. 4** is a comparison of methylmalonyl-CoA mutase enzymatic activity in (i) HeLa cells transfected with a control GFP expression construct, (ii) HeLa cells transfected with a construct for expressing methylmalonyl-CoA mutase, and (iii) a mouse liver mitochondrial extract.

[0159] **FIG. 5** is a Western blot analysis of methylmalonyl-CoA mutase expression in Hepa1-6 cells, fibroblasts from normal human subjects (NHDF), and fibroblasts from MMA patients (GM50 and GM1573) that were transfected with control mRNA, human MCM mRNA, or mouse MCM mRNA.

[0160] **FIGS. 6A-6D** show immunofluorescence analyses of the localization of exogenously expressed methylmalonyl-CoA mutase in human fibroblasts transfected with eGFP mRNAs or MCM mRNAs (also referred to as "MUT"). The left panels show the location of mitochondria using Mitotracker and the nucleus using DAPI, the middle panels show shows the location of mitochondria using MCM protein and the nucleus using DAPI, and the right panels show merged images of the left panel and the right panel. **FIGS. 6A** and **6C** are images taken of patient

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fibroblasts transfected with mRNA encoding eGFP. **FIGS. 6B** and **6D** are images taken of patient fibroblasts transfected with mRNA encoding hMCM.

[0161] **FIG. 7** is measurement of methylmalonyl-CoA mutase activity in Hepa1-6 cells, fibroblasts from normal human subjects (NHDF), and fibroblasts from MMA patients (GM50 and GM1573) that were transfected with control mRNA, human MCM mRNA, or mouse MCM mRNA.

[0162] **FIGS. 8A-8B** is an analysis of *in vivo* treatment with mRNA encoding methylmalonyl-CoA mutase. For **FIGS. 8A** and **8B**, C57B/L6 mice were injected intravenously with either control mRNA (NT-FIX) or MCM mRNA at 0.5 mg mRNA/kg body weight ("mpk"). Mice were sacrificed after 24 or 48 hours and MCM protein in mitochondria from livers were determined by capillary electrophoresis (CE). The upper panel (**FIG. 8A**) shows injection of MCM mRNA increased MCM protein expression after 24 and 48 hours, while the lower panel (**FIG. 8B**) shows the expression of the control protein citrate synthase.

[0163] **FIGS. 9-15** show exemplary codon optimized MCM sequences that encode methylmalonyl-CoA mutase. The illustrated sequences in **FIGS. 9-15** are SEQ ID NOs: 732, 733, 734, 151, 152, 153, and 154, respectively.

[0164] **FIGS. 16A-C** show analysis of MMA levels and body weight in the MCK mouse model. **FIG. 16A** shows plasma levels of methylmalonic acid (MMA) in μM measured by LC-MS/MS over time in mice treated weekly with control mRNA (NT-FIX) at 0.1 mg/kg, codon optimized MCM mRNA (encoding SEQ ID NO:734) formulated in lipid nanoparticles at 0.16 or 0.2 mg/kg for 5 injections, or codon optimized MCM mRNA (encoding SEQ ID NO:734) formulated in lipid nanoparticles at 0.2 mg/kg for 2 injections. **FIG. 16B** shows the body weight of the mice over time (measured twice a week). ***$p<0.001$; P-values obtained from repeated measures ANOVA. **FIG. 16C** shows the the increase in body weight over time in mice injected weekly with codon optimized MCM mRNA.

[0165] **FIG. 17** shows MCM expression in liver of wild-type CD1 mice dosed with codon optimized MCM mRNA (SEQ ID NO: 734) formulated in lipid nanoparticles at 0.2 mg/kg compared to endogenous human MCM and endogenous mouse MCM.

[0166] **FIGS. 18A-C** show a time course of the effects of injection of codon optimized MCM mRNA. **FIG. 18A** shows levels of lipid nanoparticles after single dose injection of codon optimized MCM mRNA. **FIG. 18B** shows Hepatic hMut mRNA levels in mouse liver after

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single dose injection of codon optimized MCM mRNA. FIG. 18C shows MCM protein levels after single dose injection of codon optimized MCM mRNA

[0167] **FIGS. 19A-B** show MCM expression in livel of wild-type CD mice dosed with codon optimized MCM mRNAs, where the mRNA is formulated either with MC3 or Compound 18. NTFIX mRNA was used as a control. **FIG. 19A** shows a Western blot of expression after dosing with different formulations, and **FIG. 19B** shows a quantification of that Western blot.

[0168] **FIGS. 20A-B** show the effects of administering codon optimized MCM mRNA to mice on the plasma levels of MMA (**FIG. 20A**) and the body weight of the mice (**FIG. 20B**).

DETAILED DESCRIPTION

[0169] The present disclosure provides polynucleotide sequences that encode a sequence-optimized nucleic acid encoding a methylmalonyl-CoA mutase polypeptide ("MCM" or "MUT"). MCM is the principal gene associated with methylmalonic acidemia ("MMA," also referred to as methylmalonic adicuria). Wild type nucleic acid and amino acid sequences for human methylmalonyl-CoA mutase (MCM) are described in NCBI sequence records gi296010795 (reference sequence NM_000255.3, "Homo sapiens methylmalonyl-CoA mutase (MUT), mRNA"; *see also*, SEQ ID NO: 214) and gi156105689 (reference sequence NP_000246.2, "methylmalonyl-CoA mutase, mitochondrial precursor [Homo sapiens]"; *see also*, SEQ ID NO: 208), respectively. Accession numbers and the associated sequences are found at the National Center for Biotechnology Information (NCBI) website.

[0170] MCM is a metabolic enzyme (E.C. 5.4.99.2), the biological function of which is to isomerize L-methylmalonyl-CoA into succinyl-CoA, a Krebs cycle intermediate. MCM localizes to the mitochondria of cells, exists as a homodimer in its native form, and is adenosylcobalamin-dependent. The precursor form of human MCM is 750 amino acids, while its mature form is 718 amino acids – a 32 amino acid leader sequence is cleaved off by mitochondrial importation and processing machinery.

I. Composition

Polynucleotides Encoding MCM

[0171] In certain aspects, the present disclosure provides nucleic acid molecules, specifically polynucleotides that encode one or more MCM polypeptides. The MCM polypeptides that are

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encoded can be mammalian MCM polypeptides, for example, human MCM peptides, or functional fragments thereof.

[0172] In some embodiments, the polynucleotides described herein encode at least one methylmalonyl-CoA mutase protein, functional fragment, or variant thereof. MCM catalyzes enzymatic transformation of methylmalonyl-CoA into succinyl-CoA, and also comprises a cobalamin-binding domain. MCM's enzymatic activity is dependent on its binding to its cofactor, denosylcobalamin.

[0173] MCM plays a critical role in the catabolism of fat and protein, specifically in disposing of methylmalonyl-CoA created during metabolism. For example, methylmalonyl-CoA is an intermediate in the catabolism of amino acids such as isoleucine, methionine, and threonine. Methylmalonyl-CoA is also an intermediate in the catabolism of cholesterol and fatty acids. Defects in the activity of this enzyme lead to inefficient metabolism and buildup of potentially toxic metabolic intermediates such as methylmalonic acid. The lack of MCM causes the disorder known as methylmalonic acidemia (MMA).

[0174] Replacement of MCM has been theorized to be a cure of this form of MMA. In some embodiments, the polynucleotides disclosed herein comprise one or more sequences encoding a methylmalonyl-CoA mutase protein, functional fragment, or variant thereof that is suitable for use in such gene replacement therapy. In certain aspects, the present application addresses the problem of the lack of methylmalonyl-CoA mutase by providing a polynucleotide, *e.g.*, mRNA, that encodes methylmalonyl-CoA mutase or functional fragment thereof, wherein the polynucleotide is sequence-optimized. In some embodiments, the polynucleotide, *e.g.*, mRNA, increases MCM expression levels in cells when introduced into those cells, *e.g.*, by at least 20%, at least 20%, at least 25%, at least 35%, at least 40%, at least 50%, at least 60%, at least 70%, at least 80%, at least 90%, or at least 100%.

[0175] In some embodiments, the polynucleotides of the disclosure encode functional MCM polypeptides or fragments thereof. In some embodiments, the polynucleotides of the disclosure encode an MCM protein or variant thereof that is full length (*i.e.*, it includes a mitochondrial transit peptide, either native or heterologous to that in native full-length MCM), while in other embodiments polynucleotides of the disclosure encode a functional MCM protein or variant thereof that is mature (*i.e.*, it lacks the mitochondrial transit peptide). In some embodiments, the polynucleotides encode a human MCM, or variant thereof, linked to a heterologous or homologous mitochondrial transit peptide.

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[0176] In some embodiments, the polynucleotides of the disclosure encode functional human MCM (SEQ ID NO: 208, SEQ ID NO: 209, SEQ ID NO: 210, SEQ ID NO: 211, SEQ ID NO: 212, and SEQ ID NO: 213) or fragments thereof. In some embodiments, the polynucleotides of the disclosure encode mutant MCM. In some embodiments, the polynucleotides encode an MCM polypeptide that comprises at least one point mutation in the MCM sequence, while still retaining MCM enzymatic activity. In some embodiments, the polynucleotides encode a functional MCM polypeptide with mutations that do not alter the function of MCM. Such functional MCM can be referred to as function-neutral. In some embodiments, the encoded MCM polypeptide comprises one or more of the function-neutral point mutations V69, T499, H532, A598, and V671. In some embodiments, the polynucleotides of the disclosure encode the polypeptide sequences in SEQ ID NO: 209, SEQ ID NO: 210, SEQ ID NO: 211, SEQ ID NO: 212, and SEQ ID NO: 213, which contain the function-neutral mutants V69, T499, H532, A598, and V671, respectively. In particular embodiments, the encoded MCM polypeptide is a V671 mutant (SEQ ID NO: 213). Polynucleotides encoding MCM polypeptides are listed in SEQ ID NOs: 1 to 207, 214, 732 to 765, and 772.

[0177] In some embodiments, the polynucleotides comprise a nucleotide sequence having significant sequence similarity to a polynucleotide selected from the group of SEQ ID NOs: 1-207, 732-765, and 772, wherein the ORF encodes an MCM polypeptide. In some embodiments, the polynucleotide comprises a nucleotide sequence having significant sequence similarity to SEQ ID NOs: 151, 152, 153, 154, 732, 733, and 734 (**FIGS. 9-15**). In some embodiments, the polynucleotide comprises a nucleotide sequence having significant sequence similarity to SEQ ID NO: 734 (**FIG. 11**).

[0178] In some embodiments, the disclosure is directed to a polynucleotide comprising an ORF having at least 99% or 100% sequence identity to nucleotide 97 to nucleotide 2250 of SEQ ID NO: 734, wherein the ORF encodes an MCM polypeptide.

[0179] In some embodiments, the disclosure is directed to a polynucleotide comprising an ORF having at least 98%, at least 99%, or 100% sequence identity to nucleotide 97 to nucleotide 2250 of SEQ ID NO: 732, wherein the ORF encodes an MCM polypeptide.

[0180] In some embodiments, the disclosure is directed to a polynucleotide comprising an ORF having at least 92%, at least 93%, at least 94%, at least 95%, at least 96%, at least 97%, at least 98%, at least 99%, or 100% sequence identity to a sequence selected from the group

consisting of nucleotides 97 to nucleotides 2250 of SEQ ID NOs: 182, 733, and 741, wherein the ORF encodes an MCM polypeptide.

[0181] In some embodiments, the disclosure is directed to a polynucleotide comprising an ORF having at least 91%, at least 92%, at least 93%, at least 94%, at least 95%, at least 96%, at least 97%, at least 98%, at least 99%, or 100% sequence identity to a sequence selected from the group consisting of nucleotides 97 to nucleotides 2250 of SEQ ID NOs: 735, 736, 738, 743, 744, 748, 749, 750, 754, 755, 758, 762, and 765, wherein the ORF encodes an MCM polypeptide.

[0182] In some embodiments, the disclosure is directed to a polynucleotide comprising an ORF having at least 90%, at least 91%, at least 92%, at least 93%, at least 94%, at least 95%, at least 96%, at least 97%, at least 98%, at least 99%, or 100% sequence identity to a sequence selected from the group consisting of nucleotides 97 to nucleotides 2250 of SEQ ID NOs: 180, 187, 737, 739, 740, 742, 745, 746, 747, 751, 752, 753, 757, 759, 760, 761, 763, and 764, wherein the ORF encodes an MCM polypeptide.

[0183] In some embodiments, the disclosure is directed to a polynucleotide comprising an ORF having at least 89%, at least 90%, at least 91%, at least 92%, at least 93%, at least 94%, at least 95%, at least 96%, at least 97%, at least 98%, at least 99%, or 100% sequence identity to a sequence selected from the group consisting of nucleotides 97 to nucleotides 2250 of SEQ ID NO: 181 and 756, wherein the ORF encodes an MCM polypeptide.

[0184] In some embodiments, the disclosure is directed to a polynucleotide comprising an ORF having at least 88%, at least 89%, at least 90%, at least 91%, at least 92%, at least 93%, at least 94%, at least 95%, at least 96%, at least 97%, at least 98%, at least 99%, or 100% sequence identity to a sequence selected from the group consisting of nucleotides 97 to nucleotides 2250 of SEQ ID NO: 154, 165, 171, 173, and 175, wherein the ORF encodes an MCM polypeptide.

[0185] In some embodiments, the disclosure is directed to a polynucleotide comprising an ORF having at least 87%, at least 88%, at least 89%, at least 90%, at least 91%, at least 92%, at least 93%, at least 94%, at least 95%, at least 96%, at least 97%, at least 98%, at least 99%, or 100% sequence identity to a sequence selected from the group consisting of nucleotides 97 to nucleotides 2250 of SEQ ID NO: 151, 152, 153, 163, 164, 166, 167, 168, 169, 170, 172, 177, 178, 179, 195, and 204, wherein the ORF encodes an MCM polypeptide.

[0186] In some embodiments, the disclosure is directed to a polynucleotide comprising an ORF having at least 86%, at least 87%, at least 88%, at least 89%, at least 90%, at least 91%, at least 92%, at least 93%, at least 94%, at least 95%, at least 96%, at least 97%, at least 98%, at

least 99%, or 100% sequence identity to a sequence selected from the group consisting of nucleotides 97 to nucleotides 2250 of SEQ ID NOs: 156, 157, 158, 159, 160, 161, 162, 174 and 176, wherein the ORF encodes an MCM polypeptide.

[0187] In some embodiments, the disclosure is directed to a polynucleotide comprising an ORF having at least 85%, at least 86%, at least 87%, at least 88%, at least 89%, at least 90%, at least 91%, at least 92%, at least 93%, at least 94%, at least 95%, at least 96%, at least 97%, at least 98%, at least 99%, or 100% sequence identity to a sequence selected from the group consisting of nucleotides 97 to nucleotides 2250 of SEQ ID NOs: 155 and 203, wherein the ORF encodes an MCM polypeptide.

[0188] In some embodiments, the disclosure is directed to a polynucleotide comprising an ORF having at least 82%, at least 83%, at least 84%, at least 85%, at least 86%, at least 87%, at least 88%, at least 89%, at least 90%, at least 91%, at least 92%, at least 93%, at least 94%, at least 95%, at least 96%, at least 97%, at least 98%, at least 99%, or 100% sequence identity to a sequence selected from the group consisting of nucleotides 97 to nucleotides 2250 of SEQ ID NOs: 64, 66, 71, 91, and 128, wherein the ORF encodes an MCM polypeptide.

[0189] In some embodiments, the disclosure is directed to a polynucleotide comprising an ORF having at least 81%, at least 82%, at least 83%, at least 84%, at least 85%, at least 86%, at least 87%, at least 88%, at least 89%, at least 90%, at least 91%, at least 92%, at least 93%, at least 94%, at least 95%, at least 96%, at least 97%, at least 98%, at least 99%, or 100% sequence identity to a sequence selected from the group consisting of nucleotides 97 to nucleotides 2250 of SEQ ID NOs: 9, 11, 18, 19, 21, 22, 23, 24, 32, 33, 37, 39, 40, 44, 45, 47, 50, 51, 52, 55, 57, 61, 65, 70, 79, 84, 86, 88, 90, 92, 98, 100, 115, 117, 126, 129, 135, 136, 137, 144, 148, 150, 184, 190, 191, and 206, wherein the ORF encodes an MCM polypeptide.

[0190] In some embodiments, the disclosure is directed to a polynucleotide comprising an ORF having at least 80%, at least 81%, at least 82%, at least 83%, at least 84%, at least 85%, at least 86%, at least 87%, at least 88%, at least 89%, at least 90%, at least 91%, at least 92%, at least 93%, at least 94%, at least 95%, at least 96%, at least 97%, at least 98%, at least 99%, or 100% sequence identity to a sequence selected from the group consisting of nucleotides 97 to nucleotides 2250 of SEQ ID NOs: 3, 5, 6, 8, 10, 12, 14, 16, 17, 20, 27, 28, 29, 31, 34, 35, 36, 38, 41, 42, 43, 46, 48, 49, 53, 54, 56, 58, 60, 63, 68, 69, 74, 77, 78, 80, 83, 85, 87, 93, 95, 96, 97, 99, 102, 103, 104, 105, 107, 110, 112, 113, 114, 116, 119, 120, 122, 123, 124, 125, 127, 131, 132,

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133, 134, 138, 139, 140, 141, 142, 143, 147, 149, 183, 186, 188, 189, 192, 193, 194, 196, 197, 198, 199, 200, 201, 202, 205, and 207, wherein the ORF encodes an MCM polypeptide.

[0191] In some embodiments, the disclosure is directed to a polynucleotide comprising an ORF having at least 79%, at least 80%, at least 81%, at least 82%, at least 83%, at least 84%, at least 85%, at least 86%, at least 87%, at least 88%, at least 89%, at least 90%, at least 91%, at least 92%, at least 93%, at least 94%, at least 95%, at least 96%, at least 97%, at least 98%, at least 99%, or 100% sequence identity to a sequence selected from the group consisting of nucleotides 97 to nucleotides 2250 of SEQ ID NOs: 1, 2, 4, 7, 13, 15, 25, 26, 30, 59, 62, 67, 72, 73, 75, 76, 81, 82, 89, 94, 101, 106, 108, 109, 111, 118, 121, 130, 145, 146, and 185, wherein the ORF encodes an MCM polypeptide.

[0192] The polynucleotides of the disclosure can also encode additional features that facilitate trafficking of the polypeptides to therapeutically relevant sites. One such feature that aids in protein trafficking is the signal sequence, or targeting sequence. The peptides encoded by these signal sequences are known by a variety of names, including targeting peptides, transit peptides, and signal peptides. The disclosure also includes a polynucleotide comprising a sequence that encodes a mitochondrial transit peptide operably linked to the polynucleotide described herein, *i.e.*, linked to a polynucleotide comprising an ORF encoding an MCM polypeptide.

[0193] As used herein, a "signal sequence" or "signal peptide" is a polynucleotide or polypeptide, respectively, which is from about 9 to 200 nucleotides (3-70 amino acids) in length that, in some embodiments, is incorporated at the 5′ (or N-terminus) of the coding region or polypeptide encoded, respectively. Addition of these sequences result in trafficking of the encoded polypeptide to a desired site, such as the endoplasmic reticulum or the mitochondria through one or more targeting pathways. Some signal peptides are cleaved from the protein, for example by a signal peptidase after the proteins are transported.

[0194] For example, human MCM's precursor protein comprises a 32-amino acid mitochondrial transit peptide, also referred to as an MCM mitochondrial targeting sequence or mitochondrial targeting peptide, that facilitates delivery of the MCM protein to, and localization in, mitochondria. The present disclosure comprises both polynucleotides that encode a homologous targeting sequence (*i.e.*, MCM's native mitochondrial transit sequence) and polynucleotides that encode a heterologous mitochondrial transit sequences (*i.e.*, a mitochondrial transit peptide that is not the native targeting peptide for the operably linked MCM protein). In

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some embodiments, the alternate targeting sequences facilitate delivery of MCM to mitochondria.

[0195] Exemplary sequences of known mitochondrial transit peptides include MLSLRQSIRFFKPATRTLCSSRYLL (SEQ ID NO: 251), MALLRGVFVVAAKRTP (SEQ ID NO: 252) and MLRIPVRKALVGLSKSSKGCVRT (SEQ ID NO: 253). Non-limiting examples of the mitochondrial transit peptides are listed below in **Table 1** (SEQ ID NOs: 251-265). Further examples of mitochondrial transit peptides are provided as SEQ ID NOs: 270-719. Additional mitochondrial transit peptides that can be utilized in the present disclosure can be identified using predictive tools known in the art. For example, mitochondrial targeting can be analyzed using the methods described in Fukusawa *et al.*, Molecular and Cellular Proteomics 14:1113-1126 (2015), the contents of which are incorporated herein in their entirety.

Table 1. Mitochondrial Transit Peptides

ID (SEQ ID NO)	Name of the protein	Sequence
COX4 (SEQ ID NO: 251)	Saccharomyces cerevisiae mitochondrial cytochrome c oxidase subunit IV	MLSLRQSIRFFKPATRTLCSSRYLL
ACAA2 (SEQ ID NO: 252)	Mitochondrial 3-ketoacyl-coa thiolase	MALLRGVFVVAAKRTP
NDUFS1 (SEQ ID NO: 253)	NADH-ubiquinone oxidoreductase 75 kDa subunit, mitochondrial isoform 2	MLRIPVRKALVGLSKSSKGCVRT
A6NK58 (SEQ ID NO: 254)	Putative lipoyltransferase 2, mitochondrial (EC 2.3.1.181) (Lipoate-protein ligase B) (Lipoyl/octanoyl transferase) (Octanoyl-[acyl-carrier-protein]-protein N-octanoyltransferase)	MRQPAVRLVRLGRVPYAELLGLQDRWLRRLQ
A8K5M9 (SEQ ID NO: 255)	Uncharacterized protein C15orf62, mitochondrial	METWRKGSFRN
A8MUP2 (SEQ ID NO: 256)	Methyltransferase-like protein 12, mitochondrial (EC 2.1.1.-)	MAALRRMLHLPSLMMGTCRPFAGSLADS
O00142 (SEQ ID NO: 257)	Thymidine kinase 2, mitochondrial (EC 2.7.1.21) (Mt-TK)	MLLWPLRGWAARALRCFGPGSRGSPASGPGPRR
O00217 (SEQ ID NO: 258)	NADH dehydrogenase [ubiquinone] iron-sulfur protein 8, mitochondrial (EC 1.6.5.3) (EC 1.6.99.3) (Complex I-23kD) (CI-23kD)	MRCLTTPMLLRALAQAARAGPPGGRSLHSSAVAA

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	(NADH-ubiquinone oxidoreductase 23 kDa subunit) (TYKY subunit)	
O00330 (SEQ ID NO: 259)	Pyruvate dehydrogenase protein X component, mitochondrial (Dihydrolipoamide dehydrogenase-binding protein of pyruvate dehydrogenase complex) (E3-binding protein) (E3BP) (Lipoyl-containing pyruvate dehydrogenase complex component X) (proX)	MAASWRLGCDPRLLRYLVGFPGRRSVGL VKGALGWSVSRGANWRWFHSTQWLR
O00411 (SEQ ID NO: 260)	DNA-directed RNA polymerase, mitochondrial (MtRPOL) (EC 2.7.7.6)	MSALCWGRGAAGLKRALRPCGRPGLPGK EGTAGGVCGPRRS
O00746 (SEQ ID NO: 261)	Nucleoside diphosphate kinase, mitochondrial (NDK) (NDP kinase, mitochondrial) (EC 2.7.4.6) (Nucleoside diphosphate kinase D) (NDPKD) (nm23-H4)	MGGLFWRSALRGLRCGPRAPGPSLLVRH GSGGP
O14521 (SEQ ID NO: 262)	Succinate dehydrogenase [ubiquinone] cytochrome b small subunit, mitochondrial (CybS) (CII-4) (QPs3) (Succinate dehydrogenase complex subunit D) (Succinate-ubiquinone oxidoreductase cytochrome b small subunit) (Succinate-ubiquinone reductase membrane anchor subunit)	MAVLWRLSAVCGALGGRALLLRTPVVRP AHISAFLQDRPIPEWCGVQHIHLSPSHH
O14548 (SEQ ID NO: 263)	Cytochrome c oxidase subunit 7A-related protein, mitochondrial (COX7a-related protein) (Cytochrome c oxidase subunit VIIa-related protein) (EB1)	MYYKFSGFTQKLAGAWASEAYSPQGLKP VVSTEAPPIIFATPTKLTSDSTVYDYA
mMCM (SEQ ID NO:264)	Mouse methylmalonyl-CoA mutase	MLRAKNQLFLLSPHYLKQLNIPSASRWK RL
hMCM (SEQ ID NO:265)	Human methylmalonyl-CoA mutase	MLRAKNQLFLLSPHYLRQVKESSGSRLI QQRL

[0196] In some embodiments, the nucleic acid sequence encoding a mitochondrial transit peptide has at least about 70%, at least about 80%, at least about 90%, at least about 95%, at least about 96%, at least about 97%, at least about 98%, at least about 99%, or about 100% sequence identity to a sequence selected from the group of nucleotides 1 to 96 of SEQ ID NOs: 1-207, 732-765, and 772, wherein the transit peptide is capable of targeting or carrying the MCM polypeptide into the mitochondria.

[0197] In some embodiments, the nucleic acid sequence encoding a mitochondrial transit peptide has at least about 70%, at least about 80%, at least about 90%, at least about 95%, at least about 96%, at least about 97%, at least about 98%, at least about 99%, or about 100% sequence identity to a sequence in **Table 1** (SEQ ID NOs: 251, 252, 253, 254, 255, 256, 257,

258, 259, 260, 261, 262, 263, 264, or 265), wherein the transit peptide is capable of targeting or carrying the MCM polypeptide into the mitochondria. In some embodiments, the nucleic acid sequence encoding a mitochondrial transit peptide has at least about 70%, at least about 80%, at least about 90%, at least about 95%, at least about 96%, at least about 97%, at least about 98%, at least about 99%, or about 100% sequence identity to a sequence selected from the group consisting of SEQ ID NOs: 270 to 719, wherein the transit peptide is capable of targeting or carrying the MCM polypeptide into the mitochondria.

[0198] In some embodiments, the disclosure is directed to a polynucleotide comprising an ORF having at least 99% or 100% sequence identity to nucleotide 1 to nucleotide 2250 of SEQ ID NO: 734, wherein the ORF encodes an MCM polypeptide.

[0199] In some embodiments, the disclosure is directed to a polynucleotide comprising an ORF having at least 98%, at least 99%, or 100% sequence identity to nucleotide 1 to nucleotide 2250 of SEQ ID NO: 732, wherein the ORF encodes an MCM polypeptide.

[0200] In some embodiments, the disclosure is directed to a polynucleotide comprising an ORF having at least 92%, at least 93%, at least 94%, at least 95%, at least 96%, at least 97%, at least 98%, at least 99%, or 100% sequence identity to a sequence selected from the group consisting of nucleotides 1 to nucleotides 2250 of SEQ ID NO: 182 and 733, wherein the ORF encodes an MCM polypeptide.

[0201] In some embodiments, the disclosure is directed to a polynucleotide comprising an ORF having at least 91%, at least 92%, at least 93%, at least 94%, at least 95%, at least 96%, at least 97%, at least 98%, at least 99%, or 100% sequence identity to a sequence selected from the group consisting of nucleotides 1 to nucleotides 2250 of SEQ ID NOs: 735, 741, 743, 744, 748, 758, 762, and 765, wherein the ORF encodes an MCM polypeptide.

[0202] In some embodiments, the disclosure is directed to a polynucleotide comprising an ORF having at least 90%, at least 91%, at least 92%, at least 93%, at least 94%, at least 95%, at least 96%, at least 97%, at least 98%, at least 99%, or 100% sequence identity to a sequence selected from the group consisting of nucleotides 1 to nucleotides 2250 of SEQ ID NOs: 180, 181 , 736, 738, 739, 740, 742, 746, 747, 749, 750, 751, 752, 753, 754, 755, 757, 759, 760, 761, and 763, wherein the ORF encodes an MCM polypeptide.

[0203] In some embodiments, the disclosure is directed to a polynucleotide comprising an ORF having at least 89%, at least 90%, at least 91%, at least 92%, at least 93%, at least 94%, at least 95%, at least 96%, at least 97%, at least 98%, at least 99%, or 100% sequence identity to a

sequence selected from the group consisting of nucleotides 1 to nucleotides 2250 of SEQ ID NO: 745, 756, and 764, wherein the ORF encodes an MCM polypeptide.

[0204] In some embodiments, the disclosure is directed to a polynucleotide comprising an ORF having at least 88%, at least 89%, at least 90%, at least 91%, at least 92%, at least 93%, at least 94%, at least 95%, at least 96%, at least 97%, at least 98%, at least 99%, or 100% sequence identity to a sequence selected from the group consisting of nucleotides 1 to nucleotides 2250 of SEQ ID NO: 154, 165, 171, 173, and 175, wherein the ORF encodes an MCM polypeptide.

[0205] In some embodiments, the disclosure is directed to a polynucleotide comprising an ORF having at least 87%, at least 88%, at least 89%, at least 90%, at least 91%, at least 92%, at least 93%, at least 94%, at least 95%, at least 96%, at least 97%, at least 98%, at least 99%, or 100% sequence identity to a sequence selected from the group consisting of nucleotides 1 to nucleotides 2250 of SEQ ID NO: 151, 152, 153, 163, 166, 167, 168, 169, 170, 172, 177, 178, 179, 187, and 204, wherein the ORF encodes an MCM polypeptide.

[0206] In some embodiments, the disclosure is directed to a polynucleotide comprising an ORF having at least 86%, at least 87%, at least 88%, at least 89%, at least 90%, at least 91%, at least 92%, at least 93%, at least 94%, at least 95%, at least 96%, at least 97%, at least 98%, at least 99%, or 100% sequence identity to a sequence selected from the group consisting of nucleotides 1 to nucleotides 2250 of SEQ ID NO: 156, 157, 158, 159, 160, 162, 164, 174, 176, 195, and 737, wherein the ORF encodes an MCM polypeptide.

[0207] In some embodiments, the disclosure is directed to a polynucleotide comprising an ORF having at least 85%, at least 86%, at least 87%, at least 88%, at least 89%, at least 90%, at least 91%, at least 92%, at least 93%, at least 94%, at least 95%, at least 96%, at least 97%, at least 98%, at least 99%, or 100% sequence identity to a sequence selected from the group consisting of nucleotides 1 to nucleotides 2250 of SEQ ID NOs: 155, 161, and 203, wherein the ORF encodes an MCM polypeptide.

[0208] In some embodiments, the disclosure is directed to a polynucleotide comprising an ORF having at least 82%, at least 83%, at least 84%, at least 85%, at least 86%, at least 87%, at least 88%, at least 89%, at least 90%, at least 91%, at least 92%, at least 93%, at least 94%, at least 95%, at least 96%, at least 97%, at least 98%, at least 99%, or 100% sequence identity to a sequence selected from the group consisting of nucleotides 1 to nucleotides 2250 of SEQ ID NOs: 71 and 128, wherein the ORF encodes an MCM polypeptide.

[0209] In some embodiments, the disclosure is directed to a polynucleotide comprising an ORF having at least 81%, at least 82%, at least 83%, at least 84%, at least 85%, at least 86%, at least 87%, at least 88%, at least 89%, at least 90%, at least 91%, at least 92%, at least 93%, at least 94%, at least 95%, at least 96%, at least 97%, at least 98%, at least 99%, or 100% sequence identity to a sequence selected from the group consisting of nucleotides 1 to nucleotides 2250 of SEQ ID NOs: 4, 6, 8, 9, 11, 19, 22, 23, 24, 32, 33, 37, 40, 44, 45, 47, 51, 61, 64, 65, 66, 79, 84, 86, 90, 91, 92, 100, 101, 112, 115, 117, 126, 129, 135, 136, 146, 148, 184, 190, and 191, wherein the ORF encodes an MCM polypeptide.

[0210] In some embodiments, the disclosure is directed to a polynucleotide comprising an ORF having at least 80%, at least 81%, at least 82%, at least 83%, at least 84%, at least 85%, at least 86%, at least 87%, at least 88%, at least 89%, at least 90%, at least 91%, at least 92%, at least 93%, at least 94%, at least 95%, at least 96%, at least 97%, at least 98%, at least 99%, or 100% sequence identity to a sequence selected from the group consisting of nucleotides 1 to nucleotides 2250 of SEQ ID NOs: 2, 3, 5, 7, 10, 12, 13, 14, 15, 16, 18, 20, 21, 26, 27, 28, 29, 31, 34, 36, 38, 39, 41, 42, 43, 46, 48, 49, 52, 53, 54, 55, 56, 57, 58, 59, 60, 62, 68, 69, 70, 72, 73, 74, 76, 77, 80, 83, 85, 88, 95, 96, 97, 98, 102, 104, 105, 106, 107, 108, 109, 110, 113, 114, 120, 121, 122, 123, 124, 127, 131, 132, 133, 134, 137, 138, 139, 140, 141, 142, 144, 145, 147, 149, 150, 186, 188, 189, 192, 193, 194, 196, 198, 199, 200, 202, 205, 206, and 207, wherein the ORF encodes an MCM polypeptide.

[0211] In some embodiments, the disclosure is directed to a polynucleotide comprising an ORF having at least 79%, at least 80%, at least 81%, at least 82%, at least 83%, at least 84%, at least 85%, at least 86%, at least 87%, at least 88%, at least 89%, at least 90%, at least 91%, at least 92%, at least 93%, at least 94%, at least 95%, at least 96%, at least 97%, at least 98%, at least 99%, or 100% sequence identity to a sequence selected from the group consisting of nucleotides 1 to nucleotides 2250 of SEQ ID NOs: 1, 17, 25, 30, 35, 50, 63, 67, 75, 78, 81, 82, 87, 89, 93, 94, 99, 103, 111, 116, 118, 119, 125, 130, 143, 183, 185, 197, and 201, wherein the ORF encodes an MCM polypeptide.

[0212] In some embodiments, the polynucleotide includes from about 1500 to about 100,000 nucleotides (*e.g.,* from about 1500 to 2500, from about 1800 to about 2600, from about 1900 to about 2600, from about 2000 to about 2700, from 2154 to 2,750, from 2154 to 3,000, from 2154 to 5,000, from 2154 to 7,000, from 2154 to 10,000, from 2154 to 25,000, from 2154 to 50,000, from 2154 to 70,000, from 2154 to 100,000, from 2250 to 2750, from 2250 to 3,000, from 2250

to 5,000, from 2250 to 7,000, from 2250 to 10,000, from 2250 to 25,000, from 2250 to 50,000, from 2250 to 70,000, and from 2250 to 100,000 nucleotides).

[0213] In some embodiments, the polynucleotides of the present disclosure can further comprise at least one nucleic acid sequence that is non-coding.

[0214] In some embodiments, the length of a region encoding at least one polypeptide of interest is greater than about 2154 nucleotides in length (*e.g.*, at least or greater than about 2154, 2,250, 2,500, 3,000, 4,000, 4,100, 4,200, 4,300, 4,400, 4,500, 4,600, 4,700, 4,800, 4,900, 5,000, 5,100, 5,200, 5,300, 5,400, 5,500, 5,600, 5,700, 5,800, 5,900, 6,000, 7,000, 8,000, 9,000, 10,000, 20,000, 30,000, 40,000, 50,000, 60,000, 70,000, 80,000, 90,000 or up to and including 100,000 nucleotides). As used herein, such a region can be referred to as a "coding region" or "region encoding."

[0215] In some embodiments, the polynucleotides of the present disclosure are, or function as, a messenger RNA (mRNA). As used herein, the term "messenger RNA" (mRNA) refers to any polynucleotide that encodes at least one polypeptide of interest and that is capable of being translated to produce the encoded polypeptide of interest *in vitro, in vivo, in situ* or *ex vivo*. Exemplary mRNAs that can be used are listed in SEQ ID NOs: 776-771.

Optimized Polynucleotides Encoding MCM

[0216] The polynucleotides of the disclosure, their regions or parts or subregions are sequence-optimized. Sequence optimization methods are known in the art and can be useful to achieve one or more desired results. These results include to match codon frequencies in target and host organisms to ensure proper folding, bias GC content to increase mRNA stability or reduce secondary structures, minimize tandem repeat codons or base runs that can impair gene construction or expression, customize transcriptional and translational control regions, insert or remove protein trafficking sequences, remove/add post translation modification sites in encoded protein (*e.g.*, glycosylation sites), add, remove or shuffle protein domains, insert or delete restriction sites, modify ribosome binding sites and mRNA degradation sites, to adjust translational rates to allow the various domains of the protein to fold properly, or to reduce or eliminate problem secondary structures within the polynucleotide. Sequence optimization tools, algorithms and services are known in the art, non-limiting examples include services from GeneArt (Life Technologies), DNA2.0 (Menlo Park CA) and/or proprietary methods. In some

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embodiments, the ORF sequence is optimized using optimization algorithms. Codon options for each amino acid are given in **Table 2**.

Table 2. Codon Options

Amino Acid	Single Letter Code	Codon Options
Isoleucine	I	ATT, ATC, ATA
Leucine	L	CTT, CTC, CTA, CTG, TTA, TTG
Valine	V	GTT, GTC, GTA, GTG
Phenylalanine	F	TTT, TTC
Methionine	M	ATG
Cysteine	C	TGT, TGC
Alanine	A	GCT, GCC, GCA, GCG
Glycine	G	GGT, GGC, GGA, GGG
Proline	P	CCT, CCC, CCA, CCG
Threonine	T	ACT, ACC, ACA, ACG
Serine	S	TCT, TCC, TCA, TCG, AGT, AGC
Tyrosine	Y	TAT, TAC
Tryptophan	W	TGG
Glutamine	Q	CAA, CAG
Asparagine	N	AAT, AAC
Histidine	H	CAT, CAC
Glutamic acid	E	GAA, GAG
Aspartic acid	D	GAT, GAC
Lysine	K	AAA, AAG
Arginine	R	CGT, CGC, CGA, CGG, AGA, AGG
Selenocysteine	Sec	UGA in mRNA in presence of Selenocysteine insertion element (SECIS)
Stop codons	Stop	TAA, TAG, TGA

[0217] In some embodiments, the percentage of uracil or thymine nucleobases in a sequence-optimized nucleotide sequence (e.g., encoding an MCM polypeptide, a functional fragment, or a variant thereof) is modified (e.g., reduced) with respect to the percentage of uracil or thymine nucleobases in the reference wild-type nucleotide sequence. Such a sequence is referred to as a uracil-modified or thymine-modified sequence. The percentage of uracil or thymine content in a nucleotide sequence can be determined by dividing the number of uracils or thymines in a sequence by the total number of nucleotides and multiplying by 100. In some embodiments, the sequence-optimized nucleotide sequence has a lower uracil or thymine content than the uracil or thymine content in the reference wild-type sequence. In some embodiments, the uracil or thymine content in a sequence-optimized nucleotide sequence of the disclosure is greater than the uracil or thymine content in the reference wild-type sequence and still maintain beneficial

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effects, e.g., increased expression and/or reduced Toll-Like Receptor (TLR) response when compared to the reference wild-type sequence.

[0218] The uracil or thymine content of wild-type MCM is about 26.67%. In some embodiments, the uracil or thymine content of a uracil- or thymine- modified sequence encoding an MCM polypeptide is less than 26.67%. In some embodiments, the uracil or thymine content of a uracil- or thymine-modified sequence encoding an MCM polypeptide of the disclosure is less than 19%, less that 18%, less than 17%, less than 16%, less than 15%, less than 14%, less than 13%, less than 12%, less than 11%, or less than 10%. In some embodiments, the uracil or thymine content is not less than 18%, 17%, 16%, 15%, 14%, 13%, 12%, or 11%. The uracil or thymine content of a sequence disclosed herein, *i.e.*, its total uracil or thymine content, is abbreviated herein as $\%U_{TL}$ or $\%T_{TL}$.

[0219] In some embodiments, the uracil or thymine content ($\%U_{TL}$ or $\%T_{TL}$) of a uracil- or thymine-modified sequence encoding an MCM polypeptide of the disclosure is between 11% and 26%, between 12% and 25%, between 12% and 24%, between 13% and 23%, between 13% and 22%, between 14% and 21%, between 14% and 20%, between 14% and 19%, between 14% and 18%, between 14% and 17%, or between 14% and 16%.

[0220] In some embodiments, the uracil or thymine content ($\%U_{TL}$ or $\%T_{TL}$) of a uracil- or thymine-modified sequence encoding an MCM polypeptide of the disclosure is between 13% and 17%, between 13% and 16%, or between 14% and 16%.

[0221] In a particular embodiment, the uracil or thymine content ($\%U_{TL}$ or $\%T_{TL}$) of a uracil- or thymine modified sequence encoding an MCM polypeptide of the disclosure is between about 14% and about 16%, e.g., between 14% and 15%.

[0222] A uracil- or thymine-modified sequence encoding an MCM polypeptide of the disclosure can also be described according to its uracil or thymine content relative to the uracil or thymine content in the corresponding wild-type nucleic acid sequence ($\%U_{WT}$ or $\%T_{WT}$), or according to its uracil or thymine content relative to the theoretical minimum uracil or thymine content of a nucleic acid encoding the wild-type protein sequence ($\%U_{TM}$ or ($\%T_{TM}$).

[0223] The phrases "uracil or thymine content relative to the uracil or thymine content in the wild type nucleic acid sequence," refers to a parameter determined by dividing the number of uracils or thymines in a sequence-optimized nucleic acid by the total number of uracils or thymines in the corresponding wild-type nucleic acid sequence and multiplying by 100. This parameter is abbreviated herein as $\%U_{WT}$ or $\%T_{WT}$.

[0224] In some embodiments, the $\%U_{WT}$ or $\%T_{WT}$ of a uracil- or thymine-modified sequence encoding an MCM polypeptide of the disclosure is above 50%, above 55%, above 60%, above 65%, above 70%, above 75%, above 80%, above 85%, above 90%, or above 95%.

[0225] In some embodiments, the $\%U_{WT}$ or $\%T_{WT}$ of a uracil- or thymine modified sequence encoding an MCM polypeptide of the disclosure is between 42% and 68%, between 43% and 67%, between 44% and 66%, between 45% and 65%, between 46% and 64%, between 47% and 63%, between 48% and 62%, between 49% and 61%, between 50% and 60%, between 51% and 59%, or between 52% and 58%.

[0226] In some embodiments, the $\%U_{WT}$ or $\%T_{WT}$ of a uracil- or thymine-modified sequence encoding an MCM polypeptide of the disclosure is between 51% and 60%, between 51% and 59%, between 52% and 59%, between 52% and 58%, or between 53% and 58%.

[0227] In a particular embodiment, the $\%U_{WT}$ or $\%T_{WT}$ of a uracil- or thymine-modified sequence encoding an MCM polypeptide of the disclosure is between about 53% and about 58%.

[0228] Uracil- or thymine- content relative to the uracil or thymine theoretical minimum, refers to a parameter determined by dividing the number of uracils or thymines in a sequence-optimized nucleotide sequence by the total number of uracils or thymines in a hypothetical nucleotide sequence in which all the codons in the hypothetical sequence are replaced with synonymous codons having the lowest possible uracil or thymine content and multiplying by 100. This parameter is abbreviated herein as $\%U_{TM}$ or $\%T_{TM}$

[0229] For DNA it is recognized that thymine is present instead of uracil, and one would substitute T where U appears. Thus, all the disclosures related to, e.g., $\%U_{TM}$, $\%U_{WT}$, or $\%U_{TL}$, with respect to RNA are equally applicable to $\%T_{TM}$, $\%T_{WT}$, or $\%T_{TL}$ with respect to DNA.

[0230] In some embodiments, the $\%U_{TM}$ of a uracil-modified sequence encoding an MCM polypeptide of the disclosure is below 300%, below 295%, below 290%, below 285%, below 280%, below 275%, below 270%, below 265%, below 260%, below 255%, below 250%, below 245%, below 240%, below 235%, below 230%, below 225%, below 220%, below 215%, below 200%, below 195%, below 190%, below 185%, below 180%, below 175%, below 170%, below 165%, below 160%, below 155%, below 150%, below 145%, below 140%, below 139%, below 138%, below 137%, below 136%, below 135%, below 134%, below 133%, below 132%, below 131%, below 130%, below 129%, below 128%, below 127%, below 126%, below 125%, below 124%, below 123%, below 122%, below 121%, below 120%, below 119%, below 118%, or below 117%.

[0231] In some embodiments, the $\%U_{TM}$ of a uracil-modified sequence encoding an MCM polypeptide of the disclosure is above 100%, above 101%, above 102%, above 103%, above 104%, above 105%, above 106%, above 107%, above 108%, above 109%, above 110%, above 111%, above 112%, above 113%, above 114%, above 115%, above 116%, above 117%, above 118%, above 119%, above 120%, above 121%, above 122%, above 123%, above 124%, above 125%, or above 126%, above 127%, above 128%, or above 129%.

[0232] In some embodiments, the $\%U_{TM}$ of a uracil-modified sequence encoding an MCM polypeptide of the disclosure is between 123% and 125%, between 122% and 126%, between 121% and 127%, between 120% and 128%, between 119% and 129%, between 118% and 130%, between 117% and 131%, between 116% and 132%, between 115% and 133%, between 114% and 134%, between 113% and 135%, between 112% and 136%, or between 111% and 137%.

[0233] In some embodiments, the $\%U_{TM}$ of a uracil-modified sequence encoding an MCM polypeptide of the disclosure is between about 118% and about 129%.

[0234] In some embodiments, a uracil-modified sequence encoding an MCM polypeptide of the disclosure has a reduced number of consecutive uracils with respect to the corresponding wild-type nucleic acid sequence. For example, two consecutive leucines can be encoded by the sequence CUUUUG, which includes a four uracil cluster. Such a subsequence can be substituted, e.g., with CUGCUC, which removes the uracil cluster.

[0235] Phenylalanine can be encoded by UUC or UUU. Thus, even if phenylalanines encoded by UUU are replaced by UUC, the synonymous codon still contains a uracil pair (UU). Accordingly, the number of phenylalanines in a sequence establishes a minimum number of uracil pairs (UU) that cannot be eliminated without altering the number of phenylalanines in the encoded polypeptide. For example, if the polypeptide, e.g., wild type MCM, has 27, 28, 29, or 30 phenylalanines, the absolute minimum number of uracil pairs (UU) in that uracil-modified sequence encoding the polypeptide, e.g., wild type MCM, can contain is 27, 28, 29, or 30, respectively.

[0236] Wild type MCM contains 82 uracil pairs (UU), and 29 uracil triplets (UUU). In some embodiments, a uracil-modified sequence encoding an MCM polypeptide of the disclosure has a reduced number of uracil triplets (UUU) with respect to the wild-type nucleic acid sequence. In some embodiments, a uracil-modified sequence encoding an MCM polypeptide of the disclosure contains 28, 27, 26, 25, 24, 23, 22, 21, 20, 19, 18 ,17, 16, 15, 14, 13,12, 11, 10, 9, 8, 7, 6, 5, 4, 3, 2, 1 or no uracil triplets (UUU).

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[0237] In some embodiments, a uracil-modified sequence encoding an MCM polypeptide has a reduced number of uracil pairs (UU) with respect to the number of uracil pairs (UU) in the wild-type nucleic acid sequence. In some embodiments, a uracil-modified sequence encoding an MCM polypeptide of the disclosure has a number of uracil pairs (UU) corresponding to the minimum possible number of uracil pairs (UU) in the wild-type nucleic acid sequence, e.g., 28 uracil pairs in the case of wild type MCM.

[0238] In some embodiments, a uracil-modified sequence encoding an MCM polypeptide of the disclosure has at least 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 26, 27, 28, 29, 30, 31, 32, 33, 34, 35, 36, 37, 38, 39, 40, 41, 42, 43, 44, 45, 46, 47, 48, 49, 50, 51, 52, 53, or 54 uracil pairs (UU) less than the number of uracil pairs (UU) in the wild-type nucleic acid sequence. In some embodiments, a uracil-modified sequence encoding an MCM polypeptide of the disclosure has between 20 and 35 uracil pairs (UU).

[0239] The phrase "uracil pairs (UU) relative to the uracil pairs (UU) in the wild type nucleic acid sequence," refers to a parameter determined by dividing the number of uracil pairs (UU) in a sequence-optimized nucleotide sequence by the total number of uracil pairs (UU) in the corresponding wild-type nucleotide sequence and multiplying by 100. This parameter is abbreviated herein as $\%UU_{wt}$.

[0240] In some embodiments, a uracil-modified sequence encoding an MCM polypeptide of the disclosure has a $\%UU_{wt}$ less than 90%, less than 85%, less than 80%, less than 75%, less than 70%, less than 65%, less than 60%, less than 65%, less than 60%, less than 55%, less than 50%, less than 40%, less than 30%, or less than 20%.

[0241] In some embodiments, a uracil-modified sequence encoding an MCM polypeptide has a $\%UU_{wt}$ between 20% and 50%. In a particular embodiment, a uracil-modified sequence encoding an MCM polypeptide of the disclosure has a $\%UU_{wt}$ between 24% and 43% .

[0242] In some embodiments, the polynucleotide of the disclosure comprises a uracil-modified sequence encoding an MCM polypeptide disclosed herein. In some embodiments, the uracil-modified sequence encoding an MCM polypeptide comprises at least one chemically modified nucleobase, e.g., 5-methoxyuracil. In some embodiments, at least 95% of a nucleobase (e.g., uracil) in a uracil-modified sequence encoding an MCM polypeptide of the disclosure are modified nucleobases. In some embodiments, at least 95% of uracil in a uracil-modified sequence encoding an MCM polypeptide is 5-methoxyuracil.

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[0243] In some embodiments, the "guanine content of the sequence optimized ORF encoding MCM with respect to the theoretical maximum guanine content of a nucleotide sequence encoding the MCM polypeptide," abbreviated as $\%G_{TMX}$ is at least 69%, at least 70%, at least 75%, at least about 80%, at least about 85%, at least about 90%, at least about 95%, or about 100%. In some embodiments, the $\%G_{TMX}$ is between about 70% and about 80%, between about 71% and about 79%, between about 71% and about 78%, between about 71% and about 77% or between about 71% and about 76%.

[0244] In some embodiments, the "cytosine content of the ORF relative to the theoretical maximum cytosine content of a nucleotide sequence encoding the MCM polypeptide," abbreviated as $\%C_{TMX}$, is at least about 68%, at least about 70%, at least about 75%, at least about 80%, at least about 85%, at least about 90%, at least about 95%, or about 100%. In some embodiments, the $\%C_{TMX}$ is between about 68% and about 77%, between about 69% and about 76%, or between about 70% and about 75%.

[0245] In some embodiments, the "guanine and cytosine content (G/C) of the ORF relative to the theoretical maximum G/C content in a nucleotide sequence encoding the MCM polypeptide," abbreviated as $\%G/C_{TMX}$ is at least about 85%, at least about 90%, at least about 95%, or about 100%. The $\%G/C_{TMX}$ is between about 85% and about 100%, between about 89% and about 96%, between about 90% and about 95%, or between about 91% and about 94%.

[0246] In some embodiments, the "G/C content in the ORF relative to the G/C content in the corresponding wild-type ORF," abbreviated as $\%G/C_{WT}$ is at least 120%, at least 130%, at least 140%, at least 141%, at least 142%, at least 143%, at least 144%, at least 145%, at least 146%, at least 147%, at least 150%,or at least 155%.

[0247] In some embodiments, the average G/C content in the 3rd codon position in the ORF is at least 50%, at least 51%, at least 52%, at least 53%, at least 54%, at least 55%, at least 56%, at least 57%, at least 58%, at least 59%, or at least 60% higher than the average G/C content in the 3rd codon position in the corresponding wild-type ORF.

[0248] In some embodiments, the polynucleotide of the disclosure comprises an open reading frame (ORF) encoding an MCM polypeptide, wherein the ORF has been sequence optimized, and wherein each of $\%U_{TL}$, $\%U_{WT}$, $\%U_{TM}$, $\%G_{TL}$, $\%G_{WT}$, $\%G_{TMX}$, $\%C_{TL}$, $\%C_{WT}$, $\%C_{TMX}$, $\%G/C_{TL}$, $\%G/C_{WT}$, or $\%G/C_{TMX}$, alone or in a combination thereof is in a range between (i) a maximum corresponding to the parameter's maximum value (MAX) plus about 0.5, 1, 1.5, 2, 2.5, 3, 3.5, 4, 4.5, 5, 5.5, 6, 6.5, 7, 7.5, 8, 8.5, 9, 9.5, or 10 standard deviations (STD DEV),

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and (ii) a minimum corresponding to the parameter's minimum value (MIN) less 0.5, 1, 1.5, 2, 2.5, 3, 3.5, 4, 4.5, 5, 5.5, 6, 6.5, 7, 7.5, 8, 8.5, 9, 9.5, or 10 standard deviations (STD DEV).

[0249] Features, which can be considered beneficial in some embodiments of the present disclosure, can be encoded by regions of the polynucleotide and such regions can be upstream (5') or downstream (3') to, or within, a region that encodes a polypeptide. These regions can be incorporated into the polynucleotide before and/or after sequence optimization of the protein encoding region or open reading frame (ORF). It is not required that a polynucleotide contain both a 5′ and 3′ flanking region. Examples of such features include, but are not limited to, untranslated regions (UTRs), Kozak sequences, an oligo(dT) sequence, and detectable tags and can include multiple cloning sites that can have XbaI recognition.

[0250] In some embodiments, a 5′ UTR and/or a 3′ UTR region can be provided as flanking regions. Multiple 5′ or 3′ UTRs can be included in the flanking regions and can be the same or of different sequences. Any portion of the flanking regions, including none, can be sequence-optimized and any can independently contain one or more different structural or chemical modifications, before and/or after sequence optimization.

[0251] In some embodiments, the polynucleotide of the disclosure comprises, consists essentially or, or consists of the sequence set forth as SEQ ID NO: 769, wherein thymidine is changed to uridine. In other embodiments, the polynucleotide of the disclosure comprises, consists essentially or, or consists of the sequence set forth as SEQ ID NO: 770, wherein thymidine is changed to uridine. In other embodiments, the polynucleotide does not comprise a polyC.

[0252] After optimization (if desired), the polynucleotides components are reconstituted and transformed into a vector such as, but not limited to, plasmids, viruses, cosmids, and artificial chromosomes. For example, the optimized polynucleotide can be reconstituted and transformed into chemically competent *E. coli,* yeast, neurospora, maize, drosophila, etc. where high copy plasmid-like or chromosome structures occur by methods described herein.

[0253] Synthetic polynucleotides and their nucleic acid analogs play an important role in the research and studies of biochemical processes. Various enzyme-assisted and chemical-based methods have been developed to synthesize polynucleotides and nucleic acids.

[0254] Enzymatic methods include *in vitro* transcription that uses RNA polymerases to synthesize the polynucleotides of the present disclosure. Enzymatic methods and RNA

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polymerases for transcription are described in International Patent Application No. PCT/US2014/53907, the contents of which are herein incorporated by reference in its entirety.

[0255] Solid-phase chemical synthesis can be used to manufacture the polynucleotides described herein or portions thereof. Solid-phase chemical synthesis manufacturing of the polynucleotides described herein are described in International Patent Application No. PCT/US2014/53907, the contents of which are herein incorporated by reference in its entirety.

[0256] Liquid phase chemical synthesis can be used to manufacture the polynucleotides described herein or portions thereof. Liquid phase chemical synthesis manufacturing of the polynucleotides described herein are described in International Patent Application No. PCT/US2014/53907, the contents of which are herein incorporated by reference in its entirety.

[0257] Combinations of different synthetic methods can be used to manufacture the polynucleotides described herein or portions thereof. These combinations are described in International Patent Application No. PCT/US2014/53907, the contents of which are herein incorporated by reference in its entirety.

[0258] Small region synthesis can be used for regions or subregions of the polynucleotides of the present disclosure. These synthesis methods are described in International Patent Application No. PCT/US2014/53907, the contents of which are herein incorporated by reference in its entirety.

[0259] Ligation of polynucleotide regions or subregions can be used to prepare the polynucleotides described herein. These ligation methods are described in International Patent Application No. PCT/US2014/53907, the contents of which are herein incorporated by reference in its entirety.

Polypeptides Encoded by the Polynucleotides of the Disclosure

[0260] In some embodiments, the MCM polypeptides encoded by polynucleotides of the disclosure peptide are functional MCM. As used herein, the term "MCM" protein is used interchangeably with "MUT" protein. Therefore, human MCM protein can be written as human MUT or hMUT, and murine MCM protein can be written as murine MUT or mMUT. In some embodiments, the MCM polypeptides encoded by polynucleotides of the disclosure peptide are variants, peptides or polypeptides containing substitutions, insertions and/or additions, deletions and covalent modifications with respect to an MCM peptide sequence. For example, sequence tags or amino acids, such as one or more lysines, can be added to the peptide sequences encoded

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by the polynucleotides of the disclosure (*e.g.,* at the N-terminal or C-terminal ends). Sequence tags can be used for peptide purification or localization. Lysines can be used to increase peptide solubility or to allow for biotinylation. In some embodiments, amino acid residues located at the carboxy and amino terminal regions of a polypeptide encoded by the polynucleotides of the disclosure can optionally be deleted providing for truncated sequences.

[0261] In some embodiments, the polynucleotides described herein encode a substitutional variant of an MCM protein. The substitutional variant can comprise one, two, three or more than three substitutions. "Substitutional variants" when referring to polypeptides are those that have at least one amino acid residue in a native or starting sequence removed and a different amino acid inserted in its place at the same position. The substitutions can be single, where only one amino acid in the molecule has been substituted, or they can be multiple, where two or more amino acids have been substituted in the same molecule.

[0262] In some embodiments, the polynucleotides described herein encode a variant of an MCM protein with one or more conservative amino acids substitutions. As used herein the term "conservative amino acid substitution" refers to the substitution of an amino acid that is normally present in the sequence with a different amino acid of similar size, charge, or polarity. Examples of conservative substitutions include the substitution of a non-polar (hydrophobic) residue such as isoleucine, valine and leucine for another non-polar residue. Likewise, examples of conservative substitutions include the substitution of one polar (hydrophilic) residue for another such as between arginine and lysine, between glutamine and asparagine, and between glycine and serine. Additionally, the substitution of a basic residue such as lysine, arginine or histidine for another, or the substitution of one acidic residue such as aspartic acid or glutamic acid for another acidic residue are additional examples of conservative substitutions. Examples of non-conservative substitutions include the substitution of a non-polar (hydrophobic) amino acid residue such as isoleucine, valine, leucine, alanine, methionine for a polar (hydrophilic) residue such as cysteine, glutamine, glutamic acid or lysine and/or a polar residue for a non-polar residue.

[0263] In other embodiments, the polynucleotides encode an insertional MCM variant. "Insertional variants" when referring to polypeptides are those with one or more amino acids inserted immediately adjacent to an amino acid at a particular position in a native or starting sequence. "Immediately adjacent" to an amino acid means connected to either the alpha-carboxy or alpha-amino functional group of the amino acid.

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[0264] In other embodiments, the polynucleotides of the disclosure encode a deletional MCM variant. "Deletional variants" when referring to polypeptides are those with one or more amino acids in the native or starting amino acid sequence removed. Ordinarily, deletional variants will have one or more amino acids deleted in a particular region of the molecule.

[0265] In some embodiments, the polynucleotides of the disclosure encode a covalent derivative. "Covalent derivatives" when referring to polypeptides include modifications of a native or starting protein with an organic proteinaceous or non-proteinaceous derivatizing agent, and/or post-translational modifications. Covalent modifications are traditionally introduced by reacting targeted amino acid residues of the protein with an organic derivatizing agent that is capable of reacting with selected side-chains or terminal residues, or by harnessing mechanisms of post-translational modifications that function in selected recombinant host cells. The resultant covalent derivatives are useful in programs directed at identifying residues important for biological activity, for immunoassays, or for the preparation of anti-protein antibodies for immunoaffinity purification of the recombinant glycoprotein. Such modifications are within the ordinary skill in the art and are performed without undue experimentation.

[0266] Certain post-translational modifications are the result of the action of recombinant host cells on the expressed polypeptide. Glutaminyl and asparaginyl residues are frequently post-translationally deamidated to the corresponding glutamyl and aspartyl residues. Alternatively, these residues are deamidated under mildly acidic conditions. Either form of these residues can be present in the polypeptides produced in accordance with the present disclosure.

[0267] Other post-translational modifications include hydroxylation of proline and lysine, phosphorylation of hydroxyl groups of seryl or threonyl residues, methylation of the alpha-amino groups of lysine, arginine, and histidine side chains (T. E. Creighton, Proteins: Structure and Molecular Properties, W.H. Freeman & Co., San Francisco, pp. 79-86 (1983)).

[0268] "Features," when referring to polypeptides, are defined as distinct amino acid sequence-based components of a molecule. Features of the polypeptides encoded by the polynucleotides of the present disclosure include surface manifestations, local conformational shape, folds, loops, half-loops, domains, half-domains, sites, termini or any combination thereof.

[0269] As used herein, when referring to polypeptides, the term "domain" refers to a motif of a polypeptide having one or more identifiable structural or functional characteristics or properties (*e.g.,* binding capacity, serving as a site for protein-protein interactions).

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[0270] As used herein, when referring to polypeptides, the terms "site" as it pertains to amino acid based embodiments is used synonymously with "amino acid residue" and "amino acid side chain." A site represents a position within a peptide or polypeptide that can be modified, manipulated, altered, derivatized or varied within the polypeptide based molecules of the present disclosure.

[0271] As used herein the terms "termini" or "terminus," when referring to polypeptides, refers to an extremity of a peptide or polypeptide. Such extremity is not limited only to the first or final site of the peptide or polypeptide but can include additional amino acids in the terminal regions. The polypeptide based molecules of the present disclosure can be characterized as having both an N-terminus (terminated by an amino acid with a free amino group (NH2)) and a C-terminus (terminated by an amino acid with a free carboxyl group (COOH)). Proteins of the disclosure are in some cases made up of multiple polypeptide chains brought together by disulfide bonds or by non-covalent forces (multimers, oligomers). These sorts of proteins will have multiple N- and C-termini. Alternatively, the termini of the polypeptides can be modified such that they begin or end, as the case can be, with a non-polypeptide based moiety such as an organic conjugate.

[0272] Once any of the features have been identified or defined as a desired component of a polypeptide to be encoded by the polynucleotide of the disclosure, any of several manipulations and/or modifications of these features can be performed by moving, swapping, inverting, deleting, randomizing or duplicating. Furthermore, it is understood that manipulation of features can result in the same outcome as a modification to the molecules of the disclosure. For example, a manipulation that involved deleting a domain would result in the alteration of the length of a molecule just as modification of a nucleic acid to encode less than a full length molecule would.

[0273] Modifications and manipulations can be accomplished by methods known in the art such as, but not limited to, site directed mutagenesis or *a priori* incorporation during chemical synthesis. The resulting modified molecules can then be tested for activity using *in vitro* or *in vivo* assays such as those described herein or any other suitable screening assay known in the art.

[0274] According to the present disclosure, the polypeptides can comprise a consensus sequence that is discovered through rounds of experimentation. As used herein a "consensus" sequence is a single sequence that represents a collective population of sequences allowing for variability at one or more sites.

[0275] As recognized by those skilled in the art, protein fragments, functional protein domains, and homologous proteins are also considered to be within the scope of polypeptides of interest of this disclosure. For example, provided herein is any protein fragment (meaning a polypeptide sequence at least one amino acid residue shorter than a reference polypeptide sequence but otherwise identical) of a reference protein 10, 20, 30, 40, 50, 60, 70, 80, 90, 100 or greater than 100 amino acids in length. In another example, any protein that includes a stretch of about 20, about 30, about 40, about 50, or about 100 amino acids that are about 40%, about 50%, about 60%, about 70%, about 80%, about 90%, about 95%, or about 100% identical to any of the sequences described herein can be utilized in accordance with the disclosure.

[0276] In certain embodiments, a polypeptide encoded by the polynucleotide of the disclosure includes 2, 3, 4, 5, 6, 7, 8, 9, 10, or more mutations as shown in any of the sequences provided or referenced herein.

[0277] In some embodiments, the encoded polypeptide variant has the same or a similar activity as the reference polypeptide. Alternatively, the variant has an altered activity (*e.g.,* increased or decreased) relative to a reference polypeptide. Generally, variants of a particular polynucleotide or polypeptide of the disclosure will have at least about 40%, 45%, 50%, 55%, 60%, 65%, 70%, 75%, 80%, 85%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99% but less than 100% sequence identity to that particular reference polynucleotide or polypeptide as determined by sequence alignment programs and parameters described herein and known to those skilled in the art. Such tools for alignment include those of the BLAST suite (Stephen F. Altschul, Thomas L. Madden, Alejandro A. Schäffer, Jinghui Zhang, Zheng Zhang, Webb Miller, and David J. Lipman (1997), "Gapped BLAST and PSI-BLAST: a new generation of protein database search programs," Nucleic Acids Res. 25:3389-3402.) Other tools are described herein, specifically in the definition of "Identity."

[0278] Default parameters in the BLAST algorithm include, for example, an expect threshold of 10, Word size of 28, Match/Mismatch Scores 1, -2, Gap costs Linear. Any filter can be applied as well as a selection for species specific repeats, *e.g.,* Homo sapiens.

[0279] According to the present disclosure, the protein is encoded by a polynucleotide that can comprise at least a first region of linked nucleosides encoding at least one polypeptide of interest. Some polypeptides encoded by the polynucleotides of interest of the present disclosure are listed in **Table 3** below. In particular, **Table 3** shows human MCM wild type and mutant amino acid sequences.

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Table 3. MCM Polypeptides and Polynucleotides

SEQ ID No	Gene	Sequence
SEQ ID NO: 208	Functional Human MCM	MLRAKNQLFLLSPHYLRQVKESSGSRLIQQRLLHQQQPLHPEWAALAKKQLKGKNPED LIWHTPEGISIKPLYSKRDTMDLPEELPGVKPFTRGPYPTMYTFRPWTIRQYAGFSTV EESNKFYKDNIKAGQQGLSVAFDLATHRGYDSDNPRVRGDVGMAGVAIDTVEDTKILF DGIPLEKMSVSMTMNGAVIPVLANFIVTGEEQGVPKEKLTGTIQNDILKEFMVRNTYI FPPEPSMKIIADIFEYTAKHMPKFNSISISGYHMQEAGADAILELAYTLADGLEYSRT GLQAGLTIDEFAPRLSFFWGIGMNFYMEIAKMRAGRRLWAHLIEKMFQPKNSKSLLLR AHCQTSGWSLTEQDPYNNIVRTAIEAMAAVFGGTQSLHTNSFDEALGLPTVKSARIAR NTQIIIQEESGIPKVADPWGGSYMMECLTNDVYDAALKLINEIEEMGGMAKAVAEGIP KLRIEECAARRQARIDSGSEVIVGVNKYQLEKEDAVEVLAIDNTSVRNRQIEKLKKIK SSRDQALAERCLAALTECAASGDGNILALAVDASRARCTVGEITDALKKVFGEHKAND RMVSGAYRQEFGESKEITSAIKRVHKFMEREGRRPRLLVAKMGQDGHDRGAKVIATGF ADLGFDVDIGPLFQTPREVAQQAVDADVHAVGISTLAAGHKTLVPELIKELNSLGRPD ILVMCGGVIPPQDYEFLFEVGVSNVFGPGTRIPKAAVQVLDDIEKCLEKKQQSV
a.a. 33 to 750 of SEQ ID NO: 208	Mature human MCM	LHQQQPLHPEWAALAKKQLKGKNPEDLIWHTPEGISIKPLYSKRDTMDLPEELPGVKP FTRGPYPTMYTFRPWTIRQYAGFSTVEESNKFYKDNIKAGQQGLSVAFDLATHRGYDS DNPRVRGDVGMAGVAIDTVEDTKILFDGIPLEKMSVSMTMNGAVIPVLANFIVTGEEQ GVPKEKLTGTIQNDILKEFMVRNTYIFPPEPSMKIIADIFEYTAKHMPKFNSISISGY HMQEAGADAILELAYTLADGLEYSRTGLQAGLTIDEFAPRLSFFWGIGMNFYMEIAKM RAGRRLWAHLIEKMFQPKNSKSLLLRAHCQTSGWSLTEQDPYNNIVRTAIEAMAAVFG GTQSLHTNSFDEALGLPTVKSARIARNTQIIIQEESGIPKVADPWGGSYMMECLTNDV YDAALKLINEIEEMGGMAKAVAEGIPKLRIEECAARRQARIDSGSEVIVGVNKYQLEK EDAVEVLAIDNTSVRNRQIEKLKKIKSSRDQALAERCLAALTECAASGDGNILALAVD ASRARCTVGEITDALKKVFGEHKANDRMVSGAYRQEFGESKEITSAIKRVHKFMEREG RRPRLLVAKMGQDGHDRGAKVIATGFADLGFDVDIGPLFQTPREVAQQAVDADVHAVG VSTLAAGHKTLVPELIKELNSLGRPDILVMCGGVIPPQDYEFLFEVGVSNVFGPGTRI PKAAVQVLDDIEKCLEKKQQSV
SEQ ID NO: 209	Functional Human MCM I69V	MLRAKNQLFLLSPHYLRQVKESSGSRLIQQRLLHQQQPLHPEWAALAKKQLKGKNPED LIWHTPEGISVKPLYSKRDTMDLPEELPGVKPFTRGPYPTMYTFRPWTIRQYAGFSTV EESNKFYKDNIKAGQQGLSVAFDLATHRGYDSDNPRVRGDVGMAGVAIDTVEDTKILF DGIPLEKMSVSMTMNGAVIPVLANFIVTGEEQGVPKEKLTGTIQNDILKEFMVRNTYI FPPEPSMKIIADIFEYTAKHMPKFNSISISGYHMQEAGADAILELAYTLADGLEYSRT GLQAGLTIDEFAPRLSFFWGIGMNFYMEIAKMRAGRRLWAHLIEKMFQPKNSKSLLLR AHCQTSGWSLTEQDPYNNIVRTAIEAMAAVFGGTQSLHTNSFDEALGLPTVKSARIAR NTQIIIQEESGIPKVADPWGGSYMMECLTNDVYDAALKLINEIEEMGGMAKAVAEGIP KLRIEECAARRQARIDSGSEVIVGVNKYQLEKEDAVEVLAIDNTSVRNRQIEKLKKIK SSRDQALAERCLAALTECAASGDGNILALAVDASRARCTVGEITDALKKVFGEHKAND RMVSGAYRQEFGESKEITSAIKRVHKFMEREGRRPRLLVAKMGQDGHDRGAKVIATGF ADLGFDVDIGPLFQTPREVAQQAVDADVHAVGISTLAAGHKTLVPELIKELNSLGRPD ILVMCGGVIPPQDYEFLFEVGVSNVFGPGTRIPKAAVQVLDDIEKCLEKKQQSV
SEQ ID NO: 210	Functional Human MCM A499T	MLRAKNQLFLLSPHYLRQVKESSGSRLIQQRLLHQQQPLHPEWAALAKKQLKGKNPED LIWHTPEGISIKPLYSKRDTMDLPEELPGVKPFTRGPYPTMYTFRPWTIRQYAGFSTV EESNKFYKDNIKAGQQGLSVAFDLATHRGYDSDNPRVRGDVGMAGVAIDTVEDTKILF DGIPLEKMSVSMTMNGAVIPVLANFIVTGEEQGVPKEKLTGTIQNDILKEFMVRNTYI FPPEPSMKIIADIFEYTAKHMPKFNSISISGYHMQEAGADAILELAYTLADGLEYSRT GLQAGLTIDEFAPRLSFFWGIGMNFYMEIAKMRAGRRLWAHLIEKMFQPKNSKSLLLR AHCQTSGWSLTEQDPYNNIVRTAIEAMAAVFGGTQSLHTNSFDEALGLPTVKSARIAR NTQIIIQEESGIPKVADPWGGSYMMECLTNDVYDAALKLINEIEEMGGMAKAVAEGIP KLRIEECAARRQARIDSGSEVIVGVNKYQLEKEDTVEVLAIDNTSVRNRQIEKLKKIK SSRDQALAERCLAALTECAASGDGNILALAVDASRARCTVGEITDALKKVFGEHKAND RMVSGAYRQEFGESKEITSAIKRVHKFMEREGRRPRLLVAKMGQDGHDRGAKVIATGF ADLGFDVDIGPLFQTPREVAQQAVDADVHAVGISTLAAGHKTLVPELIKELNSLGRPD ILVMCGGVIPPQDYEFLFEVGVSNVFGPGTRIPKAAVQVLDDIEKCLEKKQQSV
SEQ ID	Function	MLRAKNQLFLLSPHYLRQVKESSGSRLIQQRLLHQQQPLHPEWAALAKKQLKGKNPED

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NO: 211	al Human MCM R532H	LIWHTPEGISIKPLYSKRDTMDLPEELPGVKPFTRGPYPTMYTFRPWTIRQYAGFSTV EESNKFYKDNIKAGQQGLSVAFDLATHRGYDSDNPRVRGDVGMAGVAIDTVEDTKILF DGIPLEKMSVSMTMNGAVIPVLANFIVTGEEQGVPKEKLTGTIQNDILKEFMVRNTYI FPPEPSMKIIADIFEYTAKHMPKFNSISISGYHMQEAGADAILELAYTLADGLEYSRT GLQAGLTIDEFAPRLSFFWGIGMNFYMEIAKMRAGRRLWAHLIEKMFQPKNSKSLLLR AHCQTSGWSLTEQDPYNNIVRTAIEAMAAVFGGTQSLHTNSFDEALGLPTVKSARIAR NTQIIIQEESGIPKVADPWGGSYMMECLTNDVYDAALKLINEIEEMGGMAKAVAEGIP KLRIEECAARRQARIDSGSEVIVGVNKYQLEKEDAVEVLAIDNTSVRNRQIEKLKKIK SSRDQALAEHCLAALTECAASGDGNILALAVDASRARCTVGEITDALKKVFGEHKAND RMVSGAYRQEFGESKEITSAIKRVHKFMEREGRRPRLLVAKMGQDGHDRGAKVIATGF ADLGFDVDIGPLFQTPREVAQQAVDADVHAVGISTLAAGHKTLVPELIKELNSLGRPD ILVMCGGVIPPQDYEFLFEVGVSNVFGPGTRIPKAAVQVLDDIEKCLEKKQQSV
SEQ ID NO: 212	Functional Human MCM T598A	MLRAKNQLFLLSPHYLRQVKESSGSRLIQQRLLHQQQPLHPEWAALAKKQLKGKNPED LIWHTPEGISIKPLYSKRDTMDLPEELPGVKPFTRGPYPTMYTFRPWTIRQYAGFSTV EESNKFYKDNIKAGQQGLSVAFDLATHRGYDSDNPRVRGDVGMAGVAIDTVEDTKILF DGIPLEKMSVSMTMNGAVIPVLANFIVTGEEQGVPKEKLTGTIQNDILKEFMVRNTYI FPPEPSMKIIADIFEYTAKHMPKFNSISISGYHMQEAGADAILELAYTLADGLEYSRT GLQAGLTIDEFAPRLSFFWGIGMNFYMEIAKMRAGRRLWAHLIEKMFQPKNSKSLLLR AHCQTSGWSLTEQDPYNNIVRTAIEAMAAVFGGTQSLHTNSFDEALGLPTVKSARIAR NTQIIIQEESGIPKVADPWGGSYMMECLTNDVYDAALKLINEIEEMGGMAKAVAEGIP KLRIEECAARRQARIDSGSEVIVGVNKYQLEKEDAVEVLAIDNTSVRNRQIEKLKKIK SSRDQALAERCLAALTECAASGDGNILALAVDASRARCTVGEITDALKKVFGEHKAND RMVSGAYRQEFGESKEIASAIKRVHKFMEREGRRPRLLVAKMGQDGHDRGAKVIATGF ADLGFDVDIGPLFQTPREVAQQAVDADVHAVGISTLAAGHKTLVPELIKELNSLGRPD ILVMCGGVIPPQDYEFLFEVGVSNVFGPGTRIPKAAVQVLDDIEKCLEKKQQSV
SEQ ID NO: 213	Functional Human MCM I671V	MLRAKNQLFLLSPHYLRQVKESSGSRLIQQRLLHQQQPLHPEWAALAKKQLKGKNPED LIWHTPEGISIKPLYSKRDTMDLPEELPGVKPFTRGPYPTMYTFRPWTIRQYAGFSTV EESNKFYKDNIKAGQQGLSVAFDLATHRGYDSDNPRVRGDVGMAGVAIDTVEDTKILF DGIPLEKMSVSMTMNGAVIPVLANFIVTGEEQGVPKEKLTGTIQNDILKEFMVRNTYI FPPEPSMKIIADIFEYTAKHMPKFNSISISGYHMQEAGADAILELAYTLADGLEYSRT GLQAGLTIDEFAPRLSFFWGIGMNFYMEIAKMRAGRRLWAHLIEKMFQPKNSKSLLLR AHCQTSGWSLTEQDPYNNIVRTAIEAMAAVFGGTQSLHTNSFDEALGLPTVKSARIAR NTQIIIQEESGIPKVADPWGGSYMMECLTNDVYDAALKLINEIEEMGGMAKAVAEGIP KLRIEECAARRQARIDSGSEVIVGVNKYQLEKEDAVEVLAIDNTSVRNRQIEKLKKIK SSRDQALAERCLAALTECAASGDGNILALAVDASRARCTVGEITDALKKVFGEHKAND RMVSGAYRQEFGESKEITSAIKRVHKFMEREGRRPRLLVAKMGQDGHDRGAKVIATGF ADLGFDVDIGPLFQTPREVAQQAVDADVHAVGVSTLAAGHKTLVPELIKELNSLGRPD ILVMCGGVIPPQDYEFLFEVGVSNVFGPGTRIPKAAVQVLDDIEKCLEKKQQSV

II. Modified Polynucleotides

[0280] The disclosure also includes a modified polynucleotide comprising the polynucleotide described herein, *i.e.*, a polynucleotide comprising an ORF encoding an MCM polypeptide that contains polynucleotides that are chemically and/or structurally modified. When the polynucleotides of the present disclosure are chemically and/or structurally modified the polynucleotides can be referred to as "modified polynucleotides."

[0281] The present disclosure provides for modified nucleosides and nucleotides of a polynucleotide (*e.g.*, RNA polynucleotides, such as mRNA polynucleotides). A "nucleoside" refers to a compound containing a sugar molecule (*e.g.*, a pentose or ribose) or a derivative thereof in combination with an organic base (*e.g.*, a purine or pyrimidine) or a derivative thereof

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(also referred to herein as "nucleobase"). A nucleotide" refers to a nucleoside, including a phosphate group. Modified nucleotides can by synthesized by any useful method, such as, for example, chemically, enzymatically, or recombinantly, to include one or more modified or non-natural nucleosides. Polynucleotides can comprise a region or regions of linked nucleosides. Such regions can have variable backbone linkages. The linkages can be standard phosphodioester linkages, in which case the polynucleotides would comprise regions of nucleotides.

[0282] The modifications can be various distinct modifications. In some embodiments, the regions can contain one, two, or more (optionally different) nucleoside or nucleotide modifications. In some embodiments, a modified polynucleotide, introduced to a cell can exhibit reduced degradation in the cell, as compared to an unmodified polynucleotide.

Structural Modifications

[0283] In some embodiments, the polynucleotides of the present disclosure are structurally modified. As used herein, a "structural" modification is one in which two or more linked nucleosides are inserted, deleted, duplicated, inverted or randomized in a polynucleotide without significant chemical modification to the nucleotides themselves. Because chemical bonds will necessarily be broken and reformed to effect a structural modification, structural modifications are of a chemical nature and hence are chemical modifications. However, structural modifications will result in a different sequence of nucleotides. For example, the polynucleotide "ATCG" can be chemically modified to "AT-5meC-G". The same polynucleotide can be structurally modified from "ATCG" to "ATCCCG". Here, the dinucleotide "CC" has been inserted, resulting in a structural modification to the polynucleotide.

Chemical Modifications

[0284] In some embodiments, the polynucleotides of the present disclosure are chemically modified. As used herein in reference to a polynucleotide, the terms "chemical modification" or, as appropriate, "chemically modified" refer to modification with respect to adenosine (A), guanosine (G), uridine (U), thymidine (T) or cytidine (C) ribo- or deoxyribonucleosides in one or more of their position, pattern, percent or population. Generally, herein, these terms are not intended to refer to the ribonucleotide modifications in naturally occurring 5′-terminal mRNA cap moieties.

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[0285] In some embodiments, the polynucleotides of the present disclosure can have a uniform chemical modification of all or any of the same nucleoside type or a population of modifications produced by mere downward titration of the same starting modification in all or any of the same nucleoside type, or a measured percent of a chemical modification of all any of the same nucleoside type but with random incorporation, such as where all uridines are replaced by a uridine analog, *e.g.,* pseudouridine or 5-methoxyuridine. In another embodiment, the polynucleotides can have a uniform chemical modification of two, three, or four of the same nucleoside type throughout the entire polynucleotide (such as all uridines and all cytosines, etc. are modified in the same way).

[0286] Modified nucleotide base pairing encompasses not only the standard adenosine-thymine, adenosine-uracil, or guanosine-cytosine base pairs, but also base pairs formed between nucleotides and/or modified nucleotides comprising non-standard or modified bases, wherein the arrangement of hydrogen bond donors and hydrogen bond acceptors permits hydrogen bonding between a non-standard base and a standard base or between two complementary non-standard base structures. One example of such non-standard base pairing is the base pairing between the modified nucleotide inosine and adenine, cytosine or uracil. Any combination of base/sugar or linker can be incorporated into polynucleotides of the present disclosure.

[0287] The skilled artisan will appreciate that, except where otherwise noted, polynucleotide sequences set forth in the instant application will recite "T"s in a representative DNA sequence but where the sequence represents RNA, the "T"s would be substituted for "U"s.

[0288] Modifications of polynucleotides (*e.g.*, RNA polynucleotides, such as mRNA polynucleotides) that are useful in the compositions, methods and synthetic processes of the present disclosure include, but are not limited to the following nucleotides, nucleosides, and nucleobases: 2-methylthio-N6-(cis-hydroxyisopentenyl)adenosine; 2-methylthio-N6-methyladenosine; 2-methylthio-N6-threonyl carbamoyladenosine; N6-glycinylcarbamoyladenosine; N6-isopentenyladenosine; N6-methyladenosine; N6-threonylcarbamoyladenosine; 1,2′-O-dimethyladenosine; 1-methyladenosine; 2′-O-methyladenosine; 2′-O-ribosyladenosine (phosphate); 2-methyladenosine; 2-methylthio-N6 isopentenyladenosine; 2-methylthio-N6-hydroxynorvalyl carbamoyladenosine; 2'-O-methyladenosine; 2'-O-ribosyladenosine (phosphate); Isopentenyladenosine; N6-(cis-hydroxyisopentenyl)adenosine; N6,2′-O-dimethyladenosine; N6,2'-O-dimethyladenosine; N6,N6,2′-O-trimethyladenosine; N6,N6-dimethyladenosine; N6-acetyladenosine; N6-

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hydroxynorvalylcarbamoyladenosine; N6-methyl-N6-threonylcarbamoyladenosine; 2-methyladenosine; 2-methylthio-N6-isopentenyladenosine; 7-deaza-adenosine; N1-methyl-adenosine; N6, N6 (dimethyl)adenine; N6-cis-hydroxy-isopentenyl-adenosine; α-thio-adenosine; 2 (amino)adenine; 2 (aminopropyl)adenine; 2 (methylthio) N6 (isopentenyl)adenine; 2-(alkyl)adenine; 2-(aminoalkyl)adenine; 2-(aminopropyl)adenine; 2-(halo)adenine; 2-(halo)adenine; 2-(propyl)adenine; 2'-Amino-2'-deoxy-ATP; 2'-Azido-2'-deoxy-ATP; 2'-Deoxy-2'-a-aminoadenosine TP; 2'-Deoxy-2'-a-azidoadenosine TP; 6 (alkyl)adenine; 6 (methyl)adenine; 6-(alkyl)adenine; 6-(methyl)adenine; 7 (deaza)adenine; 8 (alkenyl)adenine; 8 (alkynyl)adenine; 8 (amino)adenine; 8 (thioalkyl)adenine; 8-(alkenyl)adenine; 8-(alkyl)adenine; 8-(alkynyl)adenine; 8-(amino)adenine; 8-(halo)adenine; 8-(hydroxyl)adenine; 8-(thioalkyl)adenine; 8-(thiol)adenine; 8-azido-adenosine; aza adenine; deaza adenine; N6 (methyl)adenine; N6-(isopentyl)adenine; 7-deaza-8-aza-adenosine; 7-methyladenine; 1-Deazaadenosine TP; 2'Fluoro-N6-Bz-deoxyadenosine TP; 2'-OMe-2-Amino-ATP; 2'O-methyl-N6-Bz-deoxyadenosine TP; 2'-a-Ethynyladenosine TP; 2-aminoadenine; 2-Aminoadenosine TP; 2-Amino-ATP; 2'-a-Trifluoromethyladenosine TP; 2-Azidoadenosine TP; 2'-b-Ethynyladenosine TP; 2-Bromoadenosine TP; 2'-b-Trifluoromethyladenosine TP; 2-Chloroadenosine TP; 2'-Deoxy-2',2'-difluoroadenosine TP; 2'-Deoxy-2'-a-mercaptoadenosine TP; 2'-Deoxy-2'-a-thiomethoxyadenosine TP; 2'-Deoxy-2'-b-aminoadenosine TP; 2'-Deoxy-2'-b-azidoadenosine TP; 2'-Deoxy-2'-b-bromoadenosine TP; 2'-Deoxy-2'-b-chloroadenosine TP; 2'-Deoxy-2'-b-fluoroadenosine TP; 2'-Deoxy-2'-b-iodoadenosine TP; 2'-Deoxy-2'-b-mercaptoadenosine TP; 2'-Deoxy-2'-b-thiomethoxyadenosine TP; 2-Fluoroadenosine TP; 2-Iodoadenosine TP; 2-Mercaptoadenosine TP; 2-methoxy-adenine; 2-methylthio-adenine; 2-Trifluoromethyladenosine TP; 3-Deaza-3-bromoadenosine TP; 3-Deaza-3-chloroadenosine TP; 3-Deaza-3-fluoroadenosine TP; 3-Deaza-3-iodoadenosine TP; 3-Deazaadenosine TP; 4'-Azidoadenosine TP; 4'-Carbocyclic adenosine TP; 4'-Ethynyladenosine TP; 5'-Homo-adenosine TP; 8-Aza-ATP; 8-bromo-adenosine TP; 8-Trifluoromethyladenosine TP; 9-Deazaadenosine TP; 2-aminopurine; 7-deaza-2,6-diaminopurine; 7-deaza-8-aza-2,6-diaminopurine; 7-deaza-8-aza-2-aminopurine; 2,6-diaminopurine; 7-deaza-8-aza-adenine, 7-deaza-2-aminopurine; 2-thiocytidine; 3-methylcytidine; 5-formylcytidine; 5-hydroxymethylcytidine; 5-methylcytidine; N4-acetylcytidine; 2′-O-methylcytidine; 2'-O-methylcytidine; 5,2′-O-dimethylcytidine; 5-formyl-2′-O-methylcytidine; Lysidine; N4,2′-O-dimethylcytidine; N4-acetyl-2′-O-methylcytidine; N4-methylcytidine; N4,N4-Dimethyl-2'-OMe-Cytidine TP; 4-methylcytidine; 5-aza-cytidine;

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Pseudo-iso-cytidine; pyrrolo-cytidine; α-thio-cytidine; 2-(thio)cytosine; 2'-Amino-2'-deoxy-CTP; 2'-Azido-2'-deoxy-CTP; 2'-Deoxy-2'-a-aminocytidine TP; 2'-Deoxy-2'-a-azidocytidine TP; 3 (deaza) 5 (aza)cytosine; 3 (methyl)cytosine; 3-(alkyl)cytosine; 3-(deaza) 5 (aza)cytosine; 3-(methyl)cytidine; 4,2'-O-dimethylcytidine; 5 (halo)cytosine; 5 (methyl)cytosine; 5 (propynyl)cytosine; 5 (trifluoromethyl)cytosine; 5-(alkyl)cytosine; 5-(alkynyl)cytosine; 5-(halo)cytosine; 5-(propynyl)cytosine; 5-(trifluoromethyl)cytosine; 5-bromo-cytidine; 5-iodo-cytidine; 5-propynyl cytosine; 6-(azo)cytosine; 6-aza-cytidine; aza cytosine; deaza cytosine; N4 (acetyl)cytosine; 1-methyl-1-deaza-pseudoisocytidine; 1-methyl-pseudoisocytidine; 2-methoxy-5-methyl-cytidine; 2-methoxy-cytidine; 2-thio-5-methyl-cytidine; 4-methoxy-1-methyl-pseudoisocytidine; 4-methoxy-pseudoisocytidine; 4-thio-1-methyl-1-deaza-pseudoisocytidine; 4-thio-1-methyl-pseudoisocytidine; 4-thio-pseudoisocytidine; 5-aza-zebularine; 5-methyl-zebularine; pyrrolo-pseudoisocytidine; Zebularine; (E)-5-(2-Bromo-vinyl)cytidine TP; 2,2'-anhydro-cytidine TP hydrochloride; 2'Fluor-N4-Bz-cytidine TP; 2'Fluoro-N4-Acetyl-cytidine TP; 2'-O-Methyl-N4-Acetyl-cytidine TP; 2'O-methyl-N4-Bz-cytidine TP; 2'-a-Ethynylcytidine TP; 2'-a-Trifluoromethylcytidine TP; 2'-b-Ethynylcytidine TP; 2'-b-Trifluoromethylcytidine TP; 2'-Deoxy-2',2'-difluorocytidine TP; 2'-Deoxy-2'-a-mercaptocytidine TP; 2'-Deoxy-2'-a-thiomethoxycytidine TP; 2'-Deoxy-2'-b-aminocytidine TP; 2'-Deoxy-2'-b-azidocytidine TP; 2'-Deoxy-2'-b-bromocytidine TP; 2'-Deoxy-2'-b-chlorocytidine TP; 2'-Deoxy-2'-b-fluorocytidine TP; 2'-Deoxy-2'-b-iodocytidine TP; 2'-Deoxy-2'-b-mercaptocytidine TP; 2'-Deoxy-2'-b-thiomethoxycytidine TP; 2'-O-Methyl-5-(1-propynyl)cytidine TP; 3'-Ethynylcytidine TP; 4'-Azidocytidine TP; 4'-Carbocyclic cytidine TP; 4'-Ethynylcytidine TP; 5-(1-Propynyl)ara-cytidine TP; 5-(2-Chloro-phenyl)-2-thiocytidine TP; 5-(4-Amino-phenyl)-2-thiocytidine TP; 5-Aminoallyl-CTP; 5-Cyanocytidine TP; 5-Ethynylara-cytidine TP; 5-Ethynylcytidine TP; 5'-Homo-cytidine TP; 5-Methoxycytidine TP; 5-Trifluoromethyl-Cytidine TP; N4-Amino-cytidine TP; N4-Benzoyl-cytidine TP; Pseudoisocytidine; 7-methylguanosine; N2,2′-O-dimethylguanosine; N2-methylguanosine; Wyosine; 1,2′-O-dimethylguanosine; 1-methylguanosine; 2′-O-methylguanosine; 2′-O-ribosylguanosine (phosphate); 2'-O-methylguanosine; 2'-O-ribosylguanosine (phosphate); 7-aminomethyl-7-deazaguanosine; 7-cyano-7-deazaguanosine; Archaeosine; Methylwyosine; N2,7-dimethylguanosine; N2,N2,2′-O-trimethylguanosine; N2,N2,7-trimethylguanosine; N2,N2-dimethylguanosine; N2,7,2'-O-trimethylguanosine; 6-thio-guanosine; 7-deaza-guanosine; 8-oxo-guanosine; N1-methyl-guanosine; α-thio-guanosine; 2 (propyl)guanine; 2-(alkyl)guanine; 2'-Amino-2'-deoxy-GTP; 2'-

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Azido-2'-deoxy-GTP; 2'-Deoxy-2'-a-aminoguanosine TP; 2'-Deoxy-2'-a-azidoguanosine TP; 6 (methyl)guanine; 6-(alkyl)guanine; 6-(methyl)guanine; 6-methyl-guanosine; 7 (alkyl)guanine; 7 (deaza)guanine; 7 (methyl)guanine; 7-(alkyl)guanine; 7-(deaza)guanine; 7-(methyl)guanine; 8 (alkyl)guanine; 8 (alkynyl)guanine; 8 (halo)guanine; 8 (thioalkyl)guanine; 8-(alkenyl)guanine; 8-(alkyl)guanine; 8-(alkynyl)guanine; 8-(amino)guanine; 8-(halo)guanine; 8-(hydroxyl)guanine; 8-(thioalkyl)guanine; 8-(thiol)guanine; aza guanine; deaza guanine; N (methyl)guanine; N-(methyl)guanine; 1-methyl-6-thio-guanosine; 6-methoxy-guanosine; 6-thio-7-deaza-8-aza-guanosine; 6-thio-7-deaza-guanosine; 6-thio-7-methyl-guanosine; 7-deaza-8-aza-guanosine; 7-methyl-8-oxo-guanosine; N2,N2-dimethyl-6-thio-guanosine; N2-methyl-6-thio-guanosine; 1-Me-GTP; 2'Fluoro-N2-isobutyl-guanosine TP; 2'O-methyl-N2-isobutyl-guanosine TP; 2'-a-Ethynylguanosine TP; 2'-a-Trifluoromethylguanosine TP; 2'-b-Ethynylguanosine TP; 2'-b-Trifluoromethylguanosine TP; 2'-Deoxy-2',2'-difluoroguanosine TP; 2'-Deoxy-2'-a-mercaptoguanosine TP; 2'-Deoxy-2'-a-thiomethoxyguanosine TP; 2'-Deoxy-2'-b-aminoguanosine TP; 2'-Deoxy-2'-b-azidoguanosine TP; 2'-Deoxy-2'-b-bromoguanosine TP; 2'-Deoxy-2'-b-chloroguanosine TP; 2'-Deoxy-2'-b-fluoroguanosine TP; 2'-Deoxy-2'-b-iodoguanosine TP; 2'-Deoxy-2'-b-mercaptoguanosine TP; 2'-Deoxy-2'-b-thiomethoxyguanosine TP; 4'-Azidoguanosine TP; 4'-Carbocyclic guanosine TP; 4'-Ethynylguanosine TP; 5'-Homo-guanosine TP; 8-bromo-guanosine TP; 9-Deazaguanosine TP; N2-isobutyl-guanosine TP; 1-methylinosine; Inosine; 1,2′-O-dimethylinosine; 2′-O-methylinosine; 7-methylinosine; 2'-O-methylinosine; Epoxyqueuosine; galactosyl-queuosine; Mannosylqueuosine; Queuosine; allyamino-thymidine; aza thymidine; deaza thymidine; deoxy-thymidine; 2'-O-methyluridine; 2-thiouridine; 3-methyluridine; 5-carboxymethyluridine; 5-hydroxyuridine; 5-methyluridine; 5-taurinomethyl-2-thiouridine; 5-taurinomethyluridine; Dihydrouridine; Pseudouridine; (3-(3-amino-3-carboxypropyl)uridine; 1-methyl-3-(3-amino-5-carboxypropyl)pseudouridine; 1-methylpseduouridine; 1-ethyl-pseudouridine; 2′-O-methyluridine; 2'-O-methylpseudouridine; 2'-O-methyluridine; 2-thio-2′-O-methyluridine; 3-(3-amino-3-carboxypropyl)uridine; 3,2′-O-dimethyluridine; 3-Methyl-pseudo-Uridine TP; 4-thiouridine; 5-(carboxyhydroxymethyl)uridine; 5-(carboxyhydroxymethyl)uridine methyl ester; 5,2′-O-dimethyluridine; 5,6-dihydro-uridine; 5-aminomethyl-2-thiouridine; 5-carbamoylmethyl-2′-O-methyluridine; 5-carbamoylmethyluridine; 5-carboxyhydroxymethyluridine; 5-carboxyhydroxymethyluridine methyl ester; 5-carboxymethylaminomethyl-2′-O-methyluridine; 5-carboxymethylaminomethyl-2-thiouridine; 5-carboxymethylaminomethyl-2-thiouridine; 5-carboxymethylaminomethyluridine; 5-

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carboxymethylaminomethyluridine; 5-Carbamoylmethyluridine TP; 5-methoxycarbonylmethyl-2′-O-methyluridine; 5-methoxycarbonylmethyl-2-thiouridine; 5-methoxycarbonylmethyluridine; 5-methyluridine,), 5-methoxyuridine; 5-methyl-2-thiouridine; 5-methylaminomethyl-2-selenouridine; 5-methylaminomethyl-2-thiouridine; 5-methylaminomethyluridine; 5-Methyldihydrouridine; 5-Oxyacetic acid- Uridine TP; 5-Oxyacetic acid-methyl ester-Uridine TP; N1-methyl-pseudo-uracil; N1-ethyl-pseudo-uracil; uridine 5-oxyacetic acid; uridine 5-oxyacetic acid methyl ester; 3-(3-Amino-3-carboxypropyl)-Uridine TP; 5-(iso-Pentenylaminomethyl)- 2-thiouridine TP; 5-(iso-Pentenylaminomethyl)-2'-O-methyluridine TP; 5-(iso-Pentenylaminomethyl)uridine TP; 5-propynyl uracil; α-thio-uridine; 1 (aminoalkylamino-carbonylethylenyl)-2(thio)-pseudouracil; 1 (aminoalkylaminocarbonylethylenyl)-2,4-(dithio)pseudouracil; 1 (aminoalkylaminocarbonylethylenyl)-4 (thio)pseudouracil; 1 (aminoalkylaminocarbonylethylenyl)-pseudouracil; 1 (aminocarbonylethylenyl)-2(thio)-pseudouracil; 1 (aminocarbonylethylenyl)-2,4-(dithio)pseudouracil; 1 (aminocarbonylethylenyl)-4 (thio)pseudouracil; 1 (aminocarbonylethylenyl)-pseudouracil; 1 substituted 2(thio)-pseudouracil; 1 substituted 2,4-(dithio)pseudouracil; 1 substituted 4 (thio)pseudouracil; 1 substituted pseudouracil; 1-(aminoalkylamino-carbonylethylenyl)-2-(thio)-pseudouracil; 1-Methyl-3-(3-amino-3-carboxypropyl) pseudouridine TP; 1-Methyl-3-(3-amino-3-carboxypropyl)pseudo-UTP; 1-Methyl-pseudo-UTP; 1-Ethyl-pseudo-UTP; 2 (thio)pseudouracil; 2' deoxy uridine; 2' fluorouridine; 2-(thio)uracil; 2,4-(dithio)psuedouracil; 2' methyl, 2'amino, 2'azido, 2'fluro-guanosine; 2'-Amino-2'-deoxy-UTP; 2'-Azido-2'-deoxy-UTP; 2'-Azido-deoxyuridine TP; 2'-O-methylpseudouridine; 2′ deoxy uridine; 2′ fluorouridine; 2'-Deoxy-2'-a-aminouridine TP; 2'-Deoxy-2'-a-azidouridine TP; 2-methylpseudouridine; 3 (3 amino-3 carboxypropyl)uracil; 4 (thio)pseudouracil; 4-(thio)pseudouracil; 4-(thio)uracil; 4-thiouracil; 5 (1,3-diazole-1-alkyl)uracil; 5 (2-aminopropyl)uracil; 5 (aminoalkyl)uracil; 5 (dimethylaminoalkyl)uracil; 5 (guanidiniumalkyl)uracil; 5 (methoxycarbonylmethyl)-2-(thio)uracil; 5 (methoxycarbonyl-methyl)uracil; 5 (methyl) 2 (thio)uracil; 5 (methyl) 2,4 (dithio)uracil; 5 (methyl) 4 (thio)uracil; 5 (methylaminomethyl)-2 (thio)uracil; 5 (methylaminomethyl)-2,4 (dithio)uracil; 5 (methylaminomethyl)-4 (thio)uracil; 5 (propynyl)uracil; 5 (trifluoromethyl)uracil; 5-(2-aminopropyl)uracil; 5-(alkyl)-2-(thio)pseudouracil; 5-(alkyl)-2,4 (dithio)pseudouracil; 5-(alkyl)-4 (thio)pseudouracil; 5-(alkyl)pseudouracil; 5-(alkyl)uracil; 5-(alkynyl)uracil; 5-(allylamino)uracil; 5-(cyanoalkyl)uracil; 5-(dialkylaminoalkyl)uracil; 5-(dimethylaminoalkyl)uracil; 5-(guanidiniumalkyl)uracil; 5-

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(halo)uracil; 5-(l,3-diazole-l-alkyl)uracil; 5-(methoxy)uracil; 5-(methoxycarbonylmethyl)-2-(thio)uracil; 5-(methoxycarbonyl-methyl)uracil; 5-(methyl) 2(thio)uracil; 5-(methyl) 2,4 (dithio)uracil; 5-(methyl) 4 (thio)uracil; 5-(methyl)-2-(thio)pseudouracil; 5-(methyl)-2,4 (dithio)pseudouracil; 5-(methyl)-4 (thio)pseudouracil; 5-(methyl)pseudouracil; 5-(methylaminomethyl)-2 (thio)uracil; 5-(methylaminomethyl)-2,4(dithio)uracil; 5-(methylaminomethyl)-4-(thio)uracil; 5-(propynyl)uracil; 5-(trifluoromethyl)uracil; 5-aminoallyl-uridine; 5-bromo-uridine; 5-iodo-uridine; 5-uracil; 6 (azo)uracil; 6-(azo)uracil; 6-aza-uridine; allyamino-uracil; aza uracil; deaza uracil; N3 (methyl)uracil; P seudo-UTP-1-2-ethanoic acid; Pseudouracil; 4-Thio-pseudo-UTP; 1-carboxymethyl-pseudouridine; 1-methyl-1-deaza-pseudouridine; 1-propynyl-uridine; 1-taurinomethyl-1-methyl-uridine; 1-taurinomethyl-4-thio-uridine; 1-taurinomethyl-pseudouridine; 2-methoxy-4-thio-pseudouridine; 2-thio-1-methyl-1-deaza-pseudouridine; 2-thio-1-methyl-pseudouridine; 2-thio-5-aza-uridine; 2-thio-dihydropseudouridine; 2-thio-dihydrouridine; 2-thio-pseudouridine; 4-methoxy-2-thio-pseudouridine; 4-methoxy-pseudouridine; 4-thio-1-methyl-pseudouridine; 4-thio-pseudouridine; 5-aza-uridine; Dihydropseudouridine; (±)1-(2-Hydroxypropyl)pseudouridine TP; (2R)-1-(2-Hydroxypropyl)pseudouridine TP; (2S)-1-(2-Hydroxypropyl)pseudouridine TP; (E)-5-(2-Bromo-vinyl)ara-uridine TP; (E)-5-(2-Bromo-vinyl)uridine TP; (Z)-5-(2-Bromo-vinyl)ara-uridine TP; (Z)-5-(2-Bromo-vinyl)uridine TP; 1-(2,2,2-Trifluoroethyl)-pseudo-UTP; 1-(2,2,3,3,3-Pentafluoropropyl)pseudouridine TP; 1-(2,2-Diethoxyethyl)pseudouridine TP; 1-(2,4,6-Trimethylbenzyl)pseudouridine TP; 1-(2,4,6-Trimethyl-benzyl)pseudo-UTP; 1-(2,4,6-Trimethyl-phenyl)pseudo-UTP; 1-(2-Amino-2-carboxyethyl)pseudo-UTP; 1-(2-Amino-ethyl)pseudo-UTP; 1-(2-Hydroxyethyl)pseudouridine TP; 1-(2-Methoxyethyl)pseudouridine TP; 1-(3,4-Bis-trifluoromethoxybenzyl)pseudouridine TP; 1-(3,4-Dimethoxybenzyl)pseudouridine TP; 1-(3-Amino-3-carboxypropyl)pseudo-UTP; 1-(3-Amino-propyl)pseudo-UTP; 1-(3-Cyclopropyl-prop-2-ynyl)pseudouridine TP; 1-(4-Amino-4-carboxybutyl)pseudo-UTP; 1-(4-Amino-benzyl)pseudo-UTP; 1-(4-Amino-butyl)pseudo-UTP; 1-(4-Amino-phenyl)pseudo-UTP; 1-(4-Azidobenzyl)pseudouridine TP; 1-(4-Bromobenzyl)pseudouridine TP; 1-(4-Chlorobenzyl)pseudouridine TP; 1-(4-Fluorobenzyl)pseudouridine TP; 1-(4-Iodobenzyl)pseudouridine TP; 1-(4-Methanesulfonylbenzyl)pseudouridine TP; 1-(4-Methoxybenzyl)pseudouridine TP; 1-(4-Methoxy-benzyl)pseudo-UTP; 1-(4-Methoxy-phenyl)pseudo-UTP; 1-(4-Methylbenzyl)pseudouridine TP; 1-(4-Methyl-benzyl)pseudo-UTP; 1-(4-Nitrobenzyl)pseudouridine TP; 1-(4-Nitro-benzyl)pseudo-UTP; 1(4-Nitro-phenyl)pseudo-

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UTP; 1-(4-Thiomethoxybenzyl)pseudouridine TP; 1-(4-Trifluoromethoxybenzyl)pseudouridine TP; 1-(4-Trifluoromethylbenzyl)pseudouridine TP; 1-(5-Amino-pentyl)pseudo-UTP; 1-(6-Amino-hexyl)pseudo-UTP; 1,6-Dimethyl-pseudo-UTP; 1-[3-(2-{2-[2-(2-Aminoethoxy)-ethoxy]-ethoxy}-ethoxy)-propionyl]pseudouridine TP; 1-{3-[2-(2-Aminoethoxy)-ethoxy]-propionyl } pseudouridine TP; 1-Acetylpseudouridine TP; 1-Alkyl-6-(1-propynyl)-pseudo-UTP; 1-Alkyl-6-(2-propynyl)-pseudo-UTP; 1-Alkyl-6-allyl-pseudo-UTP; 1-Alkyl-6-ethynyl-pseudo-UTP; 1-Alkyl-6-homoallyl-pseudo-UTP; 1-Alkyl-6-vinyl-pseudo-UTP; 1-Allylpseudouridine TP; 1-Aminomethyl-pseudo-UTP; 1-Benzoylpseudouridine TP; 1-Benzyloxymethylpseudouridine TP; 1-Benzyl-pseudo-UTP; 1-Biotinyl-PEG2-pseudouridine TP; 1-Biotinylpseudouridine TP; 1-Butyl-pseudo-UTP; 1-Cyanomethylpseudouridine TP; 1-Cyclobutylmethyl-pseudo-UTP; 1-Cyclobutyl-pseudo-UTP; 1-Cycloheptylmethyl-pseudo-UTP; 1-Cycloheptyl-pseudo-UTP; 1-Cyclohexylmethyl-pseudo-UTP; 1-Cyclohexyl-pseudo-UTP; 1-Cyclooctylmethyl-pseudo-UTP; 1-Cyclooctyl-pseudo-UTP; 1-Cyclopentylmethyl-pseudo-UTP; 1-Cyclopentyl-pseudo-UTP; 1-Cyclopropylmethyl-pseudo-UTP; 1-Cyclopropyl-pseudo-UTP; 1-Ethyl-pseudo-UTP; 1-Hexyl-pseudo-UTP; 1-Homoallylpseudouridine TP; 1-Hydroxymethylpseudouridine TP; 1-iso-propyl-pseudo-UTP; 1-Me-2-thio-pseudo-UTP; 1-Me-4-thio-pseudo-UTP; 1-Me-alpha-thio-pseudo-UTP; 1-Methanesulfonylmethylpseudouridine TP; 1-Methoxymethylpseudouridine TP; 1-Methyl-6-(2,2,2-Trifluoroethyl)pseudo-UTP; 1-Methyl-6-(4-morpholino)-pseudo-UTP; 1-Methyl-6-(4-thiomorpholino)-pseudo-UTP; 1-Methyl-6-(substituted phenyl)pseudo-UTP; 1-Methyl-6-amino-pseudo-UTP; 1-Methyl-6-azido-pseudo-UTP; 1-Methyl-6-bromo-pseudo-UTP; 1-Methyl-6-butyl-pseudo-UTP; 1-Methyl-6-chloro-pseudo-UTP; 1-Methyl-6-cyano-pseudo-UTP; 1-Methyl-6-dimethylamino-pseudo-UTP; 1-Methyl-6-ethoxy-pseudo-UTP; 1-Methyl-6-ethylcarboxylate-pseudo-UTP; 1-Methyl-6-ethyl-pseudo-UTP; 1-Methyl-6-fluoro-pseudo-UTP; 1-Methyl-6-formyl-pseudo-UTP; 1-Methyl-6-hydroxyamino-pseudo-UTP; 1-Methyl-6-hydroxy-pseudo-UTP; 1-Methyl-6-iodo-pseudo-UTP; 1-Methyl-6-iso-propyl-pseudo-UTP; 1-Methyl-6-methoxy-pseudo-UTP; 1-Methyl-6-methylamino-pseudo-UTP; 1-Methyl-6-phenyl-pseudo-UTP; 1-Methyl-6-propyl-pseudo-UTP; 1-Methyl-6-tert-butyl-pseudo-UTP; 1-Methyl-6-trifluoromethoxy-pseudo-UTP; 1-Methyl-6-trifluoromethyl-pseudo-UTP; 1-Morpholinomethylpseudouridine TP; 1-Pentyl-pseudo-UTP; 1-Phenyl-pseudo-UTP; 1-Pivaloylpseudouridine TP; 1-Propargylpseudouridine TP; 1-Propyl-pseudo-UTP; 1-propynyl-pseudouridine; 1-p-tolyl-pseudo-UTP; 1-tert-Butyl-pseudo-UTP; 1-Thiomethoxymethylpseudouridine TP; 1-Thiomorpholinomethylpseudouridine TP; 1-

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Trifluoroacetylpseudouridine TP; 1-Trifluoromethyl-pseudo-UTP; 1-Vinylpseudouridine TP; 2,2'-anhydro-uridine TP; 2'-bromo-deoxyuridine TP; 2'-F-5-Methyl-2'-deoxy-UTP; 2'-OMe-5-Me-UTP; 2'-OMe-pseudo-UTP; 2'-a-Ethynyluridine TP; 2'-a-Trifluoromethyluridine TP; 2'-b-Ethynyluridine TP; 2'-b-Trifluoromethyluridine TP; 2'-Deoxy-2',2'-difluorouridine TP; 2'-Deoxy-2'-a-mercaptouridine TP; 2'-Deoxy-2'-a-thiomethoxyuridine TP; 2'-Deoxy-2'-b-aminouridine TP; 2'-Deoxy-2'-b-azidouridine TP; 2'-Deoxy-2'-b-bromouridine TP; 2'-Deoxy-2'-b-chlorouridine TP; 2'-Deoxy-2'-b-fluorouridine TP; 2'-Deoxy-2'-b-iodouridine TP; 2'-Deoxy-2'-b-mercaptouridine TP; 2'-Deoxy-2'-b-thiomethoxyuridine TP; 2-methoxy-4-thio-uridine; 2-methoxyuridine; 2'-O-Methyl-5-(1-propynyl)uridine TP; 3-Alkyl-pseudo-UTP; 4'-Azidouridine TP; 4'-Carbocyclic uridine TP; 4'-Ethynyluridine TP; 5-(1-Propynyl)ara-uridine TP; 5-(2-Furanyl)uridine TP; 5-Cyanouridine TP; 5-Dimethylaminouridine TP; 5'-Homo-uridine TP; 5-iodo-2'-fluoro-deoxyuridine TP; 5-Phenylethynyluridine TP; 5-Trideuteromethyl-6-deuterouridine TP; 5-Trifluoromethyl-Uridine TP; 5-Vinylarauridine TP; 6-(2,2,2-Trifluoroethyl)-pseudo-UTP; 6-(4-Morpholino)-pseudo-UTP; 6-(4-Thiomorpholino)-pseudo-UTP; 6-(Substituted-Phenyl)-pseudo-UTP; 6-Amino-pseudo-UTP; 6-Azido-pseudo-UTP; 6-Bromo-pseudo-UTP; 6-Butyl-pseudo-UTP; 6-Chloro-pseudo-UTP; 6-Cyano-pseudo-UTP; 6-Dimethylamino-pseudo-UTP; 6-Ethoxy-pseudo-UTP; 6-Ethylcarboxylate-pseudo-UTP; 6-Ethyl-pseudo-UTP; 6-Fluoro-pseudo-UTP; 6-Formyl-pseudo-UTP; 6-Hydroxyamino-pseudo-UTP; 6-Hydroxy-pseudo-UTP; 6-Iodo-pseudo-UTP; 6-iso-Propyl-pseudo-UTP; 6-Methoxy-pseudo-UTP; 6-Methylamino-pseudo-UTP; 6-Methyl-pseudo-UTP; 6-Phenyl-pseudo-UTP; 6-Phenyl-pseudo-UTP; 6-Propyl-pseudo-UTP; 6-tert-Butyl-pseudo-UTP; 6-Trifluoromethoxy-pseudo-UTP; 6-Trifluoromethyl-pseudo-UTP; Alpha-thio-pseudo-UTP; Pseudouridine 1-(4-methylbenzenesulfonic acid) TP; Pseudouridine 1-(4-methylbenzoic acid) TP; Pseudouridine TP 1-[3-(2-ethoxy)]propionic acid; Pseudouridine TP 1-[3-{2-(2-[2-(2-ethoxy)-ethoxy]-ethoxy)-ethoxy}]propionic acid; Pseudouridine TP 1-[3-{2-(2-[2-{2(2-ethoxy)-ethoxy}-ethoxy]-ethoxy)-ethoxy}]propionic acid; Pseudouridine TP 1-[3-{2-(2-[2-ethoxy]-ethoxy)-ethoxy}]propionic acid; Pseudouridine TP 1-[3-{2-(2-ethoxy)-ethoxy}] propionic acid; Pseudouridine TP 1-methylphosphonic acid; Pseudouridine TP 1-methylphosphonic acid diethyl ester; Pseudo-UTP-N1-3-propionic acid; Pseudo-UTP-N1-4-butanoic acid; Pseudo-UTP-N1-5-pentanoic acid; Pseudo-UTP-N1-6-hexanoic acid; Pseudo-UTP-N1-7-heptanoic acid; Pseudo-UTP-N1-methyl-p-benzoic acid; Pseudo-UTP-N1-p-benzoic acid; Wybutosine; Hydroxywybutosine; Isowyosine; Peroxywybutosine; undermodified hydroxywybutosine; 4-demethylwyosine; 2,6-(diamino)purine;1-(aza)-2-(thio)-3-(aza)-

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phenoxazin-1-yl: 1,3-(diaza)-2-(oxo)-phenthiazin-l-yl;1,3-(diaza)-2-(oxo)-phenoxazin-1-yl;1,3,5-(triaza)-2,6-(dioxa)-naphthalene;2 (amino)purine;2,4,5-(trimethyl)phenyl;2' methyl, 2'amino, 2'azido, 2'fluro-cytidine;2' methyl, 2'amino, 2'azido, 2'fluro-adenine;2'methyl, 2'amino, 2'azido, 2'fluro-uridine;2'-amino-2'-deoxyribose; 2-amino-6-Chloro-purine; 2-aza-inosinyl; 2'-azido-2'-deoxyribose; 2'fluoro-2'-deoxyribose; 2'-fluoro-modified bases; 2'-O-methyl-ribose; 2-oxo-7-aminopyridopyrimidin-3-yl; 2-oxo-pyridopyrimidine-3-yl; 2-pyridinone; 3 nitropyrrole; 3-(methyl)-7-(propynyl)isocarbostyrilyl; 3-(methyl)isocarbostyrilyl; 4-(fluoro)-6-(methyl)benzimidazole; 4-(methyl)benzimidazole; 4-(methyl)indolyl; 4,6-(dimethyl)indolyl; 5 nitroindole; 5 substituted pyrimidines; 5-(methyl)isocarbostyrilyl; 5-nitroindole; 6-(aza)pyrimidine; 6-(azo)thymine; 6-(methyl)-7-(aza)indolyl; 6-chloro-purine; 6-phenyl-pyrrolo-pyrimidin-2-on-3-yl; 7-(aminoalkylhydroxy)-1-(aza)-2-(thio)-3-(aza)-phenthiazin-l-yl; 7-(aminoalkylhydroxy)-1-(aza)-2-(thio)-3-(aza)-phenoxazin-1-yl; 7-(aminoalkylhydroxy)-1,3-(diaza)-2-(oxo)-phenoxazin-1-yl; 7-(aminoalkylhydroxy)-l,3-(diaza)-2-(oxo)-phenthiazin-l-yl; 7-(aminoalkylhydroxy)-l,3-(diaza)-2-(oxo)-phenoxazin-l-yl; 7-(aza)indolyl; 7-(guanidiniumalkylhydroxy)-1-(aza)-2-(thio)-3-(aza)-phenoxazinl-yl; 7-(guanidiniumalkylhydroxy)-1-(aza)-2-(thio)-3-(aza)-phenthiazin-l-yl; 7-(guanidiniumalkylhydroxy)-1-(aza)-2-(thio)-3-(aza)-phenoxazin-1-yl; 7-(guanidiniumalkylhydroxy)-1,3-(diaza)-2-(oxo)-phenoxazin-1-yl; 7-(guanidiniumalkyl-hydroxy)-l,3-(diaza)-2-(oxo)-phenthiazin-l-yl; 7-(guanidiniumalkylhydroxy)-l,3-(diaza)-2-(oxo)-phenoxazin-l-yl; 7-(propynyl)isocarbostyrilyl; 7-(propynyl)isocarbostyrilyl, propynyl-7-(aza)indolyl; 7-deaza-inosinyl; 7-substituted 1-(aza)-2-(thio)-3-(aza)-phenoxazin-1-yl; 7-substituted 1,3-(diaza)-2-(oxo)-phenoxazin-1-yl; 9-(methyl)-imidizopyridinyl; Aminoindolyl; Anthracenyl; bis-ortho-(aminoalkylhydroxy)-6-phenyl-pyrrolo-pyrimidin-2-on-3-yl; bis-ortho-substituted-6-phenyl-pyrrolo-pyrimidin-2-on-3-yl; Difluorotolyl; Hypoxanthine; Imidizopyridinyl; Inosinyl; Isocarbostyrilyl; Isoguanisine; N2-substituted purines; N6-methyl-2-amino-purine; N6-substituted purines; N-alkylated derivative; Napthalenyl; Nitrobenzimidazolyl; Nitroimidazolyl; Nitroindazolyl; Nitropyrazolyl; Nubularine; O6-substituted purines; O-alkylated derivative; ortho-(aminoalkylhydroxy)-6-phenyl-pyrrolo-pyrimidin-2-on-3-yl; ortho-substituted-6-phenyl-pyrrolo-pyrimidin-2-on-3-yl; Oxoformycin TP; para-(aminoalkylhydroxy)-6-phenyl-pyrrolo-pyrimidin-2-on-3-yl; para-substituted-6-phenyl-pyrrolo-pyrimidin-2-on-3-yl; Pentacenyl; Phenanthracenyl; Phenyl; propynyl-7-(aza)indolyl; Pyrenyl; pyridopyrimidin-3-yl; pyridopyrimidin-3-yl, 2-oxo-7-amino-pyridopyrimidin-3-yl; pyrrolo-pyrimidin-2-on-3-yl;

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Pyrrolopyrimidinyl; Pyrrolopyrizinyl; Stilbenzyl; substituted 1,2,4-triazoles; Tetracenyl; Tubercidine; Xanthine; Xanthosine-5'-TP; 2-thio-zebularine; 5-aza-2-thio-zebularine; 7-deaza-2-amino-purine; pyridin-4-one ribonucleoside; 2-Amino-riboside-TP; Formycin A TP; Formycin B TP; Pyrrolosine TP; 2'-OH-ara-adenosine TP; 2'-OH-ara-cytidine TP; 2'-OH-ara-uridine TP; 2'-OH-ara-guanosine TP; 5-(2-carbomethoxyvinyl)uridine TP; and N6-(19-Amino-pentaoxanonadecyl)adenosine TP.

[0289] In some embodiments, the polynucleotide (*e.g.*, RNA polynucleotide, such as mRNA polynucleotide) includes a combination of at least two (*e.g.*, 2, 3, 4 or more) of the aforementioned modified nucleobases.

[0290] In some embodiments, the mRNA comprises at least one chemically modified nucleoside. In some embodiments, the at least one chemically modified nucleoside is selected from the group consisting of pseudouridine (ψ), 2-thiouridine (s2U), 4'-thiouridine, 5-methylcytosine, 2-thio-1-methyl-1-deaza-pseudouridine, 2-thio-1-methyl-pseudouridine, 2-thio-5-aza-uridine, 2-thio-dihydropseudouridine, 2-thio-dihydrouridine, 2-thio-pseudouridine, 4-methoxy-2-thio-pseudouridine, 4-methoxy-pseudouridine, 4-thio-1-methyl-pseudouridine, 4-thio-pseudouridine, 5-aza-uridine, dihydropseudouridine, 5-methyluridine, 5-methoxyuridine, 2'-O-methyl uridine, 1-methyl-pseudouridine (m1ψ), 1-ethyl-pseudouridine (e1ψ), 5-methoxy-uridine (mo5U), 5-methyl-cytidine (m5C), α-thio-guanosine, α-thio-adenosine, 5-cyano uridine, 4'-thio uridine 7-deaza-adenine, 1-methyl-adenosine (m1A), 2-methyl-adenine (m2A), N6-methyl-adenosine (m6A), and 2,6-Diaminopurine, (I), 1-methyl-inosine (m1I), wyosine (imG), methylwyosine (mimG), 7-deaza-guanosine, 7-cyano-7-deaza-guanosine (preQ0), 7-aminomethyl-7-deaza-guanosine (preQ1), 7-methyl-guanosine (m7G), 1-methyl-guanosine (m1G), 8-oxo-guanosine, 7-methyl-8-oxo-guanosine, 2,8-dimethyladenosine, 2-geranylthiouridine, 2-lysidine, 2-selenouridine, 3-(3-amino-3-carboxypropyl)-5,6-dihydrouridine, 3-(3-amino-3-carboxypropyl)pseudouridine, 3-methylpseudouridine, 5-(carboxyhydroxymethyl)-2′-O-methyluridine methyl ester, 5-aminomethyl-2-geranylthiouridine, 5-aminomethyl-2-selenouridine, 5-aminomethyluridine, 5-carbamoylhydroxymethyluridine, 5-carbamoylmethyl-2-thiouridine, 5-carboxymethyl-2-thiouridine, 5-carboxymethylaminomethyl-2-geranylthiouridine, 5-carboxymethylaminomethyl-2-selenouridine, 5-cyanomethyluridine, 5-hydroxycytidine, 5-methylaminomethyl-2-geranylthiouridine, 7-aminocarboxypropyl-demethylwyosine, 7-aminocarboxypropylwyosine, 7-aminocarboxypropylwyosine methyl ester, 8-methyladenosine, N4,N4-dimethylcytidine, N6-formyladenosine, N6-

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hydroxymethyladenosine, agmatidine, cyclic N6-threonylcarbamoyladenosine, glutamyl-queuosine, methylated undermodified hydroxywybutosine, N4,N4,2′-O-trimethylcytidine, geranylated 5-methylaminomethyl-2-thiouridine, geranylated 5-carboxymethylaminomethyl-2-thiouridine, Qbase , preQ0base, preQ1base, and two or more combinations thereof. In some embodiments, the at least one chemically modified nucleoside is selected from the group consisting of pseudouridine, 1-methyl-pseudouridine, 1-ethyl-pseudouridine, 5-methylcytosine, 5-methoxyuridine, and a combination thereof. In some embodiments, the polynucleotide (*e.g.*, RNA polynucleotide, such as mRNA polynucleotide) includes a combination of at least two (*e.g.*, 2, 3, 4 or more) of the aforementioned modified nucleobases.

Base Modifications

[0291] In certain embodiments, the chemical modification is at nucleobases in the polynucleotides (*e.g.*, RNA polynucleotide, such as mRNA polynucleotide). In some embodiments, modified nucleobases in the polynucleotide (*e.g.*, RNA polynucleotide, such as mRNA polynucleotide) are selected from the group consisting of 1-methyl-pseudouridine (m1ψ), 1-ethyl-pseudouridine (e1ψ), 5-methoxy-uridine (mo5U), 5-methyl-cytidine (m5C), pseudouridine (ψ), α-thio-guanosine and α-thio-adenosine. In some embodiments, the polynucleotide includes a combination of at least two (*e.g.*, 2, 3, 4 or more) of the aforementioned modified nucleobases.

[0292] In some embodiments, the polynucleotide (*e.g.*, RNA polynucleotide, such as mRNA polynucleotide) comprises pseudouridine (ψ) and 5-methyl-cytidine (m5C). In some embodiments, the polynucleotide (*e.g.*, RNA polynucleotide, such as mRNA polynucleotide) comprises 1-methyl-pseudouridine (m1ψ). In some embodiments, the polynucleotide (*e.g.*, RNA polynucleotide, such as mRNA polynucleotide) comprises 1-ethyl-pseudouridine (e1ψ). In some embodiments, the polynucleotide (*e.g.*, RNA polynucleotide, such as mRNA polynucleotide) comprises 1-methyl-pseudouridine (m1ψ) and 5-methyl-cytidine (m5C). In some embodiments, the polynucleotide (*e.g.*, RNA polynucleotide, such as mRNA polynucleotide) comprises 1-ethyl-pseudouridine (e1ψ) and 5-methyl-cytidine (m5C). In some embodiments, the polynucleotide (*e.g.*, RNA polynucleotide, such as mRNA polynucleotide) comprises 2-thiouridine (s2U). In some embodiments, the polynucleotide (*e.g.*, RNA polynucleotide, such as mRNA polynucleotide) comprises 2-thiouridine and 5-methyl-cytidine (m5C). In some embodiments, the polynucleotide (*e.g.*, RNA polynucleotide, such as mRNA polynucleotide)

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comprises methoxy-uridine (mo5U). In some embodiments, the polynucleotide (*e.g.*, RNA polynucleotide, such as mRNA polynucleotide) comprises 5-methoxy-uridine (mo5U) and 5-methyl-cytidine (m5C). In some embodiments, the polynucleotide (*e.g.*, RNA polynucleotide, such as mRNA polynucleotide) comprises 2'-O-methyl uridine. In some embodiments, the polynucleotide (*e.g.*, RNA polynucleotide, such as mRNA polynucleotide) comprises 2'-O-methyl uridine and 5-methyl-cytidine (m5C). In some embodiments, the polynucleotide (*e.g.*, RNA polynucleotide, such as mRNA polynucleotide) comprises N6-methyl-adenosine (m6A). In some embodiments, the polynucleotide (*e.g.*, RNA polynucleotide, such as mRNA polynucleotide) comprises N6-methyl-adenosine (m6A) and 5-methyl-cytidine (m5C).

[0293] In some embodiments, the polynucleotide (*e.g.*, RNA polynucleotide, such as mRNA polynucleotide) is uniformly modified (*e.g.*, fully modified, modified throughout the entire sequence) for a particular modification. For example, a polynucleotide can be uniformly modified with 5-methyl-cytidine (m5C), meaning that all cytosine residues in the mRNA sequence are replaced with 5-methyl-cytidine (m5C). Similarly, a polynucleotide can be uniformly modified for any type of nucleoside residue present in the sequence by replacement with a modified residue such as any of those set forth above.

[0294] In some embodiments, the chemically modified nucleosides in the open reading frame are selected from the group consisting of uridine, adenine, cytosine, guanine, and any combination thereof.

[0295] In some embodiments, the modified nucleobase is a modified cytosine. Examples of nucleobases and nucleosides having a modified cytosine include N4-acetyl-cytidine (ac4C), 5-methyl-cytidine (m5C), 5-halo-cytidine (*e.g.*, 5-iodo-cytidine), 5-hydroxymethyl-cytidine (hm5C), 1-methyl-pseudoisocytidine, 2-thio-cytidine (s2C), 2-thio-5-methyl-cytidine.

[0296] In some embodiments, a modified nucleobase is a modified uridine. Example nucleobases and nucleosides having a modified uridine include 5-cyano uridine or 4'-thio uridine.

[0297] In some embodiments, a modified nucleobase is a modified adenine. Example nucleobases and nucleosides having a modified adenine include 7-deaza-adenine, 1-methyl-adenosine (m1A), 2-methyl-adenine (m2A), N6-methyl-adenine (m6A), and 2,6-Diaminopurine.

[0298] In some embodiments, a modified nucleobase is a modified guanine. Example nucleobases and nucleosides having a modified guanine include inosine (I), 1-methyl-inosine (m1I), wyosine (imG), methylwyosine (mimG), 7-deaza-guanosine, 7-cyano-7-deaza-guanosine

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(preQ0), 7-aminomethyl-7-deaza-guanosine (preQ1), 7-methyl-guanosine (m7G), 1-methyl-guanosine (m1G), 8-oxo-guanosine, 7-methyl-8-oxo-guanosine.

[0299] In some embodiments, the nucleobase modified nucleotides in the polynucleotide (*e.g.*, RNA polynucleotide, such as mRNA polynucleotide) are 5-methoxyuridine.

[0300] In some embodiments, the polynucleotide (*e.g.*, RNA polynucleotide, such as mRNA polynucleotide) includes a combination of at least two (*e.g.*, 2, 3, 4 or more) of modified nucleobases.

[0301] In some embodiments, at least 95% of a type of nucleobases (e.g., uracil) in a polynucleotide of the disclosure (*e.g.*, an mRNA polynucleotide encoding MCM) are modified nucleobases. In some embodiments, at least 95% of uracil in a polynucleotide of the present disclosure (*e.g.*, an mRNA polynucleotide encoding MCM) is 5-methoxyuracil.

[0302] In some embodiments, the polynucleotide (*e.g.*, RNA polynucleotide, such as mRNA polynucleotide) comprises 5-methoxyuridine (5mo5U) and 5-methyl-cytidine (m5C).

[0303] In some embodiments, the polynucleotide (*e.g.*, RNA polynucleotide, such as mRNA polynucleotide) is uniformly modified (*e.g.*, fully modified, modified throughout the entire sequence) for a particular modification. For example, a polynucleotide can be uniformly modified with 5-methoxyuridine, meaning that substantially all uridine residues in the mRNA sequence are replaced with 5-methoxyuridine. Similarly, a polynucleotide can be uniformly modified for any type of nucleoside residue present in the sequence by replacement with a modified residue such as any of those set forth above.

[0304] In some embodiments, the modified nucleobase is a modified cytosine.

[0305] In some embodiments, a modified nucleobase is a modified uracil. Example nucleobases and nucleosides having a modified uracil include 5-methoxyuracil.

[0306] In some embodiments, a modified nucleobase is a modified adenine.

[0307] In some embodiments, a modified nucleobase is a modified guanine.

[0308] In some embodiments, the nucleobases, sugar, backbone, or any combination thereof in the open reading frame encoding an MCM polypeptide are chemically modified by at least 10%, at least 20%, at least 30%, at least 40%, at least 50%, at least 60%, at least 70%, at least 80%, at least 90%, at least 95%, at least 99%, or 100%.

[0309] In some embodiments, the uridine nucleosides in the open reading frame encoding an MCM polypeptide are chemically modified by at least 10%, at least 20%, at least 30%, at least

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40%, at least 50%, at least 60%, at least 70%, at least 80%, at least 90%, at least 95%, at least 99%, or 100%.

[0310] In some embodiments, the adenosine nucleosides in the open reading frame encoding an MCM polypeptide are chemically modified by at least 10%, at least 20%, at least 30%, at least 40%, at least 50%, at least 60%, at least 70%, at least 80%, at least 90%, at least 95%, at least 99%, or 100%.

[0311] In some embodiments, the cytidine nucleosides in the open reading frame encoding an MCM polypeptide are chemically modified by at least at least 10%, at least 20%, at least 30%, at least 40%, at least 50%, at least 60%, at least 70%, at least 80%, at least 90%, at least 95%, at least 99%, or 100%.

[0312] In some embodiments, the guanosine nucleosides in the open reading frame encoding an MCM polypeptide are chemically modified by at least at least 10%, at least 20%, at least 30%, at least 40%, at least 50%, at least 60%, at least 70%, at least 80%, at least 90%, at least 95%, at least 99%, or 100%.

[0313] In some embodiments, the polynucleotides can include any useful linker between the nucleosides. Such linkers, including backbone modifications, that are useful in the composition of the present disclosure include, but are not limited to the following: 3'-alkylene phosphonates, 3'-amino phosphoramidate, alkene containing backbones, aminoalkylphosphoramidates, aminoalkylphosphotriesters, boranophosphates, $-CH_2-O-N(CH_3)-CH_2-$, $-CH_2-N(CH_3)-N(CH_3)-CH_2-$, $-CH_2-NH-CH_2-$, chiral phosphonates, chiral phosphorothioates, formacetyl and thioformacetyl backbones, methylene (methylimino), methylene formacetyl and thioformacetyl backbones, methyleneimino and methylenehydrazino backbones, morpholino linkages, $-N(CH_3)-CH_2-CH_2-$, oligonucleosides with heteroatom internucleoside linkage, phosphinates, phosphoramidates, phosphorodithioates, phosphorothioate internucleoside linkages, phosphorothioates, phosphotriesters, PNA, siloxane backbones, sulfamate backbones, sulfide sulfoxide and sulfone backbones, sulfonate and sulfonamide backbones, thionoalkylphosphonates, thionoalkylphosphotriesters, and thionophosphoramidates.

Modifications on the Sugar

[0314] The modified nucleosides and nucleotides (*e.g.,* building block molecules), which can be incorporated into a polynucleotide (*e.g.,* RNA or mRNA, as described herein), can be

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modified on the sugar of the ribonucleic acid. For example, the 2′ hydroxyl group (OH) can be modified or replaced with a number of different substituents. Exemplary substitutions at the 2′-position include, but are not limited to, H, halo, optionally substituted C_{1-6} alkyl; optionally substituted C_{1-6} alkoxy; optionally substituted C_{6-10} aryloxy; optionally substituted C_{3-8} cycloalkyl; optionally substituted C_{3-8} cycloalkoxy; optionally substituted C_{6-10} aryloxy; optionally substituted C_{6-10} aryl-C_{1-6} alkoxy, optionally substituted C_{1-12} (heterocyclyl)oxy; a sugar (*e.g.,* ribose, pentose, or any described herein); a polyethyleneglycol (PEG), $-O(CH_2CH_2O)_nCH_2CH_2OR$, where R is H or optionally substituted alkyl, and n is an integer from 0 to 20 (*e.g.,* from 0 to 4, from 0 to 8, from 0 to 10, from 0 to 16, from 1 to 4, from 1 to 8, from 1 to 10, from 1 to 16, from 1 to 20, from 2 to 4, from 2 to 8, from 2 to 10, from 2 to 16, from 2 to 20, from 4 to 8, from 4 to 10, from 4 to 16, and from 4 to 20); "locked" nucleic acids (LNA) in which the 2′-hydroxyl is connected by a C_{1-6} alkylene or C_{1-6} heteroalkylene bridge to the 4'-carbon of the same ribose sugar, where exemplary bridges included methylene, propylene, ether, or amino bridges; aminoalkyl, as defined herein; aminoalkoxy, as defined herein; amino as defined herein; and amino acid, as defined herein

[0315] Generally, RNA includes the sugar group ribose, which is a 5-membered ring having an oxygen. Exemplary, non-limiting modified nucleotides include replacement of the oxygen in ribose (*e.g.,* with S, Se, or alkylene, such as methylene or ethylene); addition of a double bond (*e.g.,* to replace ribose with cyclopentenyl or cyclohexenyl); ring contraction of ribose (*e.g.,* to form a 4-membered ring of cyclobutane or oxetane); ring expansion of ribose (*e.g.,* to form a 6- or 7-membered ring having an additional carbon or heteroatom, such as for anhydrohexitol, altritol, mannitol, cyclohexanyl, cyclohexenyl, and morpholino that also has a phosphoramidate backbone); multicyclic forms (*e.g.,* tricyclo; and "unlocked" forms, such as glycol nucleic acid (GNA) (*e.g.,* R-GNA or S-GNA, where ribose is replaced by glycol units attached to phosphodiester bonds), threose nucleic acid (TNA, where ribose is replace with α-L-threofuranosyl-(3′→2′)) , and peptide nucleic acid (PNA, where 2-amino-ethyl-glycine linkages replace the ribose and phosphodiester backbone). The sugar group can also contain one or more carbons that possess the opposite stereochemical configuration than that of the corresponding carbon in ribose. Thus, a polynucleotide molecule can include nucleotides containing, *e.g.,* arabinose, as the sugar. Such sugar modifications are taught International Patent Publication No. WO2013052523 and International Patent Application No. PCT/US2013/75177, the contents of each of which are incorporated herein by reference in its entirety.

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Combinations of Modifications

[0316] The polynucleotides of the disclosure can include a combination of modifications to the sugar, the nucleobase, and/or the internucleoside linkage. These combinations can include any one or more modifications described herein.

[0317] Examples of modified nucleotides and modified nucleotide combinations are provided below in **Table 4**. These combinations of modified nucleotides can be used to form the polynucleotides of the disclosure. Unless otherwise noted, the modified nucleotides can be completely substituted for the natural nucleotides of the polynucleotides of the disclosure. As a non-limiting example, the natural nucleotide uridine can be substituted with a modified nucleoside described herein. In another non-limiting example, the natural nucleotide uridine can be partially substituted (*e.g.,* about 0.1%, 1%, 5%, 10%, 15%, 20%, 25%, 30%, 35%, 40%, 45%, 50%, 55%, 60%, 65%, 70%, 75%, 80%, 85%, 90%, 95% or 99.9%) with at least one of the modified nucleoside disclosed herein. Any combination of base/sugar or linker can be incorporated into the polynucleotides of the disclosure and such modifications are taught in International Patent Publication No. WO2013052523 and International Patent Application No. PCT/US2013/75177, the contents of each of which are incorporated herein by reference in its entirety.

Table 4. Combinations

Uracil	Cytosine	Adenine	Guanine
5-methoxy-UTP	CTP	ATP	GTP
5-Methoxy-UTP	N4Ac-CTP	ATP	GTP
5-Methoxy-UTP	5-Methyl-CTP	ATP	GTP
5-Methoxy-UTP	5-Trifluoromethyl-CTP	ATP	GTP
5-Methoxy-UTP	5-Hydroxymethyl-CTP	ATP	GTP
5-Methoxy-UTP	5-Bromo-CTP	ATP	GTP
5-Methoxy-UTP	N4Ac-CTP	ATP	GTP
5-Methoxy-UTP	CTP	ATP	GTP
5-Methoxy-UTP	5-Methyl-CTP	ATP	GTP
5-Methoxy-UTP	5-Trifluoromethyl-CTP	ATP	GTP
5-Methoxy-UTP	5-Hydroxymethyl-CTP	ATP	GTP
5-Methoxy-UTP	5-Bromo-CTP	ATP	GTP
5-Methoxy-UTP	N4-Ac-CTP	ATP	GTP
5-Methoxy-UTP	5-Iodo-CTP	ATP	GTP

5-Methoxy-UTP	5-Bromo-CTP	ATP	GTP
5-Methoxy-UTP	CTP	ATP	GTP
5-Methoxy-UTP	5-Methyl-CTP	ATP	GTP
75 % 5-Methoxy-UTP + 25 % UTP	5-Methyl-CTP	ATP	GTP
50 % 5-Methoxy-UTP + 50 % UTP	5-Methyl-CTP	ATP	GTP
25 % 5-Methoxy-UTP + 75 % UTP	5-Methyl-CTP	ATP	GTP
5-Methoxy-UTP	75 % 5-Methyl-CTP + 25 % CTP	ATP	GTP
5-Methoxy-UTP	50 % 5-Methyl-CTP + 50 % CTP	ATP	GTP
5-Methoxy-UTP	25 % 5-Methyl-CTP + 75 % CTP	ATP	GTP
75 % 5-Methoxy-UTP + 25 % UTP	75 % 5-Methyl-CTP + 25 % CTP	ATP	GTP
75 % 5-Methoxy-UTP + 25 % UTP	50 % 5-Methyl-CTP + 50 % CTP	ATP	GTP
75 % 5-Methoxy-UTP + 25 % UTP	25 % 5-Methyl-CTP + 75 % CTP	ATP	GTP
50 % 5-Methoxy-UTP + 50 % UTP	75 % 5-Methyl-CTP + 25 % CTP	ATP	GTP
50 % 5-Methoxy-UTP + 50 % UTP	50 % 5-Methyl-CTP + 50 % CTP	ATP	GTP
50 % 5-Methoxy-UTP + 50 % UTP	25 % 5-Methyl-CTP + 75 % CTP	ATP	GTP
25 % 5-Methoxy-UTP + 75 % UTP	75 % 5-Methyl-CTP + 25 % CTP	ATP	GTP
25 % 5-Methoxy-UTP + 75 % UTP	50 % 5-Methyl-CTP + 50 % CTP	ATP	GTP
25 % 5-Methoxy-UTP + 75 % UTP	25 % 5-Methyl-CTP + 75 % CTP	ATP	GTP
75 % 5-Methoxy-UTP + 25 % UTP	CTP	ATP	GTP
50 % 5-Methoxy-UTP + 50 % UTP	CTP	ATP	GTP
25 % 5-Methoxy-UTP + 75 % UTP	CTP	ATP	GTP
5-Methoxy-UTP	CTP	ATP	GTP
5-Methoxy-UTP	CTP	ATP	GTP
5-Methoxy-UTP	CTP	ATP	GTP
5-Methoxy-UTP	5-Methyl-CTP	ATP	GTP
5-Methoxy-UTP	5-Methyl-CTP	ATP	GTP
5-Methoxy-UTP	5-Methyl-CTP	ATP	GTP
5-Methoxy-UTP	CTP	Alpha-thio-ATP	GTP
5-Methoxy-UTP	5-Methyl-CTP	Alpha-thio-ATP	GTP
5-Methoxy-UTP	CTP	ATP	Alpha-thio-GTP
5-Methoxy-UTP	5-Methyl-CTP	ATP	Alpha-thio-GTP
5-Methoxy-UTP	CTP	N6-Me-ATP	GTP
5-Methoxy-UTP	5-Methyl-CTP	N6-Me-	GTP

		ATP	
5-Methoxy-UTP	CTP	ATP	GTP
5-Methoxy-UTP	5-Methyl-CTP	ATP	GTP
75 % 5-Methoxy-UTP + 25 % UTP	5-Methyl-CTP	ATP	GTP
50 % 5-Methoxy-UTP + 50 % UTP	5-Methyl-CTP	ATP	GTP
25 % 5-Methoxy-UTP + 75 % UTP	5-Methyl-CTP	ATP	GTP
5-Methoxy-UTP	75 % 5-Methyl-CTP + 25 % CTP	ATP	GTP
5-Methoxy-UTP	50 % 5-Methyl-CTP + 50 % CTP	ATP	GTP
5-Methoxy-UTP	25 % 5-Methyl-CTP + 75 % CTP	ATP	GTP
75 % 5-Methoxy-UTP + 25 % UTP	75 % 5-Methyl-CTP + 25 % CTP	ATP	GTP
75 % 5-Methoxy-UTP + 25 % UTP	50 % 5-Methyl-CTP + 50 % CTP	ATP	GTP
75 % 5-Methoxy-UTP + 25 % UTP	25 % 5-Methyl-CTP + 75 % CTP	ATP	GTP
50 % 5-Methoxy-UTP + 50 % UTP	75 % 5-Methyl-CTP + 25 % CTP	ATP	GTP
50 % 5-Methoxy-UTP + 50 % UTP	50 % 5-Methyl-CTP + 50 % CTP	ATP	GTP
50 % 5-Methoxy-UTP + 50 % UTP	25 % 5-Methyl-CTP + 75 % CTP	ATP	GTP
25 % 5-Methoxy-UTP + 75 % UTP	75 % 5-Methyl-CTP + 25 % CTP	ATP	GTP
25 % 5-Methoxy-UTP + 75 % UTP	50 % 5-Methyl-CTP + 50 % CTP	ATP	GTP
25 % 5-Methoxy-UTP + 75 % UTP	25 % 5-Methyl-CTP + 75 % CTP	ATP	GTP
75 % 5-Methoxy-UTP + 25 % UTP	CTP	ATP	GTP
50 % 5-Methoxy-UTP + 50 % UTP	CTP	ATP	GTP
25 % 5-Methoxy-UTP + 75 % UTP	CTP	ATP	GTP
5-Methoxy-UTP	5-Ethyl-CTP	ATP	GTP
5-Methoxy-UTP	5-Methoxy-CTP	ATP	GTP
5-Methoxy-UTP	5-Ethynyl-CTP	ATP	GTP
5-Methoxy-UTP	CTP	ATP	GTP
5-Methoxy-UTP	5-Methyl-CTP	ATP	GTP
5-Methoxy-UTP	CTP	ATP	GTP
5-Methoxy-UTP	5-Methyl-CTP	ATP	GTP
75 % 5-Methoxy-UTP + 25 % 1-Methyl-pseudo-UTP	5-Methyl-CTP	ATP	GTP
50 % 5-Methoxy-UTP + 50 % 1-Methyl-pseudo-UTP	5-Methyl-CTP	ATP	GTP
25 % 5-Methoxy-UTP + 75 % 1-Methyl-pseudo-UTP	5-Methyl-CTP	ATP	GTP
5-Methoxy-UTP	75 % 5-Methyl-CTP + 25 % CTP	ATP	GTP
5-Methoxy-UTP	50 % 5-Methyl-CTP + 50 % CTP	ATP	GTP
5-Methoxy-UTP	25 % 5-Methyl-CTP + 75 % CTP	ATP	GTP

75 % 5-Methoxy-UTP + 25 % 1-Methyl-pseudo-UTP	75 % 5-Methyl-CTP + 25 % CTP	ATP	GTP
75 % 5-Methoxy-UTP + 25 % 1-Methyl-pseudo-UTP	50 % 5-Methyl-CTP + 50 % CTP	ATP	GTP
75 % 5-Methoxy-UTP + 25 % 1-Methyl-pseudo-UTP	25 % 5-Methyl-CTP + 75 % CTP	ATP	GTP
50 % 5-Methoxy-UTP + 50 % 1-Methyl-pseudo-UTP	75 % 5-Methyl-CTP + 25 % CTP	ATP	GTP
50 % 5-Methoxy-UTP + 50 % 1-Methyl-pseudo-UTP	50 % 5-Methyl-CTP + 50 % CTP	ATP	GTP
50 % 5-Methoxy-UTP + 50 % 1-Methyl-pseudo-UTP	25 % 5-Methyl-CTP + 75 % CTP	ATP	GTP
25 % 5-Methoxy-UTP + 75 % 1-Methyl-pseudo-UTP	75 % 5-Methyl-CTP + 25 % CTP	ATP	GTP
25 % 5-Methoxy-UTP + 75 % 1-Methyl-pseudo-UTP	50 % 5-Methyl-CTP + 50 % CTP	ATP	GTP
25 % 5-Methoxy-UTP + 75 % 1-Methyl-pseudo-UTP	25 % 5-Methyl-CTP + 75 % CTP	ATP	GTP
75 % 5-Methoxy-UTP + 25 % 1-Methyl-pseudo-UTP	CTP	ATP	GTP
50 % 5-Methoxy-UTP + 50 % 1-Methyl-pseudo-UTP	CTP	ATP	GTP
25 % 5-Methoxy-UTP + 75 % 1-Methyl-pseudo-UTP	CTP	ATP	GTP
5-methoxy-UTP	CTP	ATP	GTP
5-methoxy-UTP	CTP	ATP	GTP
5-methoxy-UTP	5-Methyl-CTP	ATP	GTP
5-Methoxy-UTP	CTP	ATP	GTP
5-Methoxy-UTP	5-Methyl-CTP	ATP	GTP
75 % 5-Methoxy-UTP + 25 % UTP	5-Methyl-CTP	ATP	GTP
50 % 5-Methoxy-UTP + 50 % UTP	5-Methyl-CTP	ATP	GTP
25 % 5-Methoxy-UTP + 75 % UTP	5-Methyl-CTP	ATP	GTP
5-Methoxy-UTP	75 % 5-Methyl-CTP + 25 % CTP	ATP	GTP
5-Methoxy-UTP	50 % 5-Methyl-CTP + 50 % CTP	ATP	GTP
5-Methoxy-UTP	25 % 5-Methyl-CTP + 75 % CTP	ATP	GTP
75 % 5-Methoxy-UTP + 25 % UTP	75 % 5-Methyl-CTP + 25 % CTP	ATP	GTP
75 % 5-Methoxy-UTP + 25 % UTP	50 % 5-Methyl-CTP + 50 % CTP	ATP	GTP
75 % 5-Methoxy-UTP + 25 % UTP	25 % 5-Methyl-CTP + 75 % CTP	ATP	GTP
50 % 5-Methoxy-UTP + 50 % UTP	75 % 5-Methyl-CTP + 25 % CTP	ATP	GTP
50 % 5-Methoxy-UTP + 50 % UTP	50 % 5-Methyl-CTP + 50 % CTP	ATP	GTP
50 % 5-Methoxy-UTP + 50 % UTP	25 % 5-Methyl-CTP + 75 % CTP	ATP	GTP

25 % 5-Methoxy-UTP + 75 % UTP	75 % 5-Methyl-CTP + 25 % CTP	ATP	GTP
25 % 5-Methoxy-UTP + 75 % UTP	50 % 5-Methyl-CTP + 50 % CTP	ATP	GTP
25 % 5-Methoxy-UTP + 75 % UTP	25 % 5-Methyl-CTP + 75 % CTP	ATP	GTP
75 % 5-Methoxy-UTP + 25 % UTP	CTP	ATP	GTP
50 % 5-Methoxy-UTP + 50 % UTP	CTP	ATP	GTP
25 % 5-Methoxy-UTP + 75 % UTP	CTP	ATP	GTP
5-Methoxy-UTP	CTP	ATP	GTP
5-Methoxy-UTP	5-Methyl-CTP	ATP	GTP
75 % 5-Methoxy-UTP + 25 % UTP	5-Methyl-CTP	ATP	GTP
50 % 5-Methoxy-UTP + 50 % UTP	5-Methyl-CTP	ATP	GTP
25 % 5-Methoxy-UTP + 75 % UTP	5-Methyl-CTP	ATP	GTP
5-Methoxy-UTP	75 % 5-Methyl-CTP + 25 % CTP	ATP	GTP
5-Methoxy-UTP	50 % 5-Methyl-CTP + 50 % CTP	ATP	GTP
5-Methoxy-UTP	25 % 5-Methyl-CTP + 75 % CTP	ATP	GTP
75 % 5-Methoxy-UTP + 25 % UTP	75 % 5-Methyl-CTP + 25 % CTP	ATP	GTP
75 % 5-Methoxy-UTP + 25 % UTP	50 % 5-Methyl-CTP + 50 % CTP	ATP	GTP
75 % 5-Methoxy-UTP + 25 % UTP	25 % 5-Methyl-CTP + 75 % CTP	ATP	GTP
50 % 5-Methoxy-UTP + 50 % UTP	75 % 5-Methyl-CTP + 25 % CTP	ATP	GTP
50 % 5-Methoxy-UTP + 50 % UTP	50 % 5-Methyl-CTP + 50 % CTP	ATP	GTP
50 % 5-Methoxy-UTP + 50 % UTP	25 % 5-Methyl-CTP + 75 % CTP	ATP	GTP
25 % 5-Methoxy-UTP + 75 % UTP	75 % 5-Methyl-CTP + 25 % CTP	ATP	GTP
25 % 5-Methoxy-UTP + 75 % UTP	50 % 5-Methyl-CTP + 50 % CTP	ATP	GTP
25 % 5-Methoxy-UTP + 75 % UTP	25 % 5-Methyl-CTP + 75 % CTP	ATP	GTP
75 % 5-Methoxy-UTP + 25 % UTP	CTP	ATP	GTP
50 % 5-Methoxy-UTP + 50 % UTP	CTP	ATP	GTP
25 % 5-Methoxy-UTP + 75 % UTP	CTP	ATP	GTP
5-Methoxy-UTP	CTP	ATP	GTP
25 % 5-Methoxy-UTP + 75 % UTP	75 % 5-Methyl-CTP + 25 % CTP	ATP	GTP
25 % 5-Methoxy-UTP + 75 % UTP	50 % 5-Methyl-CTP + 50 % CTP	ATP	GTP
25 % 5-Methoxy-UTP + 75 % UTP	25 % 5-Methyl-CTP + 75 % CTP	ATP	GTP
75 % 5-Methoxy-UTP + 25 % UTP	75 % 5-Methyl-CTP + 25 % CTP	ATP	GTP
5-Methoxy-UTP	CTP	ATP	GTP
25 % 5-Methoxy-UTP + 75 % UTP	75 % 5-Methyl-CTP + 25 % CTP	ATP	GTP
25 % 5-Methoxy-UTP + 75 % UTP	50 % 5-Methyl-CTP + 50 % CTP	ATP	GTP
25 % 5-Methoxy-UTP + 75 % UTP	25 % 5-Methyl-CTP + 75 % CTP	ATP	GTP
75 % 5-Methoxy-UTP + 25 % UTP	75 % 5-Methyl-CTP + 25 % CTP	ATP	GTP

5-Methoxy-UTP	CTP	ATP	GTP
25 % 5-Methoxy-UTP + 75 % UTP	75 % 5-Methyl-CTP + 25 % CTP	ATP	GTP
25 % 5-Methoxy-UTP + 75 % UTP	50 % 5-Methyl-CTP + 50 % CTP	ATP	GTP
25 % 5-Methoxy-UTP + 75 % UTP	25 % 5-Methyl-CTP + 75 % CTP	ATP	GTP
75 % 5-Methoxy-UTP + 25 % UTP	75 % 5-Methyl-CTP + 25 % CTP	ATP	GTP
5-Methoxy-UTP	CTP	ATP	GTP
25 % 5-Methoxy-UTP + 75 % UTP	75 % 5-Methyl-CTP + 25 % CTP	ATP	GTP
25 % 5-Methoxy-UTP + 75 % UTP	50 % 5-Methyl-CTP + 50 % CTP	ATP	GTP
25 % 5-Methoxy-UTP + 75 % UTP	25 % 5-Methyl-CTP + 75 % CTP	ATP	GTP
75 % 5-Methoxy-UTP + 25 % UTP	75 % 5-Methyl-CTP + 25 % CTP	ATP	GTP
5-Methoxy-UTP	CTP	ATP	GTP
25 % 5-Methoxy-UTP + 75 % UTP	75 % 5-Methyl-CTP + 25 % CTP	ATP	GTP
25 % 5-Methoxy-UTP + 75 % UTP	50 % 5-Methyl-CTP + 50 % CTP	ATP	GTP
25 % 5-Methoxy-UTP + 75 % UTP	25 % 5-Methyl-CTP + 75 % CTP	ATP	GTP
75 % 5-Methoxy-UTP + 25 % UTP	75 % 5-Methyl-CTP + 25 % CTP	ATP	GTP
5-Methoxy-UTP	CTP	ATP	GTP
25 % 5-Methoxy-UTP + 75 % UTP	75 % 5-Methyl-CTP + 25 % CTP	ATP	GTP
25 % 5-Methoxy-UTP + 75 % UTP	50 % 5-Methyl-CTP + 50 % CTP	ATP	GTP
25 % 5-Methoxy-UTP + 75 % UTP	25 % 5-Methyl-CTP + 75 % CTP	ATP	GTP
75 % 5-Methoxy-UTP + 25 % UTP	75 % 5-Methyl-CTP + 25 % CTP	ATP	GTP
5-Methoxy-UTP	CTP	ATP	GTP
25 % 5-Methoxy-UTP + 75 % UTP	75 % 5-Methyl-CTP + 25 % CTP	ATP	GTP
25 % 5-Methoxy-UTP + 75 % UTP	50 % 5-Methyl-CTP + 50 % CTP	ATP	GTP
25 % 5-Methoxy-UTP + 75 % UTP	25 % 5-Methyl-CTP + 75 % CTP	ATP	GTP
75 % 5-Methoxy-UTP + 25 % UTP	75 % 5-Methyl-CTP + 25 % CTP	ATP	GTP
5-Methoxy-UTP	5-Fluoro-CTP	ATP	GTP
5-Methoxy-UTP	5-Phenyl-CTP	ATP	GTP
5-Methoxy-UTP	N4-Bz-CTP	ATP	GTP
5-Methoxy-UTP	CTP	N6-Isopentenyl-ATP	GTP
5-Methoxy-UTP	N4-Ac-CTP	ATP	GTP
25 % 5-Methoxy-UTP + 75 % UTP	25 % N4-Ac-CTP + 75 % CTP	ATP	GTP
25 % 5-Methoxy-UTP + 75 % UTP	75 % N4-Ac-CTP + 25 % CTP	ATP	GTP
75 % 5-Methoxy-UTP + 25 % UTP	25 % N4-Ac-CTP + 75 % CTP	ATP	GTP
75 % 5-Methoxy-UTP + 25 % UTP	75 % N4-Ac-CTP + 25 % CTP	ATP	GTP
5-Methoxy-UTP	5-Hydroxymethyl-CTP	ATP	GTP

25 % 5-Methoxy-UTP + 75 % UTP	25 % 5-Hydroxymethyl-CTP + 75 % CTP	ATP	GTP
25 % 5-Methoxy-UTP + 75 % UTP	75 % 5-Hydroxymethyl-CTP + 25 % CTP	ATP	GTP
75 % 5-Methoxy-UTP + 25 % UTP	25 % 5-Hydroxymethyl-CTP + 75 % CTP	ATP	GTP
75 % 5-Methoxy-UTP + 25 % UTP	75 % 5-Hydroxymethyl-CTP + 25 % CTP	ATP	GTP
5-Methoxy-UTP	N4-Methyl CTP	ATP	GTP
25 % 5-Methoxy-UTP + 75 % UTP	25 % N4-Methyl CTP + 75 % CTP	ATP	GTP
25 % 5-Methoxy-UTP + 75 % UTP	75 % N4-Methyl CTP + 25 % CTP	ATP	GTP
75 % 5-Methoxy-UTP + 25 % UTP	25 % N4-Methyl CTP + 75 % CTP	ATP	GTP
75 % 5-Methoxy-UTP + 25 % UTP	75 % N4-Methyl CTP + 25 % CTP	ATP	GTP
5-Methoxy-UTP	5-Trifluoromethyl-CTP	ATP	GTP
25 % 5-Methoxy-UTP + 75 % UTP	25 % 5-Trifluoromethyl-CTP + 75 % CTP	ATP	GTP
25 % 5-Methoxy-UTP + 75 % UTP	75 % 5-Trifluoromethyl-CTP + 25 % CTP	ATP	GTP
75 % 5-Methoxy-UTP + 25 % UTP	25 % 5-Trifluoromethyl-CTP + 75 % CTP	ATP	GTP
75 % 5-Methoxy-UTP + 25 % UTP	75 % 5-Trifluoromethyl-CTP + 25 % CTP	ATP	GTP
5-Methoxy-UTP	5-Bromo-CTP	ATP	GTP
25 % 5-Methoxy-UTP + 75 % UTP	25 % 5-Bromo-CTP + 75 % CTP	ATP	GTP
25 % 5-Methoxy-UTP + 75 % UTP	75 % 5-Bromo-CTP + 25 % CTP	ATP	GTP
75 % 5-Methoxy-UTP + 25 % UTP	25 % 5-Bromo-CTP + 75 % CTP	ATP	GTP
75 % 5-Methoxy-UTP + 25 % UTP	75 % 5-Bromo-CTP + 25 % CTP	ATP	GTP
5-Methoxy-UTP	5-Iodo-CTP	ATP	GTP
25 % 5-Methoxy-UTP + 75 % UTP	25 % 5-Iodo-CTP + 75 % CTP	ATP	GTP
25 % 5-Methoxy-UTP + 75 % UTP	75 % 5-Iodo-CTP + 25 % CTP	ATP	GTP
75 % 5-Methoxy-UTP + 25 % UTP	25 % 5-Iodo-CTP + 75 % CTP	ATP	GTP
75 % 5-Methoxy-UTP + 25 % UTP	75 % 5-Iodo-CTP + 25 % CTP	ATP	GTP
5-Methoxy-UTP	5-Ethyl-CTP	ATP	GTP
25 % 5-Methoxy-UTP + 75 % UTP	25 % 5-Ethyl-CTP + 75 % CTP	ATP	GTP
25 % 5-Methoxy-UTP + 75 % UTP	75 % 5-Ethyl-CTP + 25 % CTP	ATP	GTP
75 % 5-Methoxy-UTP + 25 % UTP	25 % 5-Ethyl-CTP + 75 % CTP	ATP	GTP
75 % 5-Methoxy-UTP + 25 % UTP	75 % 5-Ethyl-CTP + 25 % CTP	ATP	GTP
5-Methoxy-UTP	5-Methoxy-CTP	ATP	GTP
25 % 5-Methoxy-UTP + 75 % UTP	25 % 5-Methoxy-CTP + 75 % CTP	ATP	GTP

25 % 5-Methoxy-UTP + 75 % UTP	75 % 5-Methoxy-CTP + 25 % CTP	ATP	GTP
75 % 5-Methoxy-UTP + 25 % UTP	25 % 5-Methoxy-CTP + 75 % CTP	ATP	GTP
75 % 5-Methoxy-UTP + 25 % UTP	75 % 5-Methoxy-CTP + 25 % CTP	ATP	GTP
5-Methoxy-UTP	5-Ethynyl-CTP	ATP	GTP
25 % 5-Methoxy-UTP + 75 % UTP	25 % 5-Ethynyl-CTP + 75 % CTP	ATP	GTP
25 % 5-Methoxy-UTP + 75 % UTP	75 % 5-Ethynyl-CTP + 25 % CTP	ATP	GTP
75 % 5-Methoxy-UTP + 25 % UTP	25 % 5-Ethynyl-CTP + 75 % CTP	ATP	GTP
75 % 5-Methoxy-UTP + 25 % UTP	75 % 5-Ethynyl-CTP + 25 % CTP	ATP	GTP
5-Methoxy-UTP	5-Pseudo-iso-CTP	ATP	GTP
25 % 5-Methoxy-UTP + 75 % UTP	25 % 5-Pseudo-iso-CTP + 75 % CTP	ATP	GTP
25 % 5-Methoxy-UTP + 75 % UTP	75 % 5-Pseudo-iso-CTP + 25 % CTP	ATP	GTP
75 % 5-Methoxy-UTP + 25 % UTP	25 % 5-Pseudo-iso-CTP + 75 % CTP	ATP	GTP
75 % 5-Methoxy-UTP + 25 % UTP	75 % 5-Pseudo-iso-CTP + 25 % CTP	ATP	GTP
5-Methoxy-UTP	5-Formyl-CTP	ATP	GTP
25 % 5-Methoxy-UTP + 75 % UTP	25 % 5-Formyl-CTP + 75 % CTP	ATP	GTP
25 % 5-Methoxy-UTP + 75 % UTP	75 % 5-Formyl-CTP + 25 % CTP	ATP	GTP
75 % 5-Methoxy-UTP + 25 % UTP	25 % 5-Formyl-CTP + 75 % CTP	ATP	GTP
75 % 5-Methoxy-UTP + 25 % UTP	75 % 5-Formyl-CTP + 25 % CTP	ATP	GTP
5-Methoxy-UTP	5-Aminoallyl-CTP	ATP	GTP
25 % 5-Methoxy-UTP + 75 % UTP	25 % 5-Aminoallyl-CTP + 75 % CTP	ATP	GTP
25 % 5-Methoxy-UTP + 75 % UTP	75 % 5-Aminoallyl-CTP + 25 % CTP	ATP	GTP
75 % 5-Methoxy-UTP + 25 % UTP	25 % 5-Aminoallyl-CTP + 75 % CTP	ATP	GTP
75 % 5-Methoxy-UTP + 25 % UTP	75 % 5-Aminoallyl-CTP + 25 % CTP	ATP	GTP

III. Polynucleotide Architecture

[0318] Traditionally, the basic components of an mRNA molecule include at least a coding region, a 5′UTR, a 3′UTR, a 5′ cap and a poly-A tail. The polynucleotides of the present disclosure can function as mRNA but are distinguished from wild-type mRNA in their functional and/or structural design features that serve, *e.g.,* to overcome existing problems of effective polypeptide production using nucleic-acid based therapeutics.

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In Vitro Transcribed Polynucleotides

[0319] The disclosure also includes an *in vitro* transcribed polynucleotide comprising the polynucleotide described herein, *i.e.*, a polynucleotide comprising an ORF encoding an MCM polypeptide.

[0320] Polynucleotides which are made using only *in vitro* transcription (IVT) enzymatic synthesis methods are referred to as "IVT polynucleotides." Methods of making IVT polynucleotides are known in the art and are described, *e.g.*, in International Publication Nos. WO2013151666, WO2013151667, WO2013151668, WO2013151663, WO2013151669, WO2013151670, WO2013151664, WO2013151665, WO2013151671, WO2013151672 and WO2013151736; the contents of each of which are herein incorporated by reference in their entireties.

[0321] The shortest length of the first region of the primary construct of the IVT polynucleotide can be the length of a nucleic acid sequence that is sufficient to encode for MCM, a fragment thereof, or variant thereof. The length of the first region of the primary construct of the IVT polynucleotide encoding the polypeptide of interest can be greater than about 30 nucleotides in length (*e.g.*, at least or greater than about 2,154, 2,250, 2,500, and 3,000, 4,000, 4,100, 4,200, 4,300, 4,400, 4,500, 4,600, 4,700, 4,800, 4,900, 5,000, 5,100, 5,200, 5,300, 5,400, 5,500, 6,000, 7,000, 8,000, 9,000, 10,000, 20,000, 30,000, 40,000, 50,000, 60,000, 70,000, 80,000, 90,000 or up to and including 100,000 nucleotides).

[0322] In some embodiments, the first and second flanking regions of the IVT polynucleotide can range independently from 15-1,000 nucleotides in length (*e.g.*, greater than 30, 40, 45, 50, 55, 60, 70, 80, 90, 100, 120, 140, 160, 180, 200, 250, 300, 350, 400, 450, 500, 600, 700, 800, 900, 1,000, 1,500, 2,000, 2,500, 3,000, 3,500, 4,000, 4,500, 5,000, 5,500 nucleotides or at least 30, 40, 45, 50, 55, 60, 70, 80, 90, 100, 120, 140, 160, 180, 200, 250, 300, 350, 400, 450, 500, 600, 700, 800, 900, 1,000, 1,500, 2,000, 2,500, 3,000, 3,500, 4,000, 4,500, 5,000, 5,500 nucleotides).

[0323] In some embodiments, the tailing sequence of the IVT polynucleotide can range from absent to 500 nucleotides in length (*e.g.*, at least 60, 70, 80, 90, 120, 140, 160, 180, 200, 250, 300, 350, 400, 450, or 500 nucleotides). Where the tailing region is a polyA tail, the length can be determined in units of or as a function of polyA Binding Protein binding. In this embodiment, the polyA tail is long enough to bind at least 4 monomers of PolyA Binding Protein. PolyA

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Binding Protein monomers bind to stretches of approximately 38 nucleotides. As such, it has been observed that polyA tails of about 80 nucleotides and 160 nucleotides are functional.

[0324] In some embodiments, the capping region of the IVT polynucleotide can comprise a single cap or a series of nucleotides forming the cap. In this embodiment the capping region can be from 1 to 10, *e.g.*, 2-9, 3-8, 4-7, 1-5, 5-10, or at least 2, or 10 or fewer nucleotides in length. In some embodiments, the cap is absent.

[0325] In some embodiments, the first and second operational regions of the IVT polynucleotide can range from 3 to 40, *e.g.*, 5-30, 10-20, 15, or at least 4, or 30 or fewer nucleotides in length and can comprise, in addition to a Start and/or Stop codon, one or more signal and/or restriction sequences.

[0326] In some embodiments, the IVT polynucleotides can be structurally modified or chemically modified. When the IVT polynucleotides are chemically and/or structurally modified, the polynucleotides can be referred to as "modified IVT polynucleotides."

[0327] In some embodiments, if the IVT polynucleotides are chemically modified they can have a uniform chemical modification of all or any of the same nucleoside type or a population of modifications produced by mere downward titration of the same starting modification in all or any of the same nucleoside type, or a measured percent of a chemical modification of all any of the same nucleoside type but with random incorporation, such as where all uridines are replaced by a uridine analog, *e.g.*, pseudouridine or 5-methoxyuridine. In another embodiment, the IVT polynucleotides can have a uniform chemical modification of two, three, or four of the same nucleoside type throughout the entire polynucleotide (such as all uridines and all cytosines, etc. are modified in the same way).

[0328] In some embodiments, the IVT polynucleotide can encode MCM and at least one additional peptide or polypeptide of interest. In another embodiment, the IVT polynucleotide can encode MCM and two or more peptides or polypeptides of interest. Non-limiting examples of peptides or polypeptides of interest include an enzyme and its substrate, a label and its binding molecule, a second messenger and its enzyme or the components of multimeric proteins or complexes.

[0329] In some embodiments, the IVT polynucleotide encodes an MCM protein or a functional fragment thereof. In some embodiments, the IVT polynucleotides of the disclosure comprise any one of the human MCM nucleic acid sequences selected from SEQ ID NOs: 1 to 207, 732 to 765, and 772. In some embodiments, the IVT polynucleotide encodes a human MCM

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or functional fragment thereof comprising at least one amino acid mutation from the wild type sequence. In some embodiments, the IVT polynucleotide encodes an MCM mutant comprising one or more of the point mutations V69, T499, H532, A598, and V671. In some embodiments, the expression of the encoded polypeptide is increased. In some embodiments, the IVT polynucleotide increases MCM expression levels in cells when introduced into those cells, *e.g.*, by 20-50%, at least 20%, at least 25%, at least 30%, at least 35%, at least 40%, at least 45%, or at least 50%.

Chimeric Polynucleotide Architecture

[0330] The disclosure also includes a chimeric polynucleotide comprising the polynucleotide described herein, *i.e.*, a polynucleotide comprising an ORF encoding an MCM polypeptide.

[0331] Polynucleotides which have portions or regions which differ in size and/or chemical modification pattern, chemical modification position, chemical modification percent or chemical modification population and combinations of the foregoing are known as "chimeric polynucleotides." A "chimera" according to the present disclosure is an entity having two or more incongruous or heterogeneous parts or regions. As used herein a "part" or "region" of a polynucleotide is defined as any portion of the polynucleotide which is less than the entire length of the polynucleotide. Chimeric polynucleotides which are modified mRNA molecules are termed "chimeric modified mRNA" or "chimeric mRNA."

[0332] Chimeric polynucleotides have portions or regions that differ in size and/or chemical modification pattern, chemical modification position, chemical modification percent or chemical modification population and combinations of the foregoing.

[0333] Examples of parts or regions, where the chimeric polynucleotide functions as an mRNA and encodes a polypeptide of interest include, but are not limited to, untranslated regions (UTRs, such as the 5' UTR or 3' UTR), coding regions, cap regions, polyA tail regions, start regions, stop regions, signal or target sequence regions, and combinations thereof..

[0334] In some embodiments, the chimeric polynucleotides of the disclosure have a structure comprising Formula I.

$$5' [A_n]_x\text{-}L1\text{-}[B_o]_y\text{-}L2\text{-}[C_p]_z\text{-}L3\ 3'$$

Formula I

wherein:

each of A and B independently comprise a region of linked nucleosides;

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either A or B or both A and B encode MCM as described elsewhere herein;

C is an optional region of linked nucleosides;

at least one of regions A, B, or C is positionally modified, wherein said positionally modified region comprises at least two chemically modified nucleosides of one or more of the same nucleoside type of adenosine, thymidine, guanosine, cytidine, or uridine, and wherein at least two of the chemical modifications of nucleosides of the same type are different chemical modifications;

n, o and p are independently an integer between 15-10,000, representing the number of nucleosides in regions A, B, and C, respectively;

x and y are independently 1-20;

z is 0-5;

L1 and L2 are independently optional linker moieties, said linker moieties being either nucleic acid based or non-nucleic acid based; and

L3 is an optional conjugate or an optional linker moiety, said linker moiety being either nucleic acid based or non-nucleic acid based.

[0335] In some embodiments, at least one of the regions of linked nucleosides of A can comprise a sequence of linked nucleosides that can function as a 5' untranslated region (UTR). The sequence of linked nucleosides can be a natural or synthetic 5' UTR. As a non-limiting example, the chimeric polynucleotide can encode MCM and the sequence of linked nucleosides of A can encode the native 5' UTR of the MCM protein or a non-heterologous 5' UTR such as, but not limited to a synthetic UTR.

[0336] In another embodiment, at least one of the regions of linked nucleosides of A can be a cap region. The cap region can be located 5' to a region of linked nucleosides of A functioning as a 5'UTR. The cap region can comprise at least one cap such as, but not limited to, Cap0, Cap1, ARCA, inosine, N1-methyl-guanosine, 2'fluoro-guanosine, 7-deaza-guanosine, 8-oxo-guanosine, 2-amino-guanosine, LNA-guanosine, 2-azido-guanosine, Cap2 and Cap4.

[0337] In some embodiments, the polynucleotide of the disclosure comprises a Cap1 5'UTR. In some embodiments, a polynucleotide comprises the Cap1 5'UTR, wherein the polynucleotide encodes human MCM or functional fragment thereof. In some embodiments, a polynucleotide comprising 5'UTR sequence, *e.g.,* Cap1, for encoding an MCM protein as disclosed herein increases expression of MCM compared to polynucleotides encoding MCM comprising a different 5'UTR (*e.g.,* Cap0, ARCA, inosine, N1-methyl-guanosine, 2'fluoro-guanosine, 7-deaza-

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guanosine, 8-oxo-guanosine, 2-amino-guanosine, LNA-guanosine, 2-azido-guanosine, Cap2 or Cap4). In some embodiments, polynucleotide comprising the Cap1 5'UTR, increases MCM expression levels in cells when introduced into those cells, *e.g.,* by at least 20%, *e.g.*, at least 20%, at least 25%, at least 35%, or at least 40%.

[0338] In some embodiments, at least one of the regions of linked nucleosides of C can comprise a sequence of linked nucleosides that can function as a 3' UTR. The sequence of linked nucleosides can be a natural or synthetic 3' UTR. As a non-limiting example, the chimeric polynucleotide can encode MCM and the sequence of linked nucleosides of C can encode the native 3' UTR of MCM or a non-heterologous 3' UTR such as, but not limited to a synthetic UTR.

[0339] In some embodiments, at least one of the regions of linked nucleosides of A comprises a sequence of linked nucleosides that functions as a 5' UTR and at least one of the regions of linked nucleosides of C comprises a sequence of linked nucleosides that functions as a 3' UTR. In some embodiments, the 5' UTR and the 3' UTR can be from the same or different species. In another embodiment, the 5' UTR and the 3' UTR can encode the native untranslated regions from different proteins from the same or different species.

[0340] Chimeric polynucleotides, including the parts or regions thereof, of the present disclosure can be classified as hemimers, gapmers, wingmers, or blockmers.

[0341] As used herein, a "hemimer" is a chimeric polynucleotide comprising a region or part that comprises half of one pattern, percent, position or population of a chemical modification(s) and half of a second pattern, percent, position or population of a chemical modification(s). Chimeric polynucleotides of the present disclosure can also comprise hemimer subregions. In some embodiments, a part or region is 50% of one and 50% of another.

[0342] In some embodiments, the entire chimeric polynucleotide can be 50% of one and 50% of the other. Any region or part of any chimeric polynucleotide of the disclosure can be a hemimer. Types of hemimers include pattern hemimers, population hemimers or position hemimers. By definition, hemimers are 50:50 percent hemimers.

[0343] As used herein, a "gapmer" is a chimeric polynucleotide having at least three parts or regions with a gap between the parts or regions. The "gap" can comprise a region of linked nucleosides or a single nucleoside that differs from the chimeric nature of the two parts or regions flanking it. The two parts or regions of a gapmer can be the same or different from each other.

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[0344] As used herein, a "wingmer" is a chimeric polynucleotide having at least three parts or regions with a gap between the parts or regions. Unlike a gapmer, the two flanking parts or regions surrounding the gap in a wingmer are the same in degree or kind. Such similarity can be in the length of number of units of different modifications or in the number of modifications. The wings of a wingmer can be longer or shorter than the gap. The wing parts or regions can be 20, 30, 40, 50, 60 70, 80, 90 or 95% greater or shorter in length than the region that comprises the gap.

[0345] As used herein, a "blockmer" is a patterned polynucleotide where parts or regions are of equivalent size or number and type of modifications. Regions or subregions in a blockmer can be 50, 51, 52, 53, 54, 55, 56, 57, 58, 59, 60, 61 62, 63, 64, 65, 66, 67, 68, 69, 70, 71, 72, 73, 74, 75, 76, 77, 78, 79, 80, 81, 82, 83, 84, 85, 86, 87, 88, 89, 90, 91, 92, 93, 94, 95, 96, 97, 98, 99, 100, 101, 102, 103, 104, 105, 106, 107, 108, 109, 110, 111, 112, 113, 114, 115, 116, 117, 118, 119, 120, 121, 122, 123, 124, 125, 126, 127, 128, 129, 130, 131, 132, 133, 134, 135, 136, 137, 138, 139, 140, 141, 142, 143, 144, 145, 146, 147, 148, 149, 150, 151, 152, 153, 154, 155, 156, 157, 158, 159, 160, 161, 162, 163, 164, 165, 166, 167, 168, 169, 170, 171, 172, 173, 174, 175, 176, 177, 178, 179, 180, 181, 182, 183, 184, 185, 186, 187, 188, 189, 190, 191, 192, 193, 194, 195, 196, 197, 198, 199, 200, 201, 202, 203, 204, 205, 206, 207, 208, 209, 210, 211, 212, 213, 214, 215, 216, 217, 218, 219, 220, 221, 222, 223, 224, 225, 226, 227, 228, 229, 230, 231, 232, 233, 234, 235, 236, 237, 238, 239, 240, 241, 242, 243, 244, 245, 246, 247, 248, 249, 250, 251, 252, 253, 254, 255, 256, 257, 258, 259, 260, 261, 262, 263, 264, 265, 266, 267, 268, 269, 270, 271, 272, 273, 274, 275, 276, 277, 278, 279, 280, 281, 282, 283, 284, 285, 286, 287, 288, 289, 290, 291, 292, 293, 294, 295, 296, 297, 298, 299, 300, 310, 320, 330, 340, 350, 360, 370, 380, 390, 400, 410, 420, 430, 440, 450, 460, 470, 480, 490 or 500, nucleosides long.

[0346] Chimeric polynucleotides, including the parts or regions thereof, of the present disclosure having a chemical modification pattern are referred to as "pattern chimeras." Pattern chimeras can also be referred to as blockmers. Pattern chimeras are those polynucleotides having a pattern of modifications within, across or among regions or parts.

[0347] Patterns of modifications within a part or region are those that start and stop within a defined region. Patterns of modifications across a part or region are those patterns that start in on part or region and end in another adjacent part or region. Patterns of modifications among parts or regions are those that begin and end in one part or region and are repeated in a different part or region, which is not necessarily adjacent to the first region or part.

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[0348] The regions or subregions of pattern chimeras or blockmers can have simple alternating patterns such as ABAB[AB]n where each "A" and each "B" represent different chemical modifications (at least one of the base, sugar or backbone linker), different types of chemical modifications (*e.g.,* naturally occurring and non-naturally occurring), different percentages of modifications or different populations of modifications. The pattern can repeat n number of times where n=3-300. Further, each A or B can represent from 1-2500 units (*e.g.,* nucleosides) in the pattern. Patterns can also be alternating multiples such as AABBAABB[AABB]n (an alternating double multiple) or AAABBBAAABBB[AAABBB]n (an alternating triple multiple) pattern. The pattern can repeat n number of times where n=3-300.

[0349] Different patterns can also be mixed together to form a second order pattern. For example, a single alternating pattern can be combined with a triple alternating pattern to form a second order alternating pattern A'B'. One example would be [ABABAB][AAABBBAAABBB] [ABABAB][AAABBBAAABBB] [ABABAB][AAABBBAAABBB], where [ABABAB] is A' and [AAABBBAAABBB] is B'. In like fashion, these patterns can be repeated n number of times, where n=3-300.

[0350] Patterns can include three or more different modifications to form an ABCABC[ABC]n pattern. These three component patterns can also be multiples, such as AABBCCAABBCC[AABBCC]n and can be designed as combinations with other patterns such as ABCABCAABBCCABCABCAABBCC, and can be higher order patterns.

[0351] Regions or subregions of position, percent, and population modifications need not reflect an equal contribution from each modification type. They can form series such as "1-2-3-4," "1-2-4-8," where each integer represents the number of units of a particular modification type. Alternatively, they can be odd only, such as '1-3-3-1-3-1-5" or even only "2-4-2-4-6-4-8" or a mixture of both odd and even number of units such as "1-3-4-2-5-7-3-3-4".

[0352] Pattern chimeras can vary in their chemical modification by degree (such as those described above) or by kind (*e.g.,* different modifications).

[0353] Chimeric polynucleotides, including the parts or regions thereof, of the present disclosure having at least one region with two or more different chemical modifications of two or more nucleoside members of the same nucleoside type (A, C, G, T, or U) are referred to as "positionally modified" chimeras. Positionally modified chimeras are also referred to herein as "selective placement" chimeras or "selective placement polynucleotides". As the name implies, selective placement refers to the design of polynucleotides that, unlike polynucleotides in the art

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where the modification to any A, C, G, T or U is the same by virtue of the method of synthesis, can have different modifications to the individual As, Cs, Gs, Ts or Us in a polynucleotide or region thereof. For example, in a positionally modified chimeric polynucleotide, there can be two or more different chemical modifications to any of the nucleoside types of As, Cs, Gs, Ts, or Us. There can also be combinations of two or more to any two or more of the same nucleoside type. For example, a positionally modified or selective placement chimeric polynucleotide can comprise 3 different modifications to the population of adenines in the molecule and also have 3 different modifications to the population of cytosines in the construct—all of which can have a unique, non-random, placement.

[0354] Chimeric polynucleotides, including the parts or regions thereof, of the present disclosure having a chemical modification percent are referred to as "percent chimeras." Percent chimeras can have regions or parts that comprise at least 1%, at least 2%, at least 5%, at least 8%, at least 10%, at least 20%, at least 30%, at least 40%, at least 50%, at least 60%, at least 70%, at least 80%, at least 90%, at least 95%, or at least 99% positional, pattern or population of modifications. Alternatively, the percent chimera can be completely modified as to modification position, pattern, or population. The percent of modification of a percent chimera can be split between naturally occurring and non-naturally occurring modifications.

[0355] Chimeric polynucleotides, including the parts or regions thereof, of the present disclosure having a chemical modification population are referred to as "population chimeras." A population chimera can comprise a region or part where nucleosides (their base, sugar or backbone linkage, or combination thereof) have a select population of modifications. Such modifications can be selected from functional populations such as modifications that induce, alter or modulate a phenotypic outcome. For example, a functional population can be a population or selection of chemical modifications that increase the level of a cytokine. Other functional populations can individually or collectively function to decrease the level of one or more cytokines. Use of a selection of these like-function modifications in a chimeric polynucleotide would therefore constitute a "functional population chimera." As used herein, a "functional population chimera" can be one whose unique functional feature is defined by the population of modifications as described above or the term can apply to the overall function of the chimeric polynucleotide itself. For example, as a whole the chimeric polynucleotide can function in a different or superior way as compared to an unmodified or non-chimeric polynucleotide.

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[0356] It should be noted that polynucleotides that have a uniform chemical modification of all of any of the same nucleoside type or a population of modifications produced by mere downward titration of the same starting modification in all of any of the same nucleoside type, or a measured percent of a chemical modification of all any of the same nucleoside type but with random incorporation, such as where all uridines are replaced by a uridine analog, *e.g.*, pseudouridine or 5-methoxyuridine, are not considered chimeric polynucleotides. Likewise, polynucleotides having a uniform chemical modification of two, three, or four of the same nucleoside type throughout the entire polynucleotide (such as all uridines and all cytosines, etc. are modified in the same way) are not considered chimeric polynucleotides. One example of a polynucleotide that is not chimeric is the canonical pseudouridine/5-methyl cytosine modified polynucleotide. These uniform polynucleotides are arrived at entirely via *in vitro* transcription (IVT) enzymatic synthesis; and due to the limitations of the synthesizing enzymes, they contain only one kind of modification at the occurrence of each of the same nucleoside type, *i.e.*, adenosine (A), thymidine (T), guanosine (G), cytidine (C) or uridine (U), found in the polynucleotide. Such polynucleotides can be characterized as IVT polynucleotides.

[0357] The chimeric polynucleotides of the present disclosure can be structurally modified or chemically modified. When the chimeric polynucleotides of the present disclosure are chemically and/or structurally modified, the polynucleotides can be referred to as "modified chimeric polynucleotides."

[0358] In some embodiments, the chimeric polynucleotides can encode two or more peptides or polypeptides of interest. Such peptides or polypeptides of interest include an enzyme and its substrate, a label and its binding molecule, a second messenger and its enzyme, or the components of multimeric proteins or complexes.

[0359] The regions or parts of the chimeric polynucleotides can be separated by a linker or spacer moiety. Such linkers or spaces can be nucleic acid based or non-nucleosidic.

[0360] In some embodiments, the chimeric polynucleotides can include a sequence encoding a self-cleaving peptide described herein, such as, but not limited to, a 2A peptide. The polynucleotide sequence of the 2A peptide in the chimeric polynucleotide can be modified or sequence-optimized by the methods described herein and/or are known in the art.

[0361] Notwithstanding the foregoing, the chimeric polynucleotides of the present disclosure can comprise a region or part that is not positionally modified or not chimeric as defined herein. For example, a region or part of a chimeric polynucleotide can be uniformly modified at one or

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more A, T, C, G, or U, but the polynucleotides will not be uniformly modified throughout the entire region or part.

[0362] Regions or parts of chimeric polynucleotides can be, in some embodiments, from 15-10,000 nucleosides in length and, in some embodiments, a polynucleotide can have from 2-100 different regions or patterns of regions as described herein.

[0363] In some embodiments, chimeric polynucleotides encode one or more polypeptides of interest. In another embodiment, the chimeric polynucleotides are substantially non-coding. In another embodiment, the chimeric polynucleotides have both coding and non-coding regions and parts.

[0364] In some embodiments, regions or subregions of the polynucleotides can range from being absent to 500 nucleotides in length (*e.g.,* at least 60, 70, 80, 90, 100, 110, 120, 130, 140, 150, 160, 170, 180, 190, 200, 250, 300, 350, 400, 450, or 500 nucleotides). Where the region is a polyA tail, the length can be determined in units of, or as a function of, polyA Binding Protein binding. In this embodiment, the polyA tail is long enough to bind at least 4 monomers of PolyA Binding Protein. PolyA Binding Protein monomers bind to stretches of approximately 38 nucleotides. As such, it has been observed that polyA tails of about 80 nucleotides to about 160 nucleotides are functional. The chimeric polynucleotides of the present disclosure that function as an mRNA need not comprise a polyA tail.

[0365] In some embodiments of the present disclosure, chimeric polynucleotides that function as an mRNA have a capping region. The capping region can comprise a single cap or a series of nucleotides forming the cap. In this embodiment the capping region can be from 1 to 10, *e.g.*, 2-9, 3-8, 4-7, 1-5, 5-10, or at least 2, or 10 or fewer nucleotides in length. In some embodiments, the cap is absent.

[0366] The present disclosure contemplates chimeric polynucleotides that are circular or cyclic. As the name implies circular polynucleotides are circular in nature meaning that the termini are joined in some fashion, whether by ligation, covalent bond, common association with the same protein or other molecule or complex or by hybridization.

[0367] Chimeric polynucleotides, formulations and compositions comprising chimeric polynucleotides, and methods of making, using and administering chimeric polynucleotides are also described in International Patent Application No. PCT/US2014/53907, the contents of which is incorporated by reference in its entirety.

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[0368] In some embodiments, the chimeric polynucleotide encodes an MCM protein or a functional fragment thereof. In some embodiments, the chimeric polynucleotides of the disclosure comprise any one of the human MCM nucleic acid sequences selected from SEQ ID NOs: 1-207, 732-765, and 772. In some embodiments, the chimeric polynucleotide encodes a human MCM or functional fragment thereof comprising at least one amino acid mutation from the wild type sequence. In some embodiments, the chimeric polynucleotide encodes an MCM mutant comprising one or more of the point mutations V69, T499, H532, A598, and V671. In some embodiments, the expression of the encoded polypeptide is increased. In some embodiments, the chimeric polynucleotide increases MCM expression levels in cells when introduced into those cells, *e.g.,* by 20-50%, at least 20%, at least 25%, at least 30%, at least 35%, at least 40%, at least 45%, or at least 50%.

Circular Polynucleotide Architecture

[0369] The disclosure also includes a circular polynucleotide comprising the polynucleotide described herein, *i.e.*, a polynucleotide comprising an ORF encoding an MCM polypeptide.

[0370] Polynucleotides that are circular are known as "circular polynucleotides" or "circP." As used herein, "circular polynucleotides" or "circP" means a single stranded circular polynucleotide which acts substantially like, and has the properties of, an RNA. The term "circular" is also meant to encompass any secondary or tertiary configuration of the circP.

[0371] The present disclosure contemplates polynucleotides encoding MCM that are circular or cyclic. As the name implies circular polynucleotides are circular in nature meaning that the termini are joined in some fashion, whether by ligation, covalent bond, common association with the same protein or other molecule or complex or by hybridization.

[0372] The circular polynucleotides or circPs that encode at least one peptide or polypeptide of interest are known as circular RNAs or circRNA. As used herein, "circular RNA" or "circRNA" means a circular polynucleotide that can encode at least one peptide or polypeptide of interest.

[0373] The circPs that comprise at least one sensor sequence and do not encode a peptide or polypeptide of interest are known as circular sponges or circSP. As used herein, "circular sponges," "circular polynucleotide sponges" or "circSP" means a circular polynucleotide that comprises at least one sensor sequence and does not encode a polypeptide of interest.

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[0374] As used herein, "sensor sequence" means a receptor or pseudo-receptor for endogenous nucleic acid binding molecules. Non-limiting examples of sensor sequences include, microRNA binding sites, microRNA seed sequences, microRNA binding sites without the seed sequence, transcription factor binding sites and artificial binding sites engineered to act as pseudo-receptors and portions and fragments thereof.

[0375] The circPs that comprise at least one sensor sequence and encode at least one peptide or polypeptide of interest are known as circular RNA sponges or circRNA-SP. As used herein, "circular RNA sponges" or "circRNA-SP" means a circular polynucleotide that comprises at least one sensor sequence and at least one region encoding at least one peptide or polypeptide of interest.

[0376] As used herein, the term "circular construct" refers to a circular polynucleotide transcript that can act substantially similar to and have properties of a RNA molecule. In some embodiments, the circular construct acts as an mRNA. If the circular construct encodes one or more peptides or polypeptides of interest (*e.g.,* a circRNA or circRNA-SP) then the polynucleotide transcript retains sufficient structural and/or chemical features to allow the polypeptide of interest encoded therein to be translated. Circular constructs can be polynucleotides of the disclosure. When structurally or chemically modified, the construct can be referred to as a modified circP, modified circSP, modified circRNA or modified circRNA-SP.

[0377] Circular polynucleotides, formulations and compositions comprising circular polynucleotides, and methods of making, using and administering circular polynucleotides are also disclosed in International Patent Application No. PCT/US2014/53904 the contents of which is incorporated by reference in its entirety.

[0378] In some embodiments, the circular polynucleotide encodes an MCM protein or a functional fragment thereof. In some embodiments, the circular polynucleotides of the disclosure comprise any one of the human MCM nucleic acid selected from SEQ ID NOs: 1-207, 732-765, and 772. In some embodiments, the circular polynucleotide encodes a human MCM or functional fragment thereof comprising at least one amino acid mutation from the wild type sequence. In some embodiments, the circular polynucleotide encodes an MCM mutant comprising one or more of the point mutations V69, T499, H532, A598, and V671. In some embodiments, the expression of the encoded polypeptide is increased. In some embodiments, the circular polynucleotide increases MCM expression levels in cells when introduced into those cells, *e.g.,*

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by 20-50%, at least 20%, at least 25%, at least 30%, at least 35%, at least 40%, at least 45%, or at least 50%.

Multimers of Polynucleotides

[0379] The disclosure also includes multimers of polynucleotides comprising the polynucleotide described herein, *i.e.*, a polynucleotide comprising an ORF encoding an MCM polypeptide.

[0380] In some embodiments, multiple distinct chimeric polynucleotides and/or IVT polynucleotides can be linked together through the 3′-end using nucleotides that are modified at the 3′-terminus. Chemical conjugation can be used to control the stoichiometry of delivery into cells. For example, the glyoxylate cycle enzymes, isocitrate lyase and malate synthase, can be supplied into cells at a 1:1 ratio to alter cellular fatty acid metabolism. This ratio can be controlled by chemically linking chimeric polynucleotides and/or IVT polynucleotides using a 3′-azido terminated nucleotide on one polynucleotides species and a C5-ethynyl or alkynyl-containing nucleotide on the opposite polynucleotide species. The modified nucleotide is added post-transcriptionally using terminal transferase (New England Biolabs, Ipswich, MA) according to the manufacturer's protocol. After the addition of the 3′-modified nucleotide, the two polynucleotides species can be combined in an aqueous solution, in the presence or absence of copper, to form a new covalent linkage via a click chemistry mechanism as described in the literature.

[0381] In another example, more than two chimeric polynucleotides and/or IVT polynucleotides can be linked together using a functionalized linker molecule. For example, a functionalized saccharide molecule can be chemically modified to contain multiple chemical reactive groups (SH-, NH_2-, N_3, etc…) to react with the cognate moiety on a 3′-functionalized mRNA molecule (*i.e.*, a 3′-maleimide ester, 3′-NHS-ester, alkynyl). The number of reactive groups on the modified saccharide can be controlled in a stoichiometric fashion to directly control the stoichiometric ratio of conjugated chimeric polynucleotides and/or IVT polynucleotides.

[0382] In some embodiments, the chimeric polynucleotides and/or IVT polynucleotides can be linked together in a pattern. The pattern can be a simple alternating pattern such as $CD[CD]_x$ where each "C" and each "D" represent a chimeric polynucleotide, IVT polynucleotide, different chimeric polynucleotides or different IVT polynucleotides. The pattern can repeat x number of

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times, where x= 1-300. Patterns can also be alternating multiples such as CCDD[CCDD] $_x$ (an alternating double multiple) or CCCDDD[CCCDDD] $_x$ (an alternating triple multiple) pattern. The alternating double multiple or alternating triple multiple can repeat x number of times, where x= 1-300.

Conjugates and Combinations of Polynucleotides

[0383] The disclosure also includes conjugates and combinations of polynucleotides comprising the polynucleotide described herein, *i.e.*, a polynucleotide comprising an ORF encoding an MCM polypeptide.

[0384] In order to further enhance protein production, polynucleotides of the present disclosure can be designed to be conjugated to other polynucleotides, dyes, or other agents.

[0385] Conjugation can result in increased stability and/or half-life and can be particularly useful in targeting the polynucleotides to specific sites in the cell, tissue or organism.

[0386] In some embodiments, the polynucleotides can be administered with, conjugated to or further encode one or more of RNAi agents, siRNAs, shRNAs, miRNAs, miRNA binding sites, antisense RNAs, ribozymes, catalytic DNA, tRNA, RNAs that induce triple helix formation, aptamers or vectors, and the like.

Bifunctional Polynucleotides

[0387] The disclosure also includes bifunctional polynucleotides comprising the polynucleotide described herein, *i.e.*, a polynucleotide comprising an ORF encoding an MCM polypeptide.

[0388] In some embodiments of the disclosure are bifunctional polynucleotides (*e.g.*, bifunctional IVT polynucleotides, bifunctional chimeric polynucleotides or bifunctional circular polynucleotides). As the name implies, bifunctional polynucleotides are those having or capable of at least two functions. These molecules are also by convention be referred to as multi-functional.

[0389] The multiple functionalities of bifunctional polynucleotides can be encoded by the RNA (the function cannot manifest until the encoded product is translated) or can be a property of the polynucleotide itself. It can be structural or chemical. Bifunctional modified polynucleotides can comprise a function that is covalently or electrostatically associated with the

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polynucleotides. Further, the two functions can be provided in the context of a complex of a chimeric polynucleotide and another molecule.

[0390] Bifunctional polynucleotides can encode peptides that are anti-proliferative. These peptides can be linear, cyclic, constrained or random coil. They can function as aptamers, signaling molecules, ligands or mimics or mimetics thereof. Anti-proliferative peptides can, as translated, be from 3 to 50 amino acids in length. They can be 5-40, 10-30, or approximately 15 amino acids long. They can be single chain, multichain or branched and can form complexes, aggregates or any multi-unit structure once translated.

Noncoding Polynucleotides

[0391] The disclosure also includes a noncoding polynucleotide comprising the polynucleotide described herein, *i.e.*, a polynucleotide comprising an ORF encoding an MCM polypeptide.

[0392] The polynucleotides described herein can further comprise sequences that are partially or substantially not translatable, *e.g.*, having a noncoding region. As one non-limiting example, the noncoding region can be the first region of the IVT polynucleotide or the circular polynucleotide. Alternatively, the noncoding region can be a region other than the first region. As another non-limiting example, the noncoding region can be the A, B and/or C region of the chimeric polynucleotide.

[0393] Such molecules are generally not translated, but can exert an effect on protein production by one or more of binding to and sequestering one or more translational machinery components such as a ribosomal protein or a transfer RNA (tRNA), thereby effectively reducing protein expression in the cell or modulating one or more pathways or cascades in a cell that in turn alters protein levels. The polynucleotide can contain or encode one or more long noncoding RNA (lncRNA, or lincRNA) or portion thereof, a small nucleolar RNA (sno-RNA), micro RNA (miRNA), small interfering RNA (siRNA) or Piwi-interacting RNA (piRNA). Examples of such lncRNA molecules and RNAi constructs designed to target such lncRNA any of which can be encoded in the polynucleotides are disclosed in International Publication, WO2012/018881 A2, the contents of which are incorporated herein by reference in their entirety.

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Cytotoxic Nucleosides

[0394] In some embodiments, the polynucleotides of the present disclosure (*i.e.*, a polynucleotide comprising an ORF encoding an MCM polypeptide) can further incorporate one or more cytotoxic nucleosides.

Untranslated Regions (UTRs)

[0395] Untranslated regions (UTRs) are nucleic acid sections of a polynucleotide before a start codon (5'UTR) and after a stop codon (3'UTR) that are not translated. In some embodiments, a polynucleotide (e.g., a ribonucleic acid (RNA), e.g., a messenger RNA (mRNA)) of the disclosure comprising an open reading frame (ORF) encoding an MCM polypeptide further comprises UTR (e.g., a 5′UTR or functional fragment thereof, a 3′UTR or functional fragment thereof, or a combination thereof).

[0396] A UTR can be homologous or heterologous to the coding region in a polynucleotide. In some embodiments, the UTR is homologous to the ORF encoding the MCM polypeptide. In some embodiments, the UTR is heterologous to the ORF encoding the MCM polypeptide. In some embodiments, the polynucleotide comprises two or more 5′UTRs or functional fragments thereof, each of which have the same or different nucleotide sequences. In some embodiments, the polynucleotide comprises two or more 3′UTRs or functional fragments thereof, each of which have the same or different nucleotide sequences.

[0397] In some embodiments, the 5′UTR or functional fragment thereof, 3′ UTR or functional fragment thereof, or any combination thereof is sequence optimized.

[0398] In some embodiments, the 5′UTR or functional fragment thereof, 3′ UTR or functional fragment thereof, or any combination thereof comprises at least one chemically modified nucleobase, e.g., 5-methoxyuracil.

[0399] UTRs can have features that provide a regulatory role, e.g., increased or decreased stability, localization and/or translation efficiency. A polynucleotide comprising a UTR can be administered to a cell, tissue, or organism, and one or more regulatory features can be measured using routine methods. In some embodiments, a functional fragment of a 5'UTR or 3'UTR comprises one or more regulatory features of a full length 5' or 3' UTR, respectively.

[0400] Natural 5′UTRs bear features that play roles in translation initiation. They harbor signatures like Kozak sequences that are commonly known to be involved in the process by which the ribosome initiates translation of many genes. Kozak sequences have the consensus

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CCR(A/G)CCAUGG, where R is a purine (adenine or guanine) three bases upstream of the start codon (AUG), which is followed by another 'G'. 5′UTRs also have been known to form secondary structures that are involved in elongation factor binding.

[0401] By engineering the features typically found in abundantly expressed genes of specific target organs, one can enhance the stability and protein production of a polynucleotide. For example, introduction of 5′UTR of liver-expressed mRNA, such as albumin, serum amyloid A, Apolipoprotein A/B/E, transferrin, alpha fetoprotein, erythropoietin, or Factor VIII, can enhance expression of polynucleotides in hepatic cell lines or liver. Likewise, use of 5′UTR from other tissue-specific mRNA to improve expression in that tissue is possible for muscle (e.g., MyoD, Myosin, Myoglobin, Myogenin, Herculin), for endothelial cells (e.g., Tie-1, CD36), for myeloid cells (e.g., C/EBP, AML1, G-CSF, GM-CSF, CD11b, MSR, Fr-1, i-NOS), for leukocytes (e.g., CD45, CD18), for adipose tissue (e.g., CD36, GLUT4, ACRP30, adiponectin) and for lung epithelial cells (e.g., SP-A/B/C/D).

[0402] In some embodiments, UTRs are selected from a family of transcripts whose proteins share a common function, structure, feature or property. For example, an encoded polypeptide can belong to a family of proteins (i.e., that share at least one function, structure, feature, localization, origin, or expression pattern), which are expressed in a particular cell, tissue or at some time during development. The UTRs from any of the genes or mRNA can be swapped for any other UTR of the same or different family of proteins to create a new polynucleotide.

[0403] In some embodiments, the 5'UTR and the 3'UTR can be heterologous. In some embodiments, the 5'UTR can be derived from a different species than the 3'UTR. In some embodiments, the 3'UTR can be derived from a different species than the 5'UTR.

[0404] Co-owned International Patent Application No. PCT/US2014/021522 (Publ. No. WO/2014/164253, incorporated herein by reference in its entirety) provides a listing of exemplary UTRs that can be utilized in the polynucleotide of the present disclosure as flanking regions to an ORF.

[0405] Exemplary UTRs of the application include, but are not limited to, one or more 5′UTR and/or 3′UTR derived from the nucleic acid sequence of: a globin, such as an α- or β-globin (e.g., a *Xenopus*, mouse, rabbit, or human globin); a strong Kozak translational initiation signal; a CYBA (e.g., human cytochrome b-245 α polypeptide); an albumin (e.g., human albumin7); a HSD17B4 (hydroxysteroid (17-β) dehydrogenase); a virus (e.g., a tobacco etch virus (TEV), a Venezuelan equine encephalitis virus (VEEV), a Dengue virus, a cytomegalovirus

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(CMV) (e.g., CMV immediate early 1 (IE1)), a hepatitis virus (e.g., hepatitis B virus), a sindbis virus, or a PAV barley yellow dwarf virus); a heat shock protein (e.g., hsp70); a translation initiation factor (e.g., elF4G); a glucose transporter (e.g., hGLUT1 (human glucose transporter 1)); an actin (e.g., human α or β actin); a GAPDH; a tubulin; a histone; a citric acid cycle enzyme; a topoisomerase (e.g., a 5′UTR of a TOP gene lacking the 5′ TOP motif (the oligopyrimidine tract)); a ribosomal protein Large 32 (L32); a ribosomal protein (e.g., human or mouse ribosomal protein, such as, for example, rps9); an ATP synthase (e.g., ATP5A1 or the β subunit of mitochondrial H^+-ATP synthase); a growth hormone e (e.g., bovine (bGH) or human (hGH)); an elongation factor (e.g., elongation factor 1 α1 (EEF1A1)); a manganese superoxide dismutase (MnSOD); a myocyte enhancer factor 2A (MEF2A); a β-F1-ATPase, a creatine kinase, a myoglobin, a granulocyte-colony stimulating factor (G-CSF); a collagen (e.g., collagen type I, alpha 2 (Col1A2), collagen type I, alpha 1 (Col1A1), collagen type VI, alpha 2 (Col6A2), collagen type VI, alpha 1 (Col6A1)); a ribophorin (e.g., ribophorin I (RPNI)); a low density lipoprotein receptor-related protein (e.g., LRP1); a cardiotrophin-like cytokine factor (e.g., Nnt1); calreticulin (Calr); a procollagen-lysine, 2-oxoglutarate 5-dioxygenase 1 (Plod1); and a nucleobindin (e.g., Nucb1).

[0406] Other exemplary 5' and 3' UTRs include, but are not limited to, those described in Karikó et al., Mol. Ther. 2008 16(11):1833-1840; Karikó et al., Mol. Ther. 2012 20(5):948-953; Karikó et al., Nucleic Acids Res. 2011 39(21):e142; Strong et al., Gene Therapy 1997 4:624-627; Hansson et al., J. Biol. Chem. 2015 290(9):5661-5672; Yu et al., Vaccine 2007 25(10):1701-1711; Cafri et al., Mol. Ther. 2015 23(8):1391-1400; Andries et al., Mol. Pharm. 2012 9(8):2136-2145; Crowley et al., Gene Ther. 2015 Jun 30, doi:10.1038/gt.2015.68; Ramunas et al., FASEB J. 2015 29(5):1930-1939; Wang et al., Curr. Gene Ther. 2015 15(4):428-435; Holtkamp et al., Blood 2006 108(13):4009-4017; Kormann et al., Nat. Biotechnol. 2011 29(2):154-157; Poleganov et al., Hum. Gen. Ther. 2015 26(11):751-766; Warren et al., Cell Stem Cell 2010 7(5):618-630; Mandal and Rossi, Nat. Protoc. 2013 8(3):568-582; Holcik and Liebhaber, PNAS 1997 94(6):2410-2414; Ferizi et al., Lab Chip. 2015 15(17):3561-3571; Thess et al., Mol. Ther. 2015 23(9):1456-1464; Boros et al., PLoS One 2015 10(6):e0131141; Boros et al., J. Photochem. Photobiol. B. 2013 129:93-99; Andries et al., J. Control. Release 2015 217:337–344; Zinckgraf et al., Vaccine 2003 21(15):1640-9; Garneau et al., J. Virol. 2008 82(2):880-892; Holden and Harris, Virology 2004 329(1):119-133; Chiu et al., J. Virol. 2005 79(13):8303-8315; Wang et al., EMBO J. 1997 16(13):4107-4116; Al-Zoghaibi et al., Gene 2007

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391(1-2):130-9; Vivinus et al., Eur. J. Biochem. 2001 268(7):1908-1917; Gan and Rhoads, J. Biol. Chem. 1996 271(2):623-626; Boado et al., J. Neurochem. 1996 67(4):1335-1343; Knirsch and Clerch, Biochem. Biophys. Res. Commun. 2000 272(1):164-168; Chung et al., Biochemistry 1998 37(46):16298-16306; Izquierdo and Cuevza, Biochem. J. 2000 346 Pt 3:849-855; Dwyer et al., J. Neurochem. 1996 66(2):449-458; Black et al., Mol. Cell. Biol. 1997 17(5):2756-2763; Izquierdo and Cuevza, Mol. Cell. Biol. 1997 17(9):5255-5268; US8278036; US8748089; US8835108; US9012219; US2010/0129877; US2011/0065103; US2011/0086904; US2012/0195936; US2014/020675; US2013/0195967; US2014/029490; US2014/0206753; WO2007/036366; WO2011/015347; WO2012/072096; WO2013/143555; WO2014/071963; WO2013/185067; WO2013/182623; WO2014/089486; WO2013/185069; WO2014/144196; WO2014/152659; 2014/152673; WO2014/152940; WO2014/152774; WO2014/153052; WO2014/152966, WO2014/152513; WO2015/101414; WO2015/101415; WO2015/062738; and WO2015/024667; the contents of each of which are incorporated herein by reference in their entirety.

[0407] In some embodiments, the 5'UTR is selected from the group consisting of a β-globin 5'UTR; a 5′UTR containing a strong Kozak translational initiation signal; a cytochrome b-245 α polypeptide (CYBA) 5'UTR; a hydroxysteroid (17-β) dehydrogenase (HSD17B4) 5'UTR; a Tobacco etch virus (TEV) 5'UTR; a Venezuelen equine encephalitis virus (TEEV) 5'UTR; a 5' proximal open reading frame of rubella virus (RV) RNA encoding nonstructural proteins; a Dengue virus (DEN) 5'UTR; a heat shock protein 70 (Hsp70) 5'UTR; a eIF4G 5'UTR; a GLUT1 5'UTR; functional fragments thereof and any combination thereof.

[0408] In some embodiments, the 3'UTR is selected from the group consisting of a β-globin 3'UTR; a CYBA 3'UTR; an albumin 3'UTR; a growth hormone (GH) 3'UTR; a VEEV 3'UTR; a hepatitis B virus (HBV) 3'UTR; α-globin 3′UTR; a DEN 3'UTR; a PAV barley yellow dwarf virus (BYDV-PAV) 3'UTR; an elongation factor 1 α1 (EEF1A1) 3'UTR; a manganese superoxide dismutase (MnSOD) 3'UTR; a β subunit of mitochondrial H(+)-ATP synthase (β-mRNA) 3'UTR; a GLUT1 3'UTR; a MEF2A 3'UTR; a β-F1-ATPase 3'UTR; functional fragments thereof and combinations thereof.

[0409] Other exemplary UTRs include, but are not limited to, one or more of the UTRs, including any combination of UTRs, disclosed in WO2014/164253, the contents of which are incorporated herein by reference in their entirety. Shown in Table 21 of U.S. Provisional Application No. 61/775,509 and in Table 22 of U.S. Provisional Application No. 61/829,372, the

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contents of each are incorporated herein by reference in their entirety, is a listing start and stop sites for 5'UTRs and 3'UTRs. In Table 21, each 5′UTR (5′-UTR-005 to 5′-UTR 68511) is identified by its start and stop site relative to its native or wild-type (homologous) transcript (ENST; the identifier used in the ENSEMBL database).

[0410] Wild-type UTRs derived from any gene or mRNA can be incorporated into the polynucleotides of the disclosure. In some embodiments, a UTR can be altered relative to a wild type or native UTR to produce a variant UTR, e.g., by changing the orientation or location of the UTR relative to the ORF; or by inclusion of additional nucleotides, deletion of nucleotides, swapping or transposition of nucleotides. In some embodiments, variants of 5′ or 3′ UTRs can be utilized, for example, mutants of wild type UTRs, or variants wherein one or more nucleotides are added to or removed from a terminus of the UTR.

[0411] Additionally, one or more synthetic UTRs can be used in combination with one or more non-synthetic UTRs. *See*, e.g., Mandal and Rossi, Nat. Protoc. 2013 8(3):568-82, the contents of which are incorporated herein by reference in their entirety, and sequences available at www.addgene.org/Derrick_Rossi/. UTRs or portions thereof can be placed in the same orientation as in the transcript from which they were selected or can be altered in orientation or location. Hence, a 5′ and/or 3′ UTR can be inverted, shortened, lengthened, or combined with one or more other 5′ UTRs or 3′ UTRs.

[0412] In some embodiments, the polynucleotide comprises multiple UTRs, e.g., a double, a triple or a quadruple 5'UTR or 3'UTR. For example, a double UTR comprises two copies of the same UTR either in series or substantially in series. For example, a double beta-globin 3′UTR can be used (see US2010/0129877, the contents of which are incorporated herein by reference in its entirety).

[0413] **Tables 5** and **6** provide a listing of exemplary UTRs that can be utilized in the polynucleotides of the present disclosure. Shown in **Table 5** is a listing of a 5′-untranslated region of the disclosure. Variants of 5' UTRs can be utilized wherein one or more nucleotides are added or removed to the termini, including A, T, C or G.

Table 5. 5′-Untranslated Regions

5′ UTR Identifier	Name/ Description	Sequence	SEQ ID NO.
5UTR-001	Upstream UTR	GGGAAATAAGAGAGAAAAGAAGAGTAAGAAGAAATAT AAGAGCCACC	215
5UTR-002	Upstream UTR	GGGAGATCAGAGAGAAAAGAAGAGTAAGAAGAAATAT AAGAGCCACC	216

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5UTR-003	Upstream UTR	GGAATAAAAGTCTCAACACAACATATACAAAACAAAC GAATCTCAAGCAATCAAGCATTCTACTTCTATTGCAG CAATTTAAATCATTTCTTTTAAAGCAAAAGCAATTTT CTGAAAATTTTCACCATTTACGAACGATAGCAAC	217
5UTR-004	Upstream UTR	GGGAGACAAGCUUGGCAUUCCGGUACUGUUGGUAAAG CCACC	218
5UTR-005	Upstream UTR	GGGAGATCAGAGAGAAAAGAAGAGTAAGAAGAAATAT AAGAGCCACC	219
5UTR-006	Upstream UTR	GGAATAAAAGTCTCAACACAACATATACAAAACAAAC GAATCTCAAGCAATCAAGCATTCTACTTCTATTGCAG CAATTTAAATCATTTCTTTTAAAGCAAAAGCAATTTT CTGAAAATTTTCACCATTTACGAACGATAGCAAC	220
5UTR-007	Upstream UTR	GGGAGACAAGCUUGGCAUUCCGGUACUGUUGGUAAAG CCACC	221
5UTR-008	Upstream UTR	GGGAATTAACAGAGAAAAGAAGAGTAAGAAGAAATAT AAGAGCCACC	222
5UTR-009	Upstream UTR	GGGAAATTAGACAGAAAAGAAGAGTAAGAAGAAATAT AAGAGCCACC	223
5UTR-010	Upstream UTR	GGGAAATAAGAGAGTAAAGAACAGTAAGAAGAAATAT AAGAGCCACC	224
5UTR-011	Upstream UTR	GGGAAAAAAGAGAGAAAAGAAGACTAAGAAGAAATAT AAGAGCCACC	225
5UTR-012	Upstream UTR	GGGAAATAAGAGAGAAAAGAAGAGTAAGAAGATATAT AAGAGCCACC	226
5UTR-013	Upstream UTR	GGGAAATAAGAGACAAAACAAGAGTAAGAAGAAATAT AAGAGCCACC	227
5UTR-014	Upstream UTR	GGGAAATTAGAGAGTAAAGAACAGTAAGTAGAATTAA AAGAGCCACC	228
5UTR-015	Upstream UTR	GGGAAATAAGAGAGAATAGAAGAGTAAGAAGAAATAT AAGAGCCACC	229
5UTR-016	Upstream UTR	GGGAAATAAGAGAGAAAAGAAGAGTAAGAAGAAAATT AAGAGCCACC	230
5UTR-017	Upstream UTR	GGGAAATAAGAGAGAAAAGAAGAGTAAGAAGAAATTT AAGAGCCACC	231
5UTR-018	Upstream UTR	TCAAGCTTTTGGACCCTCGTACAGAAGCTAATACGAC TCACTATAGGGAAATAAGAGAGAAAAGAAGAGTAAGA AGAAATATAAGAGCCACC	266
142-3p UTR-001	Upstream UTR including miR142-3p	TGATAATAGTCCATAAAGTAGGAAACACTACAGCTGG AGCCTCGGTGGCCATGCTTCTTGCCCCTTGGGCCTCC CCCCAGCCCCTCCTCCCCTTCCTGCACCCGTACCCCC GTGGTCTTTGAATAAAGTCTGAGTGGGCGGC	725
142-3p UTR-002	Upstream UTR including miR142-3p	TGATAATAGGCTGGAGCCTCGGTGGCTCCATAAAGTA GGAAACACTACACATGCTTCTTGCCCCTTGGGCCTCC CCCCAGCCCCTCCTCCCCTTCCTGCACCCGTACCCCC GTGGTCTTTGAATAAAGTCTGAGTGGGCGGC	726
142-3p UTR-003	Upstream UTR including miR142-3p	TGATAATAGGCTGGAGCCTCGGTGGCCATGCTTCTTG CCCCTTCCATAAAGTAGGAAACACTACATGGGCCTCC CCCCAGCCCCTCCTCCCCTTCCTGCACCCGTACCCCC GTGGTCTTTGAATAAAGTCTGAGTGGGCGGC	727
142-3p UTR-004	Upstream UTR including miR142-3p	TGATAATAGGCTGGAGCCTCGGTGGCCATGCTTCTTG CCCCTTGGGCCTCCCCCCAGTCCATAAAGTAGGAAAC ACTACACCCCTCCTCCCCTTCCTGCACCCGTACCCCC GTGGTCTTTGAATAAAGTCTGAGTGGGCGGC	728
142-3p UTR-005	Upstream UTR including miR142-3p	TGATAATAGGCTGGAGCCTCGGTGGCCATGCTTCTTG CCCCTTGGGCCTCCCCCCAGCCCCTCCTCCCCTTCTC CATAAAGTAGGAAACACTACACTGCACCCGTACCCCC GTGGTCTTTGAATAAAGTCTGAGTGGGCGGC	729

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142-3p UTR-006	Upstream UTR including miR142-3p	TGATAATAGGCTGGAGCCTCGGTGGCCATGCTTCTTG CCCCTTGGGCCTCCCCCCAGCCCCTCCTCCCCTTCCT GCACCCGTACCCCCTCCATAAAGTAGGAAACACTACA GTGGTCTTTGAATAAAGTCTGAGTGGGCGGC	730
142-3p UTR-007	Upstream UTR including miR142-3p	TGATAATAGGCTGGAGCCTCGGTGGCCATGCTTCTTG CCCCTTGGGCCTCCCCCCAGCCCCTCCTCCCCTTCCT GCACCCGTACCCCCGTGGTCTTTGAATAAAGTTCCAT AAAGTAGGAAACACTACACTGAGTGGGCGGC	731

[0414] In a particular embodiment, the 5' UTR useful for the polynucleotides comprises SEQ ID NO: 266.

[0415] Shown in **Table 6** is a listing of 3′-untranslated regions of the disclosure. Variants of 3' UTRs can be utilized wherein one or more nucleotides are added or removed to the termini, including A, T, C or G.

Table 6. 3′-Untranslated Regions

3′ UTR Identifier	Name/ Description	Sequence	SEQ ID NO.
3UTR-001	Creatine Kinase	GCGCCTGCCCACCTGCCACCGACTGCTGGAACCCAGCCAGTGG GAGGGCCTGGCCCACCAGAGTCCTGCTCCCTCACTCCTCGCCC CGCCCCCTGTCCCAGAGTCCCACCTGGGGGCTCTCTCCACCCT TCTCAGAGTTCCAGTTTCAACCAGAGTTCCAACCAATGGGCTC CATCCTCTGGATTCTGGCCAATGAAATATCTCCCTGGCAGGGT CCTCTTCTTTTCCCAGAGCTCCACCCCAACCAGGAGCTCTAGT TAATGGAGAGCTCCCAGCACACTCGGAGCTTGTGCTTTGTCTC CACGCAAAGCGATAAATAAAAGCATTGGTGGCCTTTGGTCTTT GAATAAAGCCTGAGTAGGAAGTCTAGA	232
3UTR-002	Myoglobin	GCCCCTGCCGCTCCCACCCCCACCCATCTGGGCCCCGGGTTCA AGAGAGAGCGGGGTCTGATCTCGTGTAGCCATATAGAGTTTGC TTCTGAGTGTCTGCTTTGTTTAGTAGAGGTGGGCAGGAGGAGC TGAGGGGCTGGGGCTGGGGTGTTGAAGTTGGCTTTGCATGCCC AGCGATGCGCCTCCCTGTGGGATGTCATCACCCTGGGAACCGG GAGTGGCCCTTGGCTCACTGTGTTCTGCATGGTTTGGATCTGA ATTAATTGTCCTTTCTTCTAAATCCCAACCGAACTTCTTCCAA CCTCCAAACTGGCTGTAACCCCAAATCCAAGCCATTAACTACA CCTGACAGTAGCAATTGTCTGATTAATCACTGGCCCCTTGAAG ACAGCAGAATGTCCCTTTGCAATGAGGAGGAGATCTGGGCTGG GCGGGCCAGCTGGGGAAGCATTTGACTATCTGGAACTTGTGTG TGCCTCCTCAGGTATGGCAGTGACTCACCTGGTTTTAATAAAA CAACCTGCAACATCTCATGGTCTTTGAATAAAGCCTGAGTAGG AAGTCTAGA	233
3UTR-003	α-actin	ACACACTCCACCTCCAGCACGCGACTTCTCAGGACGACGAATC TTCTCAATGGGGGGGCGGCTGAGCTCCAGCCACCCCGCAGTCA CTTTCTTTGTAACAACTTCCGTTGCTGCCATCGTAAACTGACA CAGTGTTTATAACGTGTACATACATTAACTTATTACCTCATTT TGTTATTTTTCGAAACAAAGCCCTGTGGAAGAAAATGGAAAAC TTGAAGAAGCATTAAAGTCATTCTGTTAAGCTGCGTAAATGGT CTTTGAATAAAGCCTGAGTAGGAAGTCTAGA	234
3UTR-004	Albumin	CATCACATTTAAAAGCATCTCAGCCTACCATGAGAATAAGAGA AAGAAAATGAAGATCAAAAGCTTATTCATCTGTTTTTCTTTTT CGTTGGTGTAAAGCCAACACCCTGTCTAAAAAACATAAATTTC	235

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		TTTAATCATTTTGCCTCTTTTCTCTGTGCTTCAATTAATAAAA AATGGAAAGAATCTAATAGAGTGGTACAGCACTGTTATTTTTC AAAGATGTGTTGCTATCCTGAAAATTCTGTAGGTTCTGTGGAA GTTCCAGTGTTCTCTCTTATTCCACTTCGGTAGAGGATTTCTA GTTTCTTGTGGGCTAATTAAATAAATCATTAATACTCTTCTAA TGGTCTTTGAATAAAGCCTGAGTAGGAAGTCTAGA	
3UTR-005	α-globin	GCTGCCTTCTGCGGGGCTTGCCTTCTGGCCATGCCCTTCTTCT CTCCCTTGCACCTGTACCTCTTGGTCTTTGAATAAAGCCTGAG TAGGAAGGCGGCCGCTCGAGCATGCATCTAGA	236
3UTR-006	G-CSF	GCCAAGCCCTCCCCATCCCATGTATTTATCTCTATTTAATATT TATGTCTATTTAAGCCTCATATTTAAAGACAGGGAAGAGCAGA ACGGAGCCCCAGGCCTCTGTGTCCTTCCCTGCATTTCTGAGTT TCATTCTCCTGCCTGTAGCAGTGAGAAAAAGCTCCTGTCCTCC CATCCCCTGGACTGGGAGGTAGATAGGTAAATACCAAGTATTT ATTACTATGACTGCTCCCCAGCCCTGGCTCTGCAATGGGCACT GGGATGAGCCGCTGTGAGCCCCTGGTCCTGAGGGTCCCCACCT GGGACCCTTGAGAGTATCAGGTCTCCCACGTGGGAGACAAGAA ATCCCTGTTTAATATTTAAACAGCAGTGTTCCCCATCTGGGTC CTTGCACCCCTCACTCTGGCCTCAGCCGACTGCACAGCGGCCC CTGCATCCCCTTGGCTGTGAGGCCCCTGGACAAGCAGAGGTGG CCAGAGCTGGGAGGCATGGCCCTGGGGTCCCACGAATTTGCTG GGGAATCTCGTTTTTCTTCTTAAGACTTTTGGGACATGGTTTG ACTCCCGAACATCACCGACGCGTCTCCTGTTTTTCTGGGTGGC CTCGGGACACCTGCCCTGCCCCCACGAGGGTCAGGACTGTGAC TCTTTTTAGGGCCAGGCAGGTGCCTGGACATTTGCCTTGCTGG ACGGGGACTGGGGATGTGGGAGGGAGCAGACAGGAGGAATCAT GTCAGGCCTGTGTGTGAAAGGAAGCTCCACTGTCACCCTCCAC CTCTTCACCCCCCACTCACCAGTGTCCCCTCCACTGTCACATT GTAACTGAACTTCAGGATAATAAAGTGTTTGCCTCCATGGTCT TTGAATAAAGCCTGAGTAGGAAGGCGGCCGCTCGAGCATGCAT CTAGA	237
3UTR-007	Col1a2; collagen, type I, alpha 2	ACTCAATCTAAATTAAAAAAGAAAGAAATTTGAAAAAACTTTC TCTTTGCCATTTCTTCTTCTTCTTTTTTAACTGAAAGCTGAAT CCTTCCATTTCTTCTGCACATCTACTTGCTTAAATTGTGGGCA AAAGAGAAAAAGAAGGATTGATCAGAGCATTGTGCAATACAGT TTCATTAACTCCTTCCCCCGCTCCCCCAAAAATTTGAATTTTT TTTTCAACACTCTTACACCTGTTATGGAAAATGTCAACCTTTG TAAGAAAACCAAAATAAAAATTGAAAAATAAAAACCATAAACA TTTGCACCACTTGTGGCTTTTGAATATCTTCCACAGAGGGAAG TTTAAAACCCAAACTTCCAAAGGTTTAAACTACCTCAAAACAC TTTCCCATGAGTGTGATCCACATTGTTAGGTGCTGACCTAGAC AGAGATGAACTGAGGTCCTTGTTTTGTTTTGTTCATAATACAA AGGTGCTAATTAATAGTATTTCAGATACTTGAAGAATGTTGAT GGTGCTAGAAGAATTTGAGAAGAAATACTCCTGTATTGAGTTG TATCGTGTGGTGTATTTTTTAAAAAATTTGATTTAGCATTCAT ATTTTCCATCTTATTCCCAATTAAAAGTATGCAGATTATTTGC CCAAATCTTCTTCAGATTCAGCATTTGTTCTTTGCCAGTCTCA TTTTCATCTTCTTCCATGGTTCCACAGAAGCTTTGTTTCTTGG GCAAGCAGAAAAATTAAATTGTACCTATTTTGTATATGTGAGA TGTTTAAATAAATTGTGAAAAAAATGAAATAAAGCATGTTTGG TTTTCCAAAAGAACATAT	238
3UTR-008	Col6a2; collagen, type VI, alpha 2	CGCCGCCGCCCGGGCCCCGCAGTCGAGGGTCGTGAGCCCACCC CGTCCATGGTGCTAAGCGGGCCCGGGTCCCACACGGCCAGCAC CGCTGCTCACTCGGACGACGCCCTGGGCCTGCACCTCTCCAGC TCCTCCCACGGGGTCCCCGTAGCCCCGGCCCCCGCCCAGCCCC AGGTCTCCCCAGGCCCTCCGCAGGCTGCCCGGCCTCCCTCCCC CTGCAGCCATCCCAAGGCTCCTGACCTACCTGGCCCCTGAGCT CTGGAGCAAGCCCTGACCCAATAAAGGCTTTGAACCCAT	239

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3UTR-009	RPN1; ribophorin I	GGGGCTAGAGCCCTCTCCGCACAGCGTGGAGACGGGGCAAGGA GGGGGGTTATTAGGATTGGTGGTTTTGTTTTGCTTTGTTTAAA GCCGTGGGAAAATGGCACAACTTTACCTCTGTGGGAGATGCAA CACTGAGAGCCAAGGGGTGGGAGTTGGGATAATTTTTATATAA AAGAAGTTTTTCCACTTTGAATTGCTAAAAGTGGCATTTTTCC TATGTGCAGTCACTCCTCTCATTTCTAAAATAGGGACGTGGCC AGGCACGGTGGCTCATGCCTGTAATCCCAGCACTTTGGGAGGC CGAGGCAGGCGGCTCACGAGGTCAGGAGATCGAGACTATCCTG GCTAACACGGTAAAACCCTGTCTCTACTAAAAGTACAAAAAAT TAGCTGGGCGTGGTGGTGGGCACCTGTAGTCCCAGCTACTCGG GAGGCTGAGGCAGGAGAAAGGCATGAATCCAAGAGGCAGAGCT TGCAGTGAGCTGAGATCACGCCATTGCACTCCAGCCTGGGCAA CAGTGTTAAGACTCTGTCTCAAATATAAATAAATAAATAAATA AATAAATAAATAAATAAAAATAAAGCGAGATGTTGCCCTCAAA	240
3UTR-010	LRP1; low density lipoprotein receptor-related protein 1	GGCCCTGCCCCGTCGGACTGCCCCCAGAAAGCCTCCTGCCCCC TGCCAGTGAAGTCCTTCAGTGAGCCCCTCCCCAGCCAGCCCTT CCCTGGCCCCGCCGGATGTATAAATGTAAAAATGAAGGAATTA CATTTTATATGTGAGCGAGCAAGCCGGCAAGCGAGCACAGTAT TATTTCTCCATCCCCTCCCTGCCTGCTCCTTGGCACCCCCATG CTGCCTTCAGGGAGACAGGCAGGGAGGGCTTGGGGCTGCACCT CCTACCCTCCCACCAGAACGCACCCCACTGGGAGAGCTGGTGG TGCAGCCTTCCCCTCCCTGTATAAGACACTTTGCCAAGGCTCT CCCCTCTCGCCCCATCCCTGCTTGCCCGCTCCCACAGCTTCCT GAGGGCTAATTCTGGGAAGGGAGAGTTCTTTGCTGCCCCTGTC TGGAAGACGTGGCTCTGGGTGAGGTAGGCGGGAAAGGATGGAG TGTTTTAGTTCTTGGGGGAGGCCACCCCAAACCCCAGCCCCAA CTCCAGGGGCACCTATGAGATGGCCATGCTCAACCCCCCTCCC AGACAGGCCCTCCCTGTCTCCAGGGCCCCCACCGAGGTTCCCA GGGCTGGAGACTTCCTCTGGTAAACATTCCTCCAGCCTCCCCT CCCCTGGGGACGCCAAGGAGGTGGGCCACACCCAGGAAGGGAA AGCGGGCAGCCCCGTTTTGGGGACGTGAACGTTTTAATAATTT TTGCTGAATTCCTTTACAACTAAATAACACAGATATTGTTATA AATAAAATTGT	241
3UTR-011	Nnt1; cardiotrophin-like cytokine factor 1	ATATTAAGGATCAAGCTGTTAGCTAATAATGCCACCTCTGCAG TTTTGGGAACAGGCAAATAAAGTATCAGTATACATGGTGATGT ACATCTGTAGCAAAGCTCTTGGAGAAAATGAAGACTGAAGAAA GCAAAGCAAAAACTGTATAGAGAGATTTTTCAAAAGCAGTAAT CCCTCAATTTTAAAAAAGGATTGAAAATTCTAAATGTCTTTCT GTGCATATTTTTTGTGTTAGGAATCAAAAGTATTTTATAAAAG GAGAAAGAACAGCCTCATTTTAGATGTAGTCCTGTTGGATTTT TTATGCCTCCTCAGTAACCAGAAATGTTTTAAAAAACTAAGTG TTTAGGATTTCAAGACAACATTATACATGGCTCTGAAATATCT GACACAATGTAAACATTGCAGGCACCTGCATTTTATGTTTTTT TTTTCAACAAATGTGACTAATTTGAAACTTTTATGAACTTCTG AGCTGTCCCCTTGCAATTCAACCGCAGTTTGAATTAATCATAT CAAATCAGTTTTAATTTTTTAAATTGTACTTCAGAGTCTATAT TTCAAGGGCACATTTTCTCACTACTATTTTAATACATTAAAGG ACTAAATAATCTTTCAGAGATGCTGGAAACAAATCATTTGCTT TATATGTTTCATTAGAATACCAATGAAACATACAACTTGAAAA TTAGTAATAGTATTTTTGAAGATCCCATTTCTAATTGGAGATC TCTTTAATTTCGATCAACTTATAATGTGTAGTACTATATTAAG TGCACTTGAGTGGAATTCAACATTTGACTAATAAAATGAGTTC ATCATGTTGGCAAGTGATGTGGCAATTATCTCTGGTGACAAAA GAGTAAAATCAAATATTTCTGCCTGTTACAAATATCAAGGAAG ACCTGCTACTATGAAATAGATGACATTAATCTGTCTTCACTGT TTATAATACGGATGGATTTTTTTTCAAATCAGTGTGTGTTTTG AGGTCTTATGTAATTGATGACATTTGAGAGAAATGGTGGCTTT TTTTAGCTACCTCTTTGTTCATTTAAGCACCAGTAAAGATCAT	242

		GTCTTTTTATAGAAGTGTAGATTTTCTTTGTGACTTTGCTATC GTGCCTAAAGCTCTAAATATAGGTGAATGTGTGATGAATACTC AGATTATTTGTCTCTCTATATAATTAGTTTGGTACTAAGTTTC TCAAAAAATTATTAACACATGAAAGACAATCTCTAAACCAGAA AAAGAAGTAGTACAAATTTTGTTACTGTAATGCTCGCGTTTAG TGAGTTTAAAACACACAGTATCTTTTGGTTTTATAATCAGTTT CTATTTTGCTGTGCCTGAGATTAAGATCTGTGTATGTGTGTGT GTGTGTGTGTGCGTTTGTGTGTTAAAGCAGAAAAGACTTTTTT AAAAGTTTTAAGTGATAAATGCAATTTGTTAATTGATCTTAGA TCACTAGTAAACTCAGGGCTGAATTATACCATGTATATTCTAT TAGAAGAAAGTAAACACCATCTTTATTCCTGCCCTTTTTCTTC TCTCAAAGTAGTTGTAGTTATATCTAGAAAGAAGCAATTTTGA TTTCTTGAAAAGGTAGTTCCTGCACTCAGTTTAAACTAAAAAT AATCATACTTGGATTTTATTTATTTTTGTCATAGTAAAAATTT TAATTTATATATATTTTTATTTAGTATTATCTTATTCTTTGCT ATTTGCCAATCCTTTGTCATCAATTGTGTTAAATGAATTGAAA ATTCATGCCCTGTTCATTTTATTTTACTTTATTGGTTAGGATA TTTAAAGGATTTTTGTATATATAATTTCTTAAATTAATATTCC AAAAGGTTAGTGGACTTAGATTATAAATTATGGCAAAAATCTA AAAACAACAAAAATGATTTTTATACATTCTATTTCATTATTCC TCTTTTTCCAATAAGTCATACAATTGGTAGATATGACTTATTT TATTTTTGTATTATTCACTATATCTTTATGATATTTAAGTATA AATAATTAAAAAAATTTATTGTACCTTATAGTCTGTCACCAAA AAAAAAAAATTATCTGTAGGTAGTGAAATGCTAATGTTGATTT GTCTTTAAGGGCTTGTTAACTATCCTTTATTTTCTCATTTGTC TTAAATTAGGAGTTTGTGTTTAAATTACTCATCTAAGCAAAAA ATGTATATAAATCCCATTACTGGGTATATACCCAAAGGATTAT AAATCATGCTGCTATAAAGACACATGCACACGTATGTTTATTG CAGCACTATTCACAATAGCAAAGACTTGGAACCAACCCAAATG TCCATCAATGATAGACTTGATTAAGAAAATGTGCACATATACA CCATGGAATACTATGCAGCCATAAAAAAGGATGAGTTCATGTC CTTTGTAGGGACATGGATAAAGCTGGAAACCATCATTCTGAGC AAACTATTGCAAGGACAGAAAACCAAACACTGCATGTTCTCAC TCATAGGTGGGAATTGAACAATGAGAACACTTGGACACAAGGT GGGGAACACCACACACCAGGGCCTGTCATGGGGTGGGGGGAGT GGGGAGGGATAGCATTAGGAGATATACCTAATGTAAATGATGA GTTAATGGGTGCAGCACACCAACATGGCACATGTATACATATG TAGCAAACCTGCACGTTGTGCACATGTACCCTAGAACTTAAAG TATAATTAAAAAAAAAAAGAAAACAGAAGCTATTTATAAAGAA GTTATTTGCTGAAATAAATGTGATCTTTCCCATTAAAAAAATA AAGAAATTTTGGGGTAAAAAAACACAATATATTGTATTCTTGA AAAATTCTAAGAGAGTGGATGTGAAGTGTTCTCACCACAAAAG TGATAACTAATTGAGGTAATGCACATATTAATTAGAAAGATTT TGTCATTCCACAATGTATATATACTTAAAAATATGTTATACAC AATAAATACATACATTAAAAAATAAGTAAATGTA	
3UTR-012	Col6a1; collagen, type VI, alpha 1	CCCACCCTGCACGCCGGCACCAAACCCTGTCCTCCCACCCCTC CCCACTCATCACTAAACAGAGTAAAATGTGATGCGAATTTTCC CGACCAACCTGATTCGCTAGATTTTTTTTAAGGAAAAGCTTGG AAAGCCAGGACACAACGCTGCTGCCTGCTTTGTGCAGGGTCCT CCGGGGCTCAGCCCTGAGTTGGCATCACCTGCGCAGGGCCCTC TGGGGCTCAGCCCTGAGCTAGTGTCACCTGCACAGGGCCCTCT GAGGCTCAGCCCTGAGCTGGCGTCACCTGTGCAGGGCCCTCTG GGGCTCAGCCCTGAGCTGGCCTCACCTGGGTTCCCCACCCCGG GCTCTCCTGCCCTGCCCTCCTGCCCGCCCTCCCTCCTGCCTGC GCAGCTCCTTCCCTAGGCACCTCTGTGCTGCATCCCACCAGCC TGAGCAAGACGCCCTCTCGGGGCCTGTGCCGCACTAGCCTCCC TCTCCTCTGTCCCCATAGCTGGTTTTTCCCACCAATCCTCACC TAACAGTTACTTTACAATTAAACTCAAAGCAAGCTCTTCTCCT	243

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		CAGCTTGGGGCAGCCATTGGCCTCTGTCTCGTTTTGGGAAACC AAGGTCAGGAGGCCGTTGCAGACATAAATCTCGGCGACTCGGC CCCGTCTCCTGAGGGTCCTGCTGGTGACCGGCCTGGACCTTGG CCCTACAGCCCTGGAGGCCGCTGCTGACCAGCACTGACCCCGA CCTCAGAGAGTACTCGCAGGGGCGCTGGCTGCACTCAAGACCC TCGAGATTAACGGTGCTAACCCCGTCTGCTCCTCCCTCCCGCA GAGACTGGGGCCTGGACTGGACATGAGAGCCCCTTGGTGCCAC AGAGGGCTGTGTCTTACTAGAAACAACGCAAACCTCTCCTTCC TCAGAATAGTGATGTGTTCGACGTTTTATCAAAGGCCCCCTTT CTATGTTCATGTTAGTTTTGCTCCTTCTGTGTTTTTTTCTGAA CCATATCCATGTTGCTGACTTTTCCAAATAAAGGTTTTCACTC CTCTC	
3UTR-013	Calr; calreticulin	AGAGGCCTGCCTCCAGGGCTGGACTGAGGCCTGAGCGCTCCTG CCGCAGAGCTGGCCGCGCCAAATAATGTCTCTGTGAGACTCGA GAACTTTCATTTTTTTCCAGGCTGGTTCGGATTTGGGGTGGAT TTTGGTTTTGTTCCCCTCCTCCACTCTCCCCCACCCCCTCCCC GCCCTTTTTTTTTTTTTTTTTTAAACTGGTATTTTATCTTTGA TTCTCCTTCAGCCCTCACCCCTGGTTCTCATCTTTCTTGATCA ACATCTTTTCTTGCCTCTGTCCCCTTCTCTCATCTCTTAGCTC CCCTCCAACCTGGGGGGCAGTGGTGTGGAGAAGCCACAGGCCT GAGATTTCATCTGCTCTCCTTCCTGGAGCCCAGAGGAGGGCAG CAGAAGGGGGTGGTGTCTCCAACCCCCCAGCACTGAGGAAGAA CGGGGCTCTTCTCATTTCACCCCTCCCTTTCTCCCCTGCCCCC AGGACTGGGCCACTTCTGGGTGGGGCAGTGGGTCCCAGATTGG CTCACACTGAGAATGTAAGAACTACAAACAAAATTTCTATTAA ATTAAATTTTGTGTCTCC	244
3UTR-014	Col1a1; collagen, type I, alpha 1	CTCCCTCCATCCCAACCTGGCTCCCTCCCACCCAACCAACTTT CCCCCCAACCCGGAAACAGACAAGCAACCCAAACTGAACCCCC TCAAAAGCCAAAAAATGGGAGACAATTTCACATGGACTTTGGA AAATATTTTTTTCCTTTGCATTCATCTCTCAAACTTAGTTTTT ATCTTTGACCAACCGAACATGACCAAAAACCAAAAGTGCATTC AACCTTACCAAAAAAAAAAAAAAAAAAAGAATAAATAAATAAC TTTTTAAAAAAGGAAGCTTGGTCCACTTGCTTGAAGACCCATG CGGGGGTAAGTCCCTTTCTGCCCGTTGGGCTTATGAAACCCCA ATGCTGCCCTTTCTGCTCCTTTCTCCACACCCCCCTTGGGGCC TCCCCTCCACTCCTTCCCAAATCTGTCTCCCCAGAAGACACAG GAAACAATGTATTGTCTGCCCAGCAATCAAAGGCAATGCTCAA ACACCCAAGTGGCCCCCACCCTCAGCCCGCTCCTGCCCGCCCA GCACCCCCAGGCCCTGGGGGACCTGGGGTTCTCAGACTGCCAA AGAAGCCTTGCCATCTGGCGCTCCCATGGCTCTTGCAACATCT CCCCTTCGTTTTTGAGGGGGTCATGCCGGGGGAGCCACCAGCC CCTCACTGGGTTCGGAGGAGAGTCAGGAAGGGCCACGACAAAG CAGAAACATCGGATTTGGGGAACGCGTGTCAATCCCTTGTGCC GCAGGGCTGGGCGGGAGAGACTGTTCTGTTCCTTGTGTAACTG TGTTGCTGAAAGACTACCTCGTTCTTGTCTTGATGTGTCACCG GGGCAACTGCCTGGGGGCGGGGATGGGGGCAGGGTGGAAGCGG CTCCCCATTTTATACCAAAGGTGCTACATCTATGTGATGGGTG GGGTGGGGAGGGAATCACTGGTGCTATAGAAATTGAGATGCCC CCCCAGGCCAGCAAATGTTCCTTTTTGTTCAAAGTCTATTTTT ATTCCTTGATATTTTTCTTTTTTTTTTTTTTTTTTGTGGATG GGGACTTGTGAATTTTTCTAAAGGTGCTATTTAACATGGGAGG AGAGCGTGTGCGGCTCCAGCCCAGCCCGCTGCTCACTTTCCAC CCTCTCTCCACCTGCCTCTGGCTTCTCAGGCCTCTGCTCTCCG ACCTCTCTCCTCTGAAACCCTCCTCCACAGCTGCAGCCCATCC TCCCGGCTCCCTCCTAGTCTGTCCTGCGTCCTCTGTCCCCGGG TTTCAGAGACAACTTCCCAAAGCACAAAGCAGTTTTTCCCCCT AGGGGTGGGAGGAAGCAAAAGACTCTGTACCTATTTTGTATGT GTATAATAATTTGAGATGTTTTTAATTATTTTGATTGCTGGAA	245

		TAAAGCATGTGGAAATGACCCAAACATAATCCGCAGTGGCCTC CTAATTTCCTTCTTTGGAGTTGGGGGAGGGGTAGACATGGGGA AGGGGCTTTGGGGTGATGGGCTTGCCTTCCATTCCTGCCCTTT CCCTCCCCACTATTCTCTTCTAGATCCCTCCATAACCCCACTC CCCTTTCTCTCACCCTTCTTATACCGCAAACCTTTCTACTTCC TCTTTCATTTTCTATTCTTGCAATTTCCTTGCACCTTTTCCAA ATCCTCTTCTCCCCTGCAATACCATACAGGCAATCCACGTGCA CAACACACACACACACTCTTCACATCTGGGGTTGTCCAAACCT CATACCCACTCCCCTTCAAGCCCATCCACTCTCCACCCCCTGG ATGCCCTGCACTTGGTGGCGGTGGGATGCTCATGGATACTGGG AGGGTGAGGGGAGTGGAACCCGTGAGGAGGACCTGGGGGCCTC TCCTTGAACTGACATGAAGGGTCATCTGGCCTCTGCTCCCTTC TCACCCACGCTGACCTCCTGCCGAAGGAGCAACGCAACAGGAG AGGGGTCTGCTGAGCCTGGCGAGGGTCTGGGAGGGACCAGGAG GAAGGCGTGCTCCCTGCTCGCTGTCCTGGCCCTGGGGGAGTGA GGGAGACAGACACCTGGGAGAGCTGTGGGGAAGGCACTCGCAC CGTGCTCTTGGGAAGGAAGGAGACCTGGCCCTGCTCACCACGG ACTGGGTGCCTCGACCTCCTGAATCCCCAGAACACAACCCCCC TGGGCTGGGGTGGTCTGGGGAACCATCGTGCCCCCGCCTCCCG CCTACTCCTTTTTAAGCTT	
3UTR-015	Plod1; procollagen-lysine, 2-oxoglutarate 5-dioxygenase 1	TTGGCCAGGCCTGACCCTCTTGGACCTTTCTTCTTTGCCGACA ACCACTGCCCAGCAGCCTCTGGGACCTCGGGGTCCCAGGGAAC CCAGTCCAGCCTCCTGGCTGTTGACTTCCCATTGCTCTTGGAG CCACCAATCAAAGAGATTCAAAGAGATTCCTGCAGGCCAGAGG CGGAACACACCTTTATGGCTGGGGCTCTCCGTGGTGTTCTGGA CCCAGCCCCTGGAGACACCATTCACTTTTACTGCTTTGTAGTG ACTCGTGCTCTCCAACCTGTCTTCCTGAAAAACCAAGGCCCCC TTCCCCCACCTCTTCCATGGGGTGAGACTTGAGCAGAACAGGG GCTTCCCCAAGTTGCCCAGAAAGACTGTCTGGGTGAGAAGCCA TGGCCAGAGCTTCTCCCAGGCACAGGTGTTGCACCAGGGACTT CTGCTTCAAGTTTTGGGGTAAAGACACCTGGATCAGACTCCAA GGGCTGCCCTGAGTCTGGGACTTCTGCCTCCATGGCTGGTCAT GAGAGCAAACCGTAGTCCCCTGGAGACAGCGACTCCAGAGAAC CTCTTGGGAGACAGAAGAGGCATCTGTGCACAGCTCGATCTTC TACTTGCCTGTGGGGAGGGGAGTGACAGGTCCACACACCACAC TGGGTCACCCTGTCCTGGATGCCTCTGAAGAGAGGGACAGACC GTCAGAAACTGGAGAGTTTCTATTAAAGGTCATTTAAACCA	246
3UTR-016	Nucb1; nucleobindin 1	TCCTCCGGGACCCCAGCCCTCAGGATTCCTGATGCTCCAAGGC GACTGATGGGCGCTGGATGAAGTGGCACAGTCAGCTTCCCTGG GGGCTGGTGTCATGTTGGGCTCCTGGGGCGGGGGCACGGCCTG GCATTTCACGCATTGCTGCCACCCCAGGTCCACCTGTCTCCAC TTTCACAGCCTCCAAGTCTGTGGCTCTTCCCTTCTGTCCTCCG AGGGGCTTGCCTTCTCTCGTGTCCAGTGAGGTGCTCAGTGATC GGCTTAACTTAGAGAAGCCCGCCCCCTCCCCTTCTCCGTCTGT CCCAAGAGGGTCTGCTCTGAGCCTGCGTTCCTAGGTGGCTCGG CCTCAGCTGCCTGGGTTGTGGCCGCCCTAGCATCCTGTATGCC CACAGCTACTGGAATCCCCGCTGCTGCTCCGGGCCAAGCTTCT GGTTGATTAATGAGGGCATGGGGTGGTCCCTCAAGACCTTCCC CTACCTTTTGTGGAACCAGTGATGCCTCAAAGACAGTGTCCCC TCCACAGCTGGGTGCCAGGGGCAGGGGATCCTCAGTATAGCCG GTGAACCCTGATACCAGGAGCCTGGGCCTCCCTGAACCCCTGG CTTCCAGCCATCTCATCGCCAGCCTCCTCCTGGACCTCTTGGC CCCCAGCCCCTTCCCCACACAGCCCCAGAAGGGTCCCAGAGCT GACCCCACTCCAGGACCTAGGCCCAGCCCCTCAGCCTCATCTG GAGCCCCTGAAGACCAGTCCCACCCACCTTTCTGGCCTCATCT GACACTGCTCCGCATCCTGCTGTGTGTCCTGTTCCATGTTCCG GTTCCATCCAAATACACTTTCTGGAACAAA	247
3UTR-017	α-globin	GCTGGAGCCTCGGTGGCCATGCTTCTTGCCCCTTGGGCCTCCC	248

		CCCAGCCCCTCCTCCCCTTCCTGCACCCGTACCCCCGTGGTCT TTGAATAAAGTCTGAGTGGGCGGC	
3UTR-018		TGATAATAGGCTGGAGCCTCGGTGGCCATGCTTCTTGCCCCTT GGGCCTCCCCCCAGCCCCTCCTCCCCTTCCTGCACCCGTACCC CCGTGGTCTTTGAATAAAGTCTGAGTGGGCGGC	267
3UTR-019		TGATAATAGTCCATAAAGTAGGAAACACTACAGCTGGAGCCTC GGTGGCCATGCTTCTTGCCCCTTGGGCCTCCCCCCAGCCCCTC CTCCCCTTCCTGCACCCGTACCCCCCGCATTATTACTCACGGT ACGAGTGGTCTTTGAATAAAGTCTGAGTGGGCGGC	773
3UTR-020		TGATAATAGGCTGGAGCCTCGGTGGCCATGCTTCTTGCCCCTT GGGCCTCCCCCCAGCCCCTCCTCCCCTTCCTGCACCCGTACCC CCCGCATTATTACTCACGGTACGAGTGGTCTTTGAATAAAGTC TGAGTGGGCGGC	774

[0416] In certain embodiments, the 3' UTR useful for the polynucleotides comprises SEQ ID NO: 267.

[0417] In certain embodiments, the 5'UTR and/or 3'UTR sequence of the disclosure comprises a nucleotide sequence at least about 60%, at least about 70%, at least about 80%, at least about 90%, at least about 95%, at least about 96%, at least about 97%, at least about 98%, at least about 99%, or about 100% identical to a sequence selected from the group consisting of 5'UTR sequences comprising any of SEQ ID NOs: 215-231 and/or 3'UTR sequences comprises any of SEQ ID NOs: 232-248, and any combination thereof. The polynucleotides of the disclosure can comprise combinations of features. For example, the ORF can be flanked by a 5′UTR that comprises a strong Kozak translational initiation signal and/or a 3′UTR comprising an oligo(dT) sequence for templated addition of a poly-A tail. A 5′UTR can comprise a first polynucleotide fragment and a second polynucleotide fragment from the same and/or different UTRs (see, e.g., US2010/0293625, herein incorporated by reference in its entirety).

[0418] It is also within the scope of the present disclosure to have patterned UTRs. As used herein "patterned UTRs" include a repeating or alternating pattern, such as ABABAB or AABBAABBAABB or ABCABCABC or variants thereof repeated once, twice, or more than 3 times. In these patterns, each letter, A, B, or C represent a different UTR nucleic acid sequence.

[0419] Other non-UTR sequences can be used as regions or subregions within the polynucleotides of the disclosure. For example, introns or portions of intron sequences can be incorporated into the polynucleotides of the disclosure. Incorporation of intronic sequences can increase protein production as well as polynucleotide expression levels. In some embodiments, the polynucleotide of the disclosure comprises an internal ribosome entry site (IRES) instead of or in addition to a UTR (see, e.g., Yakubov et al., Biochem. Biophys. Res. Commun. 2010

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394(1):189-193, the contents of which are incorporated herein by reference in their entirety). In some embodiments, the polynucleotide of the disclosure comprises 5′ and/or 3′ sequence associated with the 5′ and/or 3′ ends of rubella virus (RV) genomic RNA, respectively, or deletion derivatives thereof, including the 5′ proximal open reading frame of RV RNA encoding nonstructural proteins (e.g., see Pogue et al., J. Virol. 67(12):7106-7117, the contents of which are incorporated herein by reference in their entirety). Viral capsid sequences can also be used as a translational enhancer, e.g., the 5′ portion of a capsid sequence, (e.g., semliki forest virus and sindbis virus capsid RNAs as described in Sjöberg et al., Biotechnology (NY) 1994 12(11):1127-1131, and Frolov and Schlesinger J. Virol. 1996 70(2):1182-1190, the contents of each of which are incorporated herein by reference in their entirety). In some embodiments, the polynucleotide comprises an IRES instead of a 5'UTR sequence. In some embodiments, the polynucleotide comprises an ORF and a viral capsid sequence. In some embodiments, the polynucleotide comprises a synthetic 5'UTR in combination with a non-synthetic 3'UTR.

[0420] In some embodiments, the UTR can also include at least one translation enhancer polynucleotide, translation enhancer element, or translational enhancer elements (collectively, "TEE," which refers to nucleic acid sequences that increase the amount of polypeptide or protein produced from a polynucleotide. As a non-limiting example, the TEE can include those described in US2009/0226470, incorporated herein by reference in its entirety, and others known in the art. As a non-limiting example, the TEE can be located between the transcription promoter and the start codon. In some embodiments, the 5'UTR comprises a TEE.

[0421] In one aspect, a TEE is a conserved element in a UTR that can promote translational activity of a nucleic acid such as, but not limited to, cap-dependent or cap-independent translation. The conservation of these sequences has been shown across 14 species including humans. See, e.g., Panek et al., "An evolutionary conserved pattern of 18S rRNA sequence complementarity to mRNA 5′UTRs and its implications for eukaryotic gene translation regulation," Nucleic Acids Research 2013, doi:10.1093/nar/gkt548, incorporated herein by reference in its entirety.

[0422] In one non-limiting example, the TEE comprises the TEE sequence in the 5′-leader of the Gtx homeodomain protein. See Chappell et al., PNAS 2004 101:9590-9594, incorporated herein by reference in its entirety.

[0423] In another non-limiting example, the TEE comprises a TEE having one or more of the sequences of SEQ ID NOs: 1-35 in US2009/0226470, US2013/0177581, and WO2009/075886;

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SEQ ID NOs: 1-5 and 7-645 in WO2012/009644; and SEQ ID NO: 1 WO1999/024595, US6310197, and US6849405; the contents of each of which are incorporated herein by reference in their entirety.

[0424] In some embodiments, the TEE is an internal ribosome entry site (IRES), HCV-IRES, or an IRES element such as, but not limited to, those described in: US7468275, US2007/0048776, US2011/0124100, WO2007/025008, and WO2001/055369; the contents of each of which re incorporated herein by reference in their entirety. The IRES elements can include, but are not limited to, the Gtx sequences (e.g., Gtx9-nt, Gtx8-nt, Gtx7-nt) as described by Chappell et al., PNAS 2004 101:9590-9594, Zhou et al., PNAS 2005 102:6273-6278, US2007/0048776, US2011/0124100, and WO2007/025008; the contents of each of which are incorporated herein by reference in their entirety.

[0425] "Translational enhancer polynucleotide" or "translation enhancer polynucleotide sequence" refer to a polynucleotide that includes one or more of the TEE provided herein and/or known in the art (see. e.g., US6310197, US6849405, US7456273, US7183395, US2009/0226470, US2007/0048776, US2011/0124100, US2009/0093049, US2013/0177581, WO2009/075886, WO2007/025008, WO2012/009644, WO2001/055371, WO1999/024595, EP2610341A1, and EP2610340A1; the contents of each of which are incorporated herein by reference in their entirety), or their variants, homologs, or functional derivatives. In some embodiments, the polynucleotide of the disclosure comprises one or multiple copies of a TEE. The TEE in a translational enhancer polynucleotide can be organized in one or more sequence segments. A sequence segment can harbor one or more of the TEEs provided herein, with each TEE being present in one or more copies. When multiple sequence segments are present in a translational enhancer polynucleotide, they can be homogenous or heterogeneous. Thus, the multiple sequence segments in a translational enhancer polynucleotide can harbor identical or different types of the TEE provided herein, identical or different number of copies of each of the TEE, and/or identical or different organization of the TEE within each sequence segment. In one embodiment, the polynucleotide of the disclosure comprises a translational enhancer polynucleotide sequence.

[0426] In some embodiments, a 5'UTR and/or 3'UTR of a polynucleotide of the disclosure comprises at least one TEE or portion thereof that is disclosed in: WO1999/024595, WO2012/009644, WO2009/075886, WO2007/025008, WO1999/024595, WO2001/055371, EP2610341A1, EP2610340A1, US6310197, US6849405, US7456273, US7183395,

US2009/0226470, US2011/0124100, US2007/0048776, US2009/0093049, or US2013/0177581, the contents of each are incorporated herein by reference in their entirety.

[0427] In some embodiments, a 5'UTR and/or 3'UTR of a polynucleotide of the disclosure comprises a TEE that is at least 5%, at least 10%, at least 15%, at least 20%, at least 25%, at least 30%, at least 35%, at least 40%, at least 45%, at least 50%, at least 55%, at least 60%, at least 65%, at least 70%, at least 75%, at least 80%, at least 85%, at least 90%, at least 95%, at least 96%, at least 97%, at least 98%, at least 99%, or 100% identical to a TEE disclosed in: US2009/0226470, US2007/0048776, US2013/0177581, US2011/0124100, WO1999/024595, WO2012/009644, WO2009/075886, WO2007/025008, EP2610341A1, EP2610340A1, US6310197, US6849405, US7456273, US7183395, Chappell et al., PNAS 2004 101:9590-9594, Zhou et al., PNAS 2005 102:6273-6278, and Supplemental Table 1 and in Supplemental Table 2 of Wellensiek et al., "Genome-wide profiling of human cap-independent translation-enhancing elements," Nature Methods 2013, DOI:10.1038/NMETH.2522; the contents of each of which are incorporated herein by reference in their entirety.

[0428] In some embodiments, a 5'UTR and/or 3'UTR of a polynucleotide of the disclosure comprises a TEE which is selected from a 5-30 nucleotide fragment, a 5-25 nucleotide fragment, a 5-20 nucleotide fragment, a 5-15 nucleotide fragment, or a 5-10 nucleotide fragment (including a fragment of 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 26, 27, 28, 29, or 30 nucleotides) of a TEE sequence disclosed in: US2009/0226470, US2007/0048776, US2013/0177581, US2011/0124100, WO1999/024595, WO2012/009644, WO2009/075886, WO2007/025008, EP2610341A1, EP2610340A1, US6310197, US6849405, US7456273, US7183395, Chappell et al., PNAS 2004 101:9590-9594, Zhou et al., PNAS 2005 102:6273-6278, and Supplemental Table 1 and in Supplemental Table 2 of Wellensiek et al., "Genome-wide profiling of human cap-independent translation-enhancing elements," Nature Methods 2013, DOI:10.1038/NMETH.2522.

[0429] In some embodiments, a 5'UTR and/or 3'UTR of a polynucleotide of the disclosure comprises a TEE which is a transcription regulatory element described in any of US7456273, US7183395, US2009/0093049, and WO2001/055371, the contents of each of which are incorporated herein by reference in their entirety. The transcription regulatory elements can be identified by methods known in the art, such as, but not limited to, the methods described in US7456273, US7183395, US2009/0093049, and WO2001/055371.

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[0430] In some embodiments, a 5′UTR and/or 3'UTR comprising at least one TEE described herein can be incorporated in a monocistronic sequence such as, but not limited to, a vector system or a nucleic acid vector. As non-limiting examples, the vector systems and nucleic acid vectors can include those described in US7456273, US7183395, US2007/0048776, US2009/0093049, US2011/0124100, WO2007/025008, and WO2001/055371.

[0431] In some embodiments, a 5′UTR and/or 3′UTR of a polynucleotide of the disclosure comprises a TEE or portion thereof described herein. In some embodiments, the TEEs in the 3′UTR can be the same and/or different from the TEE located in the 5′UTR.

[0432] In some embodiments, a 5'UTR and/or 3'UTR of a polynucleotide of the disclosure can include at least 1, at least 2, at least 3, at least 4, at least 5, at least 6, at least 7, at least 8, at least 9, at least 10, at least 11, at least 12, at least 13, at least 14, at least 15, at least 16, at least 17, at least 18 at least 19, at least 20, at least 21, at least 22, at least 23, at least 24, at least 25, at least 30, at least 35, at least 40, at least 45, at least 50, at least 55 or more than 60 TEE sequences. In one embodiment, the 5′UTR of a polynucleotide of the disclosure can include 1-60, 1-55, 1-50, 1-45, 1-40, 1-35, 1-30, 1-25, 1-20, 1-15, 1-10, 9, 8, 7, 6, 5, 4, 3, 2, or 1 TEE sequences. The TEE sequences in the 5′UTR of the polynucleotide of the disclosure can be the same or different TEE sequences. A combination of different TEE sequences in the 5′UTR of the polynucleotide of the disclosure can include combinations in which more than one copy of any of the different TEE sequences are incorporated. The TEE sequences can be in a pattern such as ABABAB or AABBAABBAABB or ABCABCABC or variants thereof repeated one, two, three, or more than three times. In these patterns, each letter, A, B, or C represent a different TEE nucleotide sequence.

[0433] In some embodiments, the TEE can be identified by the methods described in US2007/0048776, US2011/0124100, WO2007/025008, WO2012/009644, the contents of each of which are incorporated herein by reference in their entirety.

[0434] In some embodiments, the 5′UTR and/or 3'UTR comprises a spacer to separate two TEE sequences. As a non-limiting example, the spacer can be a 15 nucleotide spacer and/or other spacers known in the art. As another non-limiting example, the 5′UTR and/or 3'UTR comprises a TEE sequence-spacer module repeated at least once, at least twice, at least 3 times, at least 4 times, at least 5 times, at least 6 times, at least 7 times, at least 8 times, at least 9 times, at least 10 times, or more than 10 times in the 5′UTR and/or 3'UTR, respectively. In some

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embodiments, the 5′UTR and/or 3'UTR comprises a TEE sequence-spacer module repeated 1, 2, 3, 4, 5, 6, 7, 8, 9, or 10 times.

[0435] In some embodiments, the spacer separating two TEE sequences can include other sequences known in the art that can regulate the translation of the polynucleotide of the disclosure, e.g., miR sequences described herein (e.g., miR binding sites and miR seeds). As a non-limiting example, each spacer used to separate two TEE sequences can include a different miR sequence or component of a miR sequence (e.g., miR seed sequence).

[0436] In some embodiments, a polynucleotide of the disclosure comprises a miR and/or TEE sequence. In some embodiments, the incorporation of a miR sequence and/or a TEE sequence into a polynucleotide of the disclosure can change the shape of the stem loop region, which can increase and/or decrease translation. See e.g., Kedde et al., Nature Cell Biology 2010 12(10):1014-20, herein incorporated by reference in its entirety).

Sensor Sequences and MicroRNA (miRNA) Binding Sites

[0437] Polynucleotides of the disclosure can include regulatory elements, for example, microRNA (miRNA) binding sites, transcription factor binding sites, structured mRNA sequences and/or motifs, artificial binding sites engineered to act as pseudo-receptors for endogenous nucleic acid binding molecules, and combinations thereof. In some embodiments, polynucleotides including such regulatory elements are referred to as including "sensor sequences". Non-limiting examples of sensor sequences are described in U.S. Publication 2014/0200261, the contents of which are incorporated herein by reference in their entirety.

[0438] In some embodiments, a polynucleotide (e.g., a ribonucleic acid (RNA), e.g., a messenger RNA (mRNA)) of the disclosure comprises an open reading frame (ORF) encoding a polypeptide of interest and further comprises one or more miRNA binding site(s). Inclusion or incorporation of miRNA binding site(s) provides for regulation of polynucleotides of the disclosure, and in turn, of the polypeptides encoded therefrom, based on tissue-specific and/or cell-type specific expression of naturally-occurring miRNAs.

[0439] A miRNA, e.g., a natural-occurring miRNA, is a 19-25 nucleotide long noncoding RNA that binds to a polynucleotide and down-regulates gene expression either by reducing stability or by inhibiting translation of the polynucleotide. A miRNA sequence comprises a "seed" region, i.e., a sequence in the region of positions 2-8 of the mature miRNA. A miRNA

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seed can comprise positions 2-8 or 2-7 of the mature miRNA. In some embodiments, a miRNA seed can comprise 7 nucleotides (e.g., nucleotides 2-8 of the mature miRNA), wherein the seed-complementary site in the corresponding miRNA binding site is flanked by an adenosine (A) opposed to miRNA position 1. In some embodiments, a miRNA seed can comprise 6 nucleotides (e.g., nucleotides 2-7 of the mature miRNA), wherein the seed-complementary site in the corresponding miRNA binding site is flanked by an adenosine (A) opposed to miRNA position 1. See, for example, Grimson A, Farh KK, Johnston WK, Garrett-Engele P, Lim LP, Bartel DP; Mol Cell. 2007 Jul 6;27(1):91-105. miRNA profiling of the target cells or tissues can be conducted to determine the presence or absence of miRNA in the cells or tissues. In some embodiments, a polynucleotide (e.g., a ribonucleic acid (RNA), e.g., a messenger RNA (mRNA)) of the disclosure comprises one or more microRNA binding sites, microRNA target sequences, microRNA complementary sequences, or microRNA seed complementary sequences. Such sequences can correspond to, e.g., have complementarity to, any known microRNA such as those taught in US Publication US2005/0261218 and US Publication US2005/0059005, the contents of each of which are incorporated herein by reference in their entirety.

[0440] As used herein, the term "microRNA (miRNA or miR) binding site" refers to a sequence within a polynucleotide, e.g., within a DNA or within an RNA transcript, including in the 5′UTR and/or 3′UTR, that has sufficient complementarity to all or a region of a miRNA to interact with, associate with or bind to the miRNA. In some embodiments, a polynucleotide of the disclosure comprising an ORF encoding a polypeptide of interest and further comprises one or more miRNA binding site(s). In exemplary embodiments, a 5'UTR and/or 3'UTR of the polynucleotide (e.g., a ribonucleic acid (RNA), e.g., a messenger RNA (mRNA)) comprises the one or more miRNA binding site(s).

[0441] A miRNA binding site having sufficient complementarity to a miRNA refers to a degree of complementarity sufficient to facilitate miRNA-mediated regulation of a polynucleotide, e.g., miRNA-mediated translational repression or degradation of the polynucleotide. In exemplary aspects of the disclosure, a miRNA binding site having sufficient complementarity to the miRNA refers to a degree of complementarity sufficient to facilitate miRNA-mediated degradation of the polynucleotide, e.g., miRNA-guided RNA-induced silencing complex (RISC)-mediated cleavage of mRNA. The miRNA binding site can have complementarity to, for example, a 19-25 nucleotide miRNA sequence, to a 19-23 nucleotide miRNA sequence, or to a 22 nucleotide miRNA sequence. A miRNA binding site can be

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complementary to only a portion of a miRNA, e.g., to a portion less than 1, 2, 3, or 4 nucleotides of the full length of a naturally-occurring miRNA sequence. Full or complete complementarity (e.g., full complementarity or complete complementarity over all or a significant portion of the length of a naturally-occurring miRNA) is preferred when the desired regulation is mRNA degradation.

[0442] In some embodiments, a miRNA binding site includes a sequence that has complementarity (e.g., partial or complete complementarity) with an miRNA seed sequence. In some embodiments, the miRNA binding site includes a sequence that has complete complementarity with a miRNA seed sequence. In some embodiments, a miRNA binding site includes a sequence that has complementarity (e.g., partial or complete complementarity) with an miRNA sequence. In some embodiments, the miRNA binding site includes a sequence that has complete complementarity with a miRNA sequence. In some embodiments, a miRNA binding site has complete complementarity with a miRNA sequence but for 1, 2, or 3 nucleotide substitutions, terminal additions, and/or truncations.

[0443] In some embodiments, the miRNA binding site is the same length as the corresponding miRNA. In other embodiments, the miRNA binding site is one, two, three, four, five, six, seven, eight, nine, ten, eleven or twelve nucleotide(s) shorter than the corresponding miRNA at the 5' terminus, the 3' terminus, or both. In still other embodiments, the microRNA binding site is two nucleotides shorter than the corresponding microRNA at the 5' terminus, the 3' terminus, or both. The miRNA binding sites that are shorter than the corresponding miRNAs are still capable of degrading the mRNA incorporating one or more of the miRNA binding sites or preventing the mRNA from translation.

[0444] In some embodiments, the miRNA binding site binds the corresponding mature miRNA that is part of an active RISC containing Dicer. In another embodiment, binding of the miRNA binding site to the corresponding miRNA in RISC degrades the mRNA containing the miRNA binding site or prevents the mRNA from being translated. In some embodiments, the miRNA binding site has sufficient complementarity to miRNA so that a RISC complex comprising the miRNA cleaves the polynucleotide comprising the miRNA binding site. In other embodiments, the miRNA binding site has imperfect complementarity so that a RISC complex comprising the miRNA induces instability in the polynucleotide comprising the miRNA binding site. In another embodiment, the miRNA binding site has imperfect complementarity so that a

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RISC complex comprising the miRNA represses transcription of the polynucleotide comprising the miRNA binding site.

[0445] In some embodiments, the miRNA binding site has one, two, three, four, five, six, seven, eight, nine, ten, eleven or twelve mismatch(es) from the corresponding miRNA.

[0446] In some embodiments, the miRNA binding site has at least about ten, at least about eleven, at least about twelve, at least about thirteen, at least about fourteen, at least about fifteen, at least about sixteen, at least about seventeen, at least about eighteen, at least about nineteen, at least about twenty, or at least about twenty-one contiguous nucleotides complementary to at least about ten, at least about eleven, at least about twelve, at least about thirteen, at least about fourteen, at least about fifteen, at least about sixteen, at least about seventeen, at least about eighteen, at least about nineteen, at least about twenty, or at least about twenty-one, respectively, contiguous nucleotides of the corresponding miRNA, .

[0447] By engineering one or more miRNA binding sites into a polynucleotide of the disclosure, the polynucleotide can be targeted for degradation or reduced translation, provided the miRNA in question is available. This can reduce off-target effects upon delivery of the polynucleotide. For example, if a polynucleotide of the disclosure is not intended to be delivered to a tissue or cell but ends up is said tissue or cell, then a miRNA abundant in the tissue or cell can inhibit the expression of the gene of interest if one or multiple binding sites of the miRNA are engineered into the 5′UTR and/or 3′UTR of the polynucleotide.

[0448] Conversely, miRNA binding sites can be removed from polynucleotide sequences in which they naturally occur in order to increase protein expression in specific tissues. For example, a binding site for a specific miRNA can be removed from a polynucleotide to improve protein expression in tissues or cells containing the miRNA.

[0449] In one embodiment, a polynucleotide of the disclosure can include at least one miRNA-binding site in the 5'UTR and/or 3′UTR in order to regulate cytotoxic or cytoprotective mRNA therapeutics to specific cells such as, but not limited to, normal and/or cancerous cells. In another embodiment, a polynucleotide of the disclosure can include two, three, four, five, six, seven, eight, nine, ten, or more miRNA-binding sites in the 5'-UTR and/or 3′-UTR in order to regulate cytotoxic or cytoprotective mRNA therapeutics to specific cells such as, but not limited to, normal and/or cancerous cells.

[0450] Regulation of expression in multiple tissues can be accomplished through introduction or removal of one or more miRNA binding sites, e.g., one or more distinct miRNA

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binding sites. The decision whether to remove or insert a miRNA binding site can be made based on miRNA expression patterns and/or their profilings in tissues and/or cells in development and/or disease. Identification of miRNAs, miRNA binding sites, and their expression patterns and role in biology have been reported (e.g., Bonauer et al., Curr Drug Targets 2010 11:943-949; Anand and Cheresh Curr Opin Hematol 2011 18:171-176; Contreras and Rao Leukemia 2012 26:404-413 (2011 Dec 20. doi: 10.1038/leu.2011.356); Bartel Cell 2009 136:215-233; Landgraf et al, Cell, 2007 129:1401-1414; Gentner and Naldini, Tissue Antigens. 2012 80:393-403 and all references therein; each of which is incorporated herein by reference in its entirety).

[0451] miRNAs and miRNA binding sites can correspond to any known sequence, including non-limiting examples described in U.S. Publication Nos. 2014/0200261, 2005/0261218, and 2005/0059005, each of which are incorporated herein by reference in their entirety.

[0452] Examples of tissues where miRNA are known to regulate mRNA, and thereby protein expression, include, but are not limited to, liver (miR-122), muscle (miR-133, miR-206, miR-208), endothelial cells (miR-17-92, miR-126), myeloid cells (miR-142-3p, miR-142-5p, miR-16, miR-21, miR-223, miR-24, miR-27), adipose tissue (let-7, miR-30c), heart (miR-1d, miR-149), kidney (miR-192, miR-194, miR-204), and lung epithelial cells (let-7, miR-133, miR-126).

[0453] Specifically, miRNAs are known to be differentially expressed in immune cells (also called hematopoietic cells), such as antigen presenting cells (APCs) (e.g., dendritic cells and macrophages), macrophages, monocytes, B lymphocytes, T lymphocytes, granulocytes, natural killer cells, etc. Immune cell specific miRNAs are involved in immunogenicity, autoimmunity, the immune-response to infection, inflammation, as well as unwanted immune response after gene therapy and tissue/organ transplantation. Immune cells specific miRNAs also regulate many aspects of development, proliferation, differentiation and apoptosis of hematopoietic cells (immune cells). For example, miR-142 and miR-146 are exclusively expressed in immune cells, particularly abundant in myeloid dendritic cells. It has been demonstrated that the immune response to a polynucleotide can be shut-off by adding miR-142 binding sites to the 3′-UTR of the polynucleotide, enabling more stable gene transfer in tissues and cells. miR-142 efficiently degrades exogenous polynucleotides in antigen presenting cells and suppresses cytotoxic elimination of transduced cells (e.g., Annoni A et al., blood, 2009, 114, 5152-5161; Brown BD, et al., Nat med. 2006, 12(5), 585-591; Brown BD, et al., blood, 2007, 110(13): 4144-4152, each of which is incorporated herein by reference in its entirety).

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[0454] An antigen-mediated immune response can refer to an immune response triggered by foreign antigens, which, when entering an organism, are processed by the antigen presenting cells and displayed on the surface of the antigen presenting cells. T cells can recognize the presented antigen and induce a cytotoxic elimination of cells that express the antigen.

[0455] Introducing a miR-142 binding site into the 5'UTR and/or 3'UTR of a polynucleotide of the disclosure can selectively repress gene expression in antigen presenting cells through miR-142 mediated degradation, limiting antigen presentation in antigen presenting cells (e.g., dendritic cells) and thereby preventing antigen-mediated immune response after the delivery of the polynucleotide. The polynucleotide is then stably expressed in target tissues or cells without triggering cytotoxic elimination.

[0456] In one embodiment, binding sites for miRNAs that are known to be expressed in immune cells, in particular, antigen presenting cells, can be engineered into a polynucleotide of the disclosure to suppress the expression of the polynucleotide in antigen presenting cells through miRNA mediated RNA degradation, subduing the antigen-mediated immune response. Expression of the polynucleotide is maintained in non-immune cells where the immune cell specific miRNAs are not expressed. For example, in some embodiments, to prevent an immunogenic reaction against a liver specific protein, any miR-122 binding site can be removed and a miR-142 (and/or mirR-146) binding site can be engineered into the 5'UTR and/or 3'UTR of a polynucleotide of the disclosure.

[0457] To further drive the selective degradation and suppression in APCs and macrophage, a polynucleotide of the disclosure can include a further negative regulatory element in the 5'UTR and/or 3'UTR, either alone or in combination with miR-142 and/or miR-146 binding sites. As a non-limiting example, the further negative regulatory element is a Constitutive Decay Element (CDE).

[0458] Immune cell specific miRNAs include, but are not limited to, hsa-let-7a-2-3p, hsa-let-7a-3p, hsa-7a-5p, hsa-let-7c, hsa-let-7e-3p, hsa-let-7e-5p, hsa-let-7g-3p, hsa-let-7g-5p, hsa-let-7i-3p, hsa-let-7i-5p, miR-10a-3p, miR-10a-5p, miR-1184, hsa-let-7f-1--3p, hsa-let-7f-2--5p, hsa-let-7f-5p, miR-125b-1-3p, miR-125b-2-3p, miR-125b-5p, miR-1279, miR-130a-3p, miR-130a-5p, miR-132-3p, miR-132-5p, miR-142-3p, miR-142-5p, miR-143-3p, miR-143-5p, miR-146a-3p, miR-146a-5p, miR-146b-3p, miR-146b-5p, miR-147a, miR-147b, miR-148a-5p, miR-148a-3p, miR-150-3p, miR-150-5p, miR-151b, miR-155-3p, miR-155-5p, miR-15a-3p, miR-15a-5p, miR-15b-5p, miR-15b-3p, miR-16-1-3p, miR-16-2-3p, miR-16-5p, miR-17-5p, miR-181a-3p,

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miR-181a-5p, miR-181a-2-3p, miR-182-3p, miR-182-5p, miR-197-3p, miR-197-5p, miR-21-5p, miR-21-3p, miR-214-3p, miR-214-5p, miR-223-3p, miR-223-5p, miR-221-3p, miR-221-5p, miR-23b-3p, miR-23b-5p, miR-24-1-5p,miR-24-2-5p, miR-24-3p, miR-26a-1-3p, miR-26a-2-3p, miR-26a-5p, miR-26b-3p, miR-26b-5p, miR-27a-3p, miR-27a-5p, miR-27b-3p,miR-27b-5p, miR-28-3p, miR-28-5p, miR-2909, miR-29a-3p, miR-29a-5p, miR-29b-1-5p, miR-29b-2-5p, miR-29c-3p, miR-29c-5p,, miR-30e-3p, miR-30e-5p, miR-331-5p, miR-339-3p, miR-339-5p, miR-345-3p, miR-345-5p, miR-346, miR-34a-3p, miR-34a-5p, , miR-363-3p, miR-363-5p, miR-372, miR-377-3p, miR-377-5p, miR-493-3p, miR-493-5p, miR-542, miR-548b-5p, miR548c-5p, miR-548i, miR-548j, miR-548n, miR-574-3p, miR-598, miR-718, miR-935, miR-99a-3p, miR-99a-5p, miR-99b-3p, and miR-99b-5p. Furthermore, novel miRNAs can be identified in immune cell through micro-array hybridization and microtome analysis (e.g., Jima DD et al, Blood, 2010, 116:e118-e127; Vaz C et al., BMC Genomics, 2010, 11,288, the content of each of which is incorporated herein by reference in its entirety.)

[0459] miRNAs that are known to be expressed in the liver include, but are not limited to, miR-107, miR-122-3p, miR-122-5p, miR-1228-3p, miR-1228-5p, miR-1249, miR-129-5p, miR-1303, miR-151a-3p, miR-151a-5p, miR-152, miR-194-3p, miR-194-5p, miR-199a-3p, miR-199a-5p, miR-199b-3p, miR-199b-5p, miR-296-5p, miR-557, miR-581, miR-939-3p, and miR-939-5p. MiRNA binding sites from any liver specific miRNA can be introduced to or removed from a polynucleotide of the disclosure to regulate expression of the polynucleotide in the liver. Liver specific miRNA binding sites can be engineered alone or further in combination with immune cell (e.g., APC) miRNA binding sites in a polynucleotide of the disclosure.

[0460] miRNAs that are known to be expressed in the lung include, but are not limited to, let-7a-2-3p, let-7a-3p, let-7a-5p, miR-126-3p, miR-126-5p, miR-127-3p, miR-127-5p, miR-130a-3p, miR-130a-5p, miR-130b-3p, miR-130b-5p, miR-133a, miR-133b, miR-134, miR-18a-3p, miR-18a-5p, miR-18b-3p, miR-18b-5p, miR-24-1-5p, miR-24-2-5p, miR-24-3p, miR-296-3p, miR-296-5p, miR-32-3p, miR-337-3p, miR-337-5p, miR-381-3p, and miR-381-5p. miRNA binding sites from any lung specific miRNA can be introduced to or removed from a polynucleotide of the disclosure to regulate expression of the polynucleotide in the lung. Lung specific miRNA binding sites can be engineered alone or further in combination with immune cell (e.g., APC) miRNA binding sites in a polynucleotide of the disclosure.

[0461] miRNAs that are known to be expressed in the heart include, but are not limited to, miR-1, miR-133a, miR-133b, miR-149-3p, miR-149-5p, miR-186-3p, miR-186-5p, miR-208a,

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miR-208b, miR-210, miR-296-3p, miR-320, miR-451a, miR-451b, miR-499a-3p, miR-499a-5p, miR-499b-3p, miR-499b-5p, miR-744-3p, miR-744-5p, miR-92b-3p, and miR-92b-5p. mMiRNA binding sites from any heart specific microRNA can be introduced to or removed from a polynucleotide of the disclosure to regulate expression of the polynucleotide in the heart. Heart specific miRNA binding sites can be engineered alone or further in combination with immune cell (e.g., APC) miRNA binding sites in a polynucleotide of the disclosure.

[0462] miRNAs that are known to be expressed in the nervous system include, but are not limited to, miR-124-5p, miR-125a-3p, miR-125a-5p, miR-125b-1-3p, miR-125b-2-3p, miR-125b-5p,miR-1271-3p, miR-1271-5p, miR-128, miR-132-5p, miR-135a-3p, miR-135a-5p, miR-135b-3p, miR-135b-5p, miR-137, miR-139-5p, miR-139-3p, miR-149-3p, miR-149-5p, miR-153, miR-181c-3p, miR-181c-5p, miR-183-3p, miR-183-5p, miR-190a, miR-190b, miR-212-3p, miR-212-5p, miR-219-1-3p, miR-219-2-3p, miR-23a-3p, miR-23a-5p,miR-30a-5p, miR-30b-3p, miR-30b-5p, miR-30c-1-3p, miR-30c-2-3p, miR-30c-5p, miR-30d-3p, miR-30d-5p, miR-329, miR-342-3p, miR-3665, miR-3666, miR-380-3p, miR-380-5p, miR-383, miR-410, miR-425-3p, miR-425-5p, miR-454-3p, miR-454-5p, miR-483, miR-510, miR-516a-3p, miR-548b-5p, miR-548c-5p, miR-571, miR-7-1-3p, miR-7-2-3p, miR-7-5p, miR-802, miR-922, miR-9-3p, and miR-9-5p. miRNAs enriched in the nervous system further include those specifically expressed in neurons, including, but not limited to, miR-132-3p, miR-132-3p, miR-148b-3p, miR-148b-5p, miR-151a-3p, miR-151a-5p, miR-212-3p, miR-212-5p, miR-320b, miR-320e, miR-323a-3p, miR-323a-5p, miR-324-5p, miR-325, miR-326, miR-328, miR-922 and those specifically expressed in glial cells, including, but not limited to, miR-1250, miR-219-1-3p, miR-219-2-3p, miR-219-5p, miR-23a-3p, miR-23a-5p, miR-3065-3p, miR-3065-5p, miR-30e-3p, miR-30e-5p, miR-32-5p, miR-338-5p, and miR-657. miRNA binding sites from any CNS specific miRNA can be introduced to or removed from a polynucleotide of the disclosure to regulate expression of the polynucleotide in the nervous system. Nervous system specific miRNA binding sites can be engineered alone or further in combination with immune cell (e.g., APC) miRNA binding sites in a polynucleotide of the disclosure.

[0463] miRNAs that are known to be expressed in the pancreas include, but are not limited to, miR-105-3p, miR-105-5p, miR-184, miR-195-3p, miR-195-5p, miR-196a-3p, miR-196a-5p, miR-214-3p, miR-214-5p, miR-216a-3p, miR-216a-5p, miR-30a-3p, miR-33a-3p, miR-33a-5p, miR-375, miR-7-1-3p, miR-7-2-3p, miR-493-3p, miR-493-5p, and miR-944. MiRNA binding sites from any pancreas specific miRNA can be introduced to or removed from a polynucleotide

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of the disclosure to regulate expression of the polynucleotide in the pancreas. Pancreas specific miRNA binding sites can be engineered alone or further in combination with immune cell (e.g. APC) miRNA binding sites in a polynucleotide of the disclosure.

[0464] miRNAs that are known to be expressed in the kidney include, but are not limited to, miR-122-3p, miR-145-5p, miR-17-5p, miR-192-3p, miR-192-5p, miR-194-3p, miR-194-5p, miR-20a-3p, miR-20a-5p, miR-204-3p, miR-204-5p, miR-210, miR-216a-3p, miR-216a-5p, miR-296-3p, miR-30a-3p, miR-30a-5p, miR-30b-3p, miR-30b-5p, miR-30c-1-3p, miR-30c-2-3p, miR30c-5p, miR-324-3p, miR-335-3p, miR-335-5p, miR-363-3p, miR-363-5p, and miR-562. miRNA binding sites from any kidney specific miRNA can be introduced to or removed from a polynucleotide of the disclosure to regulate expression of the polynucleotide in the kidney. Kidney specific miRNA binding sites can be engineered alone or further in combination with immune cell (e.g., APC) miRNA binding sites in a polynucleotide of the disclosure.

[0465] miRNAs that are known to be expressed in the muscle include, but are not limited to, let-7g-3p, let-7g-5p, miR-1, miR-1286, miR-133a, miR-133b, miR-140-3p, miR-143-3p, miR-143-5p, miR-145-3p, miR-145-5p, miR-188-3p, miR-188-5p, miR-206, miR-208a, miR-208b, miR-25-3p, and miR-25-5p. MiRNA binding sites from any muscle specific miRNA can be introduced to or removed from a polynucleotide of the disclosure to regulate expression of the polynucleotide in the muscle. Muscle specific miRNA binding sites can be engineered alone or further in combination with immune cell (e.g., APC) miRNA binding sites in a polynucleotide of the disclosure.

[0466] miRNAs are also differentially expressed in different types of cells, such as, but not limited to, endothelial cells, epithelial cells, and adipocytes.

[0467] miRNAs that are known to be expressed in endothelial cells include, but are not limited to, let-7b-3p, let-7b-5p, miR-100-3p, miR-100-5p, miR-101-3p, miR-101-5p, miR-126-3p, miR-126-5p, miR-1236-3p, miR-1236-5p, miR-130a-3p, miR-130a-5p, miR-17-5p, miR-17-3p, miR-18a-3p, miR-18a-5p, miR-19a-3p, miR-19a-5p, miR-19b-1-5p, miR-19b-2-5p, miR-19b-3p, miR-20a-3p, miR-20a-5p, miR-217, miR-210, miR-21-3p, miR-21-5p, miR-221-3p, miR-221-5p, miR-222-3p, miR-222-5p, miR-23a-3p, miR-23a-5p, miR-296-5p, miR-361-3p, miR-361-5p, miR-421, miR-424-3p, miR-424-5p, miR-513a-5p, miR-92a-1-5p, miR-92a-2-5p, miR-92a-3p, miR-92b-3p, and miR-92b-5p. Many novel miRNAs are discovered in endothelial cells from deep-sequencing analysis (e.g., Voellenkle C et al., RNA, 2012, 18, 472-484, herein incorporated by reference in its entirety). miRNA binding sites from any endothelial cell specific

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miRNA can be introduced to or removed from a polynucleotide of the disclosure to regulate expression of the polynucleotide in the endothelial cells.

[0468] miRNAs that are known to be expressed in epithelial cells include, but are not limited to, let-7b-3p, let-7b-5p, miR-1246, miR-200a-3p, miR-200a-5p, miR-200b-3p, miR-200b-5p, miR-200c-3p, miR-200c-5p, miR-338-3p, miR-429, miR-451a, miR-451b, miR-494, miR-802 and miR-34a, miR-34b-5p, miR-34c-5p, miR-449a, miR-449b-3p, miR-449b-5p specific in respiratory ciliated epithelial cells, let-7 family, miR-133a, miR-133b, miR-126 specific in lung epithelial cells, miR-382-3p, miR-382-5p specific in renal epithelial cells, and miR-762 specific in corneal epithelial cells. miRNA binding sites from any epithelial cell specific miRNA can be introduced to or removed from a polynucleotide of the disclosure to regulate expression of the polynucleotide in the epithelial cells.

[0469] In addition, a large group of miRNAs are enriched in embryonic stem cells, controlling stem cell self-renewal as well as the development and/or differentiation of various cell lineages, such as neural cells, cardiac, hematopoietic cells, skin cells, osteogenic cells and muscle cells (e.g., Kuppusamy KT et al., Curr. Mol Med, 2013, 13(5), 757-764; Vidigal JA and Ventura A, Semin Cancer Biol. 2012, 22(5-6), 428-436; Goff LA et al., PLoS One, 2009, 4:e7192; Morin RD et al., Genome Res,2008,18, 610-621; Yoo JK et al., Stem Cells Dev. 2012, 21(11), 2049-2057, each of which is herein incorporated by reference in its entirety). MiRNAs abundant in embryonic stem cells include, but are not limited to, let-7a-2-3p, let-a-3p, let-7a-5p, let7d-3p, let-7d-5p, miR-103a-2-3p, miR-103a-5p, miR-106b-3p, miR-106b-5p, miR-1246, miR-1275, miR-138-1-3p, miR-138-2-3p, miR-138-5p, miR-154-3p, miR-154-5p, miR-200c-3p, miR-200c-5p, miR-290, miR-301a-3p, miR-301a-5p, miR-302a-3p, miR-302a-5p, miR-302b-3p, miR-302b-5p, miR-302c-3p, miR-302c-5p, miR-302d-3p, miR-302d-5p, miR-302e, miR-367-3p, miR-367-5p, miR-369-3p, miR-369-5p, miR-370, miR-371, miR-373, miR-380-5p, miR-423-3p, miR-423-5p, miR-486-5p, miR-520c-3p, miR-548e, miR-548f, miR-548g-3p, miR-548g-5p, miR-548i, miR-548k, miR-548l, miR-548m, miR-548n, miR-548o-3p, miR-548o-5p, miR-548p, miR-664a-3p, miR-664a-5p, miR-664b-3p, miR-664b-5p, miR-766-3p, miR-766-5p, miR-885-3p, miR-885-5p,miR-93-3p, miR-93-5p, miR-941,miR-96-3p, miR-96-5p, miR-99b-3p and miR-99b-5p. Many predicted novel miRNAs are discovered by deep sequencing in human embryonic stem cells (e.g., Morin RD et al., Genome Res,2008,18, 610-621; Goff LA et al., PLoS One, 2009, 4:e7192; Bar M et al., Stem cells, 2008, 26, 2496-2505, the content of each of which is incorporated herein by reference in its entirety).

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[0470] In one embodiment, the binding sites of embryonic stem cell specific miRNAs can be included in or removed from the 3'UTR of a polynucleotide of the disclosure to modulate the development and/or differentiation of embryonic stem cells, to inhibit the senescence of stem cells in a degenerative condition (e.g. degenerative diseases), or to stimulate the senescence and apoptosis of stem cells in a disease condition (e.g. cancer stem cells).

[0471] Many miRNA expression studies are conducted to profile the differential expression of miRNAs in various cancer cells/tissues and other diseases. Some miRNAs are abnormally over-expressed in certain cancer cells and others are under-expressed. For example, miRNAs are differentially expressed in cancer cells (WO2008/154098, US2013/0059015, US2013/0042333, WO2011/157294); cancer stem cells (US2012/0053224); pancreatic cancers and diseases (US2009/0131348, US2011/0171646, US2010/0286232, US8389210); asthma and inflammation (US8415096); prostate cancer (US2013/0053264); hepatocellular carcinoma (WO2012/151212, US2012/0329672, WO2008/054828, US8252538); lung cancer cells (WO2011/076143, WO2013/033640, WO2009/070653, US2010/0323357); cutaneous T cell lymphoma (WO2013/011378); colorectal cancer cells (WO2011/0281756, WO2011/076142); cancer positive lymph nodes (WO2009/100430, US2009/0263803); nasopharyngeal carcinoma (EP2112235); chronic obstructive pulmonary disease (US2012/0264626, US2013/0053263); thyroid cancer (WO2013/066678); ovarian cancer cells (US2012/0309645, WO2011/095623); breast cancer cells (WO2008/154098, WO2007/081740, US2012/0214699), leukemia and lymphoma (WO2008/073915, US2009/0092974, US2012/0316081, US2012/0283310, WO2010/018563, the content of each of which is incorporated herein by reference in its entirety.)

[0472] As a non-limiting example, miRNA binding sites for miRNAs that are over-expressed in certain cancer and/or tumor cells can be removed from the 3'UTR of a polynucleotide of the disclosure, restoring the expression suppressed by the over-expressed miRNAs in cancer cells, thus ameliorating the corresponsive biological function, for instance, transcription stimulation and/or repression, cell cycle arrest, apoptosis and cell death. Normal cells and tissues, wherein miRNAs expression is not up-regulated, will remain unaffected.

[0473] miRNA can also regulate complex biological processes such as angiogenesis (e.g., miR-132) (Anand and Cheresh Curr Opin Hematol 2011 18:171-176). In the polynucleotides of the disclosure, miRNA binding sites that are involved in such processes can be removed or introduced, in order to tailor the expression of the polynucleotides to biologically relevant cell

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types or relevant biological processes. In this context, the polynucleotides of the disclosure are defined as auxotrophic polynucleotides.

[0474] In some embodiments, a polynucleotide of the disclosure comprises a miRNA binding site, wherein the miRNA binding site comprises one or more nucleotide sequences selected from **Table 7**, including one or more copies of any one or more of the miRNA binding site sequences. In some embodiments, a polynucleotide of the disclosure further comprises at least one, two, three, four, five, six, seven, eight, nine, ten, or more of the same or different miRNA binding sites selected from **Table 7**, including any combination thereof. In some embodiments, the miRNA binding site binds to miR-142 or is complementary to miR-142. In some embodiments, the miR-142 comprises SEQ ID NO: 720. In some embodiments, the miRNA binding site binds to miR-142-3p or miR-142-5p. In some embodiments, the miR-142-3p binding site comprises SEQ ID NO: 721. In some embodiments, the miR-142-5p binding site comprises SEQ ID NO: 723. In some embodiments, the miRNA binding site comprises a nucleotide sequence at least 80%, at least 85%, at least 90%, at least 95%, or 100% identical to SEQ ID NO: 722 or SEQ ID NO: 724.

Table 7. miR-142 and miR-142 binding sites

SEQ ID NO.	Description	Sequence
720	miR-142	GACAGUGCAGUCACCCAUAAAGUAGAAAGCA CUACUAACAGCACUGGAGGGUGUAGUGUUUC CUACUUUAUGGAUGAGUGUACUGUG
721	miR-142-3p	UGUAGUGUUUCCUACUUUAUGGA
722	miR-142-3p binding site	UCCAUAAAGUAGGAAACACUACA
723	miR-142-5p	CAUAAAGUAGAAAGCACUACU
724	miR-142-5p binding site	AGUAGUGCUUUCUACUUUAUG

[0475] In some embodiments, a miRNA binding site is inserted in the polynucleotide of the disclosure in any position of the polynucleotide (e.g., the 5'UTR and/or 3'UTR). In some embodiments, the 5'UTR comprises a miRNA binding site. In some embodiments, the 3'UTR comprises a miRNA binding site. In some embodiments, the 5'UTR and the 3'UTR comprise a miRNA binding site. The insertion site in the polynucleotide can be anywhere in the polynucleotide as long as the insertion of the miRNA binding site in the polynucleotide does not

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interfere with the translation of a functional polypeptide in the absence of the corresponding miRNA; and in the presence of the miRNA, the insertion of the miRNA binding site in the polynucleotide and the binding of the miRNA binding site to the corresponding miRNA are capable of degrading the polynucleotide or preventing the translation of the polynucleotide.

[0476] In some embodiments, a miRNA binding site is inserted in at least about 30 nucleotides downstream from the stop codon of an ORF in a polynucleotide of the disclosure comprising the ORF. In some embodiments, a miRNA binding site is inserted in at least about 10 nucleotides, at least about 15 nucleotides, at least about 20 nucleotides, at least about 25 nucleotides, at least about 30 nucleotides, at least about 35 nucleotides, at least about 40 nucleotides, at least about 45 nucleotides, at least about 50 nucleotides, at least about 55 nucleotides, at least about 60 nucleotides, at least about 65 nucleotides, at least about 70 nucleotides, at least about 75 nucleotides, at least about 80 nucleotides, at least about 85 nucleotides, at least about 90 nucleotides, at least about 95 nucleotides, or at least about 100 nucleotides downstream from the stop codon of an ORF in a polynucleotide of the disclosure. In some embodiments, a miRNA binding site is inserted in about 10 nucleotides to about 100 nucleotides, about 20 nucleotides to about 90 nucleotides, about 30 nucleotides to about 80 nucleotides, about 40 nucleotides to about 70 nucleotides, about 50 nucleotides to about 60 nucleotides, about 45 nucleotides to about 65 nucleotides downstream from the stop codon of an ORF in a polynucleotide of the disclosure.

[0477] miRNA gene regulation can be influenced by the sequence surrounding the miRNA such as, but not limited to, the species of the surrounding sequence, the type of sequence (e.g., heterologous, homologous, exogenous, endogenous, or artificial), regulatory elements in the surrounding sequence and/or structural elements in the surrounding sequence. The miRNA can be influenced by the 5′UTR and/or 3′UTR. As a non-limiting example, a non-human 3′UTR can increase the regulatory effect of the miRNA sequence on the expression of a polypeptide of interest compared to a human 3′UTR of the same sequence type.

[0478] In one embodiment, other regulatory elements and/or structural elements of the 5′UTR can influence miRNA mediated gene regulation. One example of a regulatory element and/or structural element is a structured IRES (Internal Ribosome Entry Site) in the 5′UTR, which is necessary for the binding of translational elongation factors to initiate protein translation. EIF4A2 binding to this secondarily structured element in the 5′-UTR is necessary for miRNA mediated gene expression (Meijer HA et al., Science, 2013, 340, 82-85, herein

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incorporated by reference in its entirety). The polynucleotides of the disclosure can further include this structured 5′UTR in order to enhance microRNA mediated gene regulation.

[0479] At least one miRNA binding site can be engineered into the 3′UTR of a polynucleotide of the disclosure. In this context, at least two, at least three, at least four, at least five, at least six, at least seven, at least eight, at least nine, at least ten, or more miRNA binding sites can be engineered into a 3′UTR of a polynucleotide of the disclosure. For example, 1 to 10, 1 to 9, 1 to 8, 1 to 7, 1 to 6, 1 to 5, 1 to 4, 1 to 3, 2, or 1 miRNA binding sites can be engineered into the 3′UTR of a polynucleotide of the disclosure. In one embodiment, miRNA binding sites incorporated into a polynucleotide of the disclosure can be the same or can be different miRNA sites. A combination of different miRNA binding sites incorporated into a polynucleotide of the disclosure can include combinations in which more than one copy of any of the different miRNA sites are incorporated. In another embodiment, miRNA binding sites incorporated into a polynucleotide of the disclosure can target the same or different tissues in the body. As a non-limiting example, through the introduction of tissue-, cell-type-, or disease-specific miRNA binding sites in the 3′-UTR of a polynucleotide of the disclosure, the degree of expression in specific cell types (e.g., hepatocytes, myeloid cells, endothelial cells, cancer cells, etc.) can be reduced.

[0480] In one embodiment, a miRNA binding site can be engineered near the 5′ terminus of the 3′UTR, about halfway between the 5′ terminus and 3′ terminus of the 3′UTR and/or near the 3′ terminus of the 3′UTR in a polynucleotide of the disclosure. As a non-limiting example, a miRNA binding site can be engineered near the 5′ terminus of the 3′UTR and about halfway between the 5′ terminus and 3′ terminus of the 3′UTR. As another non-limiting example, a miRNA binding site can be engineered near the 3′ terminus of the 3′UTR and about halfway between the 5′ terminus and 3′ terminus of the 3′UTR. As yet another non-limiting example, a miRNA binding site can be engineered near the 5′ terminus of the 3′UTR and near the 3′ terminus of the 3′UTR.

[0481] In another embodiment, a 3′UTR can comprise 1, 2, 3, 4, 5, 6, 7, 8, 9, or 10 miRNA binding sites. The miRNA binding sites can be complementary to a miRNA, miRNA seed sequence, and/or miRNA sequences flanking the seed sequence.

[0482] In one embodiment, a polynucleotide of the disclosure can be engineered to include more than one miRNA site expressed in different tissues or different cell types of a subject. As a non-limiting example, a polynucleotide of the disclosure can be engineered to include miR-192

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and miR-122 to regulate expression of the polynucleotide in the liver and kidneys of a subject. In another embodiment, a polynucleotide of the disclosure can be engineered to include more than one miRNA site for the same tissue.

[0483] In some embodiments, the therapeutic window and or differential expression associated with the polypeptide encoded by a polynucleotide of the disclosure can be altered with a miRNA binding site. For example, a polynucleotide encoding a polypeptide that provides a death signal can be designed to be more highly expressed in cancer cells by virtue of the miRNA signature of those cells. Where a cancer cell expresses a lower level of a particular miRNA, the polynucleotide encoding the binding site for that miRNA (or miRNAs) would be more highly expressed. Hence, the polypeptide that provides a death signal triggers or induces cell death in the cancer cell. Neighboring noncancer cells, harboring a higher expression of the same miRNA would be less affected by the encoded death signal as the polynucleotide would be expressed at a lower level due to the effects of the miRNA binding to the binding site or "sensor" encoded in the 3′UTR. Conversely, cell survival or cytoprotective signals can be delivered to tissues containing cancer and non-cancerous cells where a miRNA has a higher expression in the cancer cells—the result being a lower survival signal to the cancer cell and a larger survival signal to the normal cell. Multiple polynucleotides can be designed and administered having different signals based on the use of miRNA binding sites as described herein.

[0484] In some embodiments, the expression of a polynucleotide of the disclosure can be controlled by incorporating at least one sensor sequence in the polynucleotide and formulating the polynucleotide for administration. As a non-limiting example, a polynucleotide of the disclosure can be targeted to a tissue or cell by incorporating a miRNA binding site and formulating the polynucleotide in a lipid nanoparticle comprising a cationic lipid, including any of the lipids described herein.

[0485] A polynucleotide of the disclosure can be engineered for more targeted expression in specific tissues, cell types, or biological conditions based on the expression patterns of miRNAs in the different tissues, cell types, or biological conditions. Through introduction of tissue-specific miRNA binding sites, a polynucleotide of the disclosure can be designed for optimal protein expression in a tissue or cell, or in the context of a biological condition.

[0486] In some embodiments, a polynucleotide of the disclosure can be designed to incorporate miRNA binding sites that either have 100% identity to known miRNA seed sequences or have less than 100% identity to miRNA seed sequences. In some embodiments, a

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polynucleotide of the disclosure can be designed to incorporate miRNA binding sites that have at least: 60%, 65%, 70%, 75%, 80%, 85%, 90%, 95%, 96%, 97%, 98%, or 99% identity to known miRNA seed sequences. The miRNA seed sequence can be partially mutated to decrease miRNA binding affinity and as such result in reduced downmodulation of the polynucleotide. In essence, the degree of match or mis-match between the miRNA binding site and the miRNA seed can act as a rheostat to more finely tune the ability of the miRNA to modulate protein expression. In addition, mutation in the non-seed region of a miRNA binding site can also impact the ability of a miRNA to modulate protein expression.

[0487] In one embodiment, a miRNA sequence can be incorporated into the loop of a stem loop.

[0488] In another embodiment, a miRNA seed sequence can be incorporated in the loop of a stem loop and a miRNA binding site can be incorporated into the 5′ or 3′ stem of the stem loop.

[0489] In one embodiment, a translation enhancer element (TEE) can be incorporated on the 5′end of the stem of a stem loop and a miRNA seed can be incorporated into the stem of the stem loop. In another embodiment, a TEE can be incorporated on the 5′ end of the stem of a stem loop, a miRNA seed can be incorporated into the stem of the stem loop and a miRNA binding site can be incorporated into the 3′ end of the stem or the sequence after the stem loop. The miRNA seed and the miRNA binding site can be for the same and/or different miRNA sequences.

[0490] In one embodiment, the incorporation of a miRNA sequence and/or a TEE sequence changes the shape of the stem loop region which can increase and/or decrease translation. (see e.g, Kedde et al., "A Pumilio-induced RNA structure switch in p27-3′UTR controls miR-221 and miR-22 accessibility." Nature Cell Biology. 2010, incorporated herein by reference in its entirety).

[0491] In one embodiment, the 5′-UTR of a polynucleotide of the disclosure can comprise at least one miRNA sequence. The miRNA sequence can be, but is not limited to, a 19 or 22 nucleotide sequence and/or a miRNA sequence without the seed.

[0492] In one embodiment the miRNA sequence in the 5′UTR can be used to stabilize a polynucleotide of the disclosure described herein.

[0493] In another embodiment, a miRNA sequence in the 5′UTR of a polynucleotide of the disclosure can be used to decrease the accessibility of the site of translation initiation such as, but not limited to a start codon. See, e.g., Matsuda et al., PLoS One. 2010 11(5):e15057;

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incorporated herein by reference in its entirety, which used antisense locked nucleic acid (LNA) oligonucleotides and exon-junction complexes (EJCs) around a start codon (-4 to +37 where the A of the AUG codons is +1) in order to decrease the accessibility to the first start codon (AUG). Matsuda showed that altering the sequence around the start codon with an LNA or EJC affected the efficiency, length and structural stability of a polynucleotide. A polynucleotide of the disclosure can comprise a miRNA sequence, instead of the LNA or EJC sequence described by Matsuda et al, near the site of translation initiation in order to decrease the accessibility to the site of translation initiation. The site of translation initiation can be prior to, after or within the miRNA sequence. As a non-limiting example, the site of translation initiation can be located within a miRNA sequence such as a seed sequence or binding site. As another non-limiting example, the site of translation initiation can be located within a miR-122 sequence such as the seed sequence or the mir-122 binding site.

[0494] In some embodiments, a polynucleotide of the disclosure can include at least one miRNA in order to dampen the antigen presentation by antigen presenting cells. The miRNA can be the complete miRNA sequence, the miRNA seed sequence, the miRNA sequence without the seed, or a combination thereof. As a non-limiting example, a miRNA incorporated into a polynucleotide of the disclosure can be specific to the hematopoietic system. As another non-limiting example, a miRNA incorporated into a polynucleotide of the disclosure to dampen antigen presentation is miR-142-3p.

[0495] In some embodiments, a polynucleotide of the disclosure can include at least one miRNA in order to dampen expression of the encoded polypeptide in a tissue or cell of interest. As a non-limiting example, a polynucleotide of the disclosure can include at least one miR-122 binding site in order to dampen expression of an encoded polypeptide of interest in the liver. As another non-limiting example a polynucleotide of the disclosure can include at least one miR-142-3p binding site, miR-142-3p seed sequence, miR-142-3p binding site without the seed, miR-142-5p binding site, miR-142-5p seed sequence, miR-142-5p binding site without the seed, miR-146 binding site, miR-146 seed sequence and/or miR-146 binding site without the seed sequence.

[0496] In some embodiments, a polynucleotide of the disclosure can comprise at least one miRNA binding site in the 3′UTR in order to selectively degrade mRNA therapeutics in the immune cells to subdue unwanted immunogenic reactions caused by therapeutic delivery. As a non-limiting example, the miRNA binding site can make a polynucleotide of the disclosure more

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unstable in antigen presenting cells. Non-limiting examples of these miRNAs include mir-142-5p, mir-142-3p, mir-146a-5p, and mir-146-3p.

[0497] In one embodiment, a polynucleotide of the disclosure comprises at least one miRNA sequence in a region of the polynucleotide that can interact with a RNA binding protein.

[0498] In some embodiments, the polynucleotide of the disclosure (e.g., a RNA, e.g., a mRNA) comprising (i) a sequence-optimized nucleotide sequence (e.g., an ORF) encoding a MCM polypeptide (e.g., the wild-type sequence, functional fragment, or variant thereof) and (ii) a miRNA binding site (e.g., a miRNA binding site that binds to miR-142).

[0499] In some embodiments, the polynucleotide of the disclosure comprises a uracil-modified sequence encoding a MCM polypeptide disclosed herein and a miRNA binding site disclosed herein, e.g., a miRNA binding site that binds to miR-142. In some embodiments, the uracil-modified sequence encoding a MCM polypeptide comprises at least one chemically modified nucleobase, e.g., 5-methoxyuracil. In some embodiments, at least 95% of a type of nucleobase (e.g., uracil) in a uracil-modified sequence encoding a MCM polypeptide of the disclosure are modified nucleobases. In some embodiments, at least 95% of uracil in a uracil-modified sequence encoding a MCM polypeptide is 5-methoxyuridine. In some embodiments, the polynucleotide comprising a nucleotide sequence encoding a MCM polypeptide disclosed herein and a miRNA binding site is formulated with a delivery agent, e.g., a compound having the Formula (I), e.g., any of Compounds 1-147.

3′ UTR and the AU Rich Elements

[0500] The disclosure also includes a polynucleotide that comprises both one or more 3' untranslated regions as well as the polynucleotide described herein, *i.e.*, a polynucleotide comprising an ORF encoding an MCM polypeptide.

[0501] Natural or wild type 3′ UTRs are known to have stretches of Adenosines and Uridines embedded in them. These AU rich signatures are particularly prevalent in genes with high rates of turnover. Based on their sequence features and functional properties, the AU rich elements (AREs) can be separated into three classes (Chen et al, 1995): Class I AREs contain several dispersed copies of an AUUUA motif within U-rich regions. C-Myc and MyoD contain class I AREs. Class II AREs possess two or more overlapping UUAUUUA(U/A)(U/A) nonamers. Molecules containing this type of AREs include GM-CSF and TNF-a. Class III ARES are less well defined. These U rich regions do not contain an AUUUA motif. c-Jun and Myogenin are

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two well-studied examples of this class. Most proteins binding to the AREs are known to destabilize the messenger, whereas members of the ELAV family, most notably HuR, have been documented to increase the stability of mRNA. HuR binds to AREs of all the three classes. Engineering the HuR specific binding sites into the 3′ UTR of nucleic acid molecules will lead to HuR binding and thus, stabilization of the message *in vivo*.

[0502] Introduction, removal or modification of 3′ UTR AU rich elements (AREs) can be used to modulate the stability of polynucleotides of the disclosure. When engineering specific polynucleotides, one or more copies of an ARE can be introduced to make polynucleotides of the disclosure less stable and thereby curtail translation and decrease production of the resultant protein. Likewise, AREs can be identified and removed or mutated to increase the intracellular stability and thus increase translation and production of the resultant protein. Transfection experiments can be conducted in relevant cell lines, using polynucleotides of the disclosure and protein production can be assayed at various time points post-transfection. For example, cells can be transfected with different ARE-engineering molecules and by using an ELISA kit to the relevant protein and assaying protein produced at 6 hour, 12 hour, 24 hour, 48 hour, and 7 days post-transfection.

Regions having a 5′ Cap

[0503] The disclosure also includes a polynucleotide that comprises both a 5′ Cap and the polynucleotide described herein, *i.e.*, a polynucleotide comprising an ORF encoding an MCM polypeptide.

[0504] The 5′ cap structure of a natural mRNA is involved in nuclear export, increasing mRNA stability and binds the mRNA Cap Binding Protein (CBP), which is responsible for mRNA stability in the cell and translation competency through the association of CBP with poly(A) binding protein to form the mature cyclic mRNA species. The cap further assists the removal of 5′ proximal introns during mRNA splicing.

[0505] Endogenous mRNA molecules can be 5′-end capped generating a 5′-ppp-5′-triphosphate linkage between a terminal guanosine cap residue and the 5′-terminal transcribed sense nucleotide of the mRNA molecule. This 5′-guanylate cap can then be methylated to generate an N7-methyl-guanylate residue. The ribose sugars of the terminal and/or anteterminal transcribed nucleotides of the 5′ end of the mRNA can optionally also be 2′-O-methylated. 5′-

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decapping through hydrolysis and cleavage of the guanylate cap structure can target a nucleic acid molecule, such as an mRNA molecule, for degradation.

[0506] In some embodiments, polynucleotides can be designed to incorporate a cap moiety. Modifications to the polynucleotides of the present disclosure can generate a non-hydrolyzable cap structure preventing decapping and thus increasing mRNA half-life. Because cap structure hydrolysis requires cleavage of 5′-ppp-5′ phosphorodiester linkages, modified nucleotides can be used during the capping reaction. For example, a Vaccinia Capping Enzyme from New England Biolabs (Ipswich, MA) can be used with α-thio-guanosine nucleotides according to the manufacturer's instructions to create a phosphorothioate linkage in the 5′-ppp-5′ cap. Additional modified guanosine nucleotides can be used such as α-methyl-phosphonate and seleno-phosphate nucleotides.

[0507] Additional modifications include, but are not limited to, 2′-O-methylation of the ribose sugars of 5′-terminal and/or 5′-anteterminal nucleotides of the polynucleotide (as mentioned above) on the 2′-hydroxyl group of the sugar ring. Multiple distinct 5′-cap structures can be used to generate the 5′-cap of a nucleic acid molecule, such as a polynucleotide that functions as an mRNA molecule.

[0508] Cap analogs, which herein are also referred to as synthetic cap analogs, chemical caps, chemical cap analogs, or structural or functional cap analogs, differ from natural (*i.e.*, endogenous, wild-type or physiological) 5′-caps in their chemical structure, while retaining cap function. Cap analogs can be chemically (*i.e.*, non-enzymatically) or enzymatically synthesized and/or linked to the polynucleotides of the disclosure.

[0509] For example, the Anti-Reverse Cap Analog (ARCA) cap contains two guanines linked by a 5′-5′-triphosphate group, wherein one guanine contains an N7 methyl group as well as a 3′-O-methyl group (*i.e.*, N7,3′-O-dimethyl-guanosine-5′-triphosphate-5′-guanosine (m^7G-3′mppp-G; which can equivalently be designated 3′ O-Me-m7G(5')ppp(5')G). The 3′-O atom of the other, unmodified, guanine becomes linked to the 5′-terminal nucleotide of the capped polynucleotide. The N7- and 3′-O-methlyated guanine provides the terminal moiety of the capped polynucleotide.

[0510] Another exemplary cap is mCAP, which is similar to ARCA but has a 2′-O-methyl group on guanosine (*i.e.*, N7,2′-O-dimethyl-guanosine-5′-triphosphate-5′-guanosine, m^7Gm-ppp-G).

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[0511] In some embodiments, the cap is a dinucleotide cap analog. As a non-limiting example, the dinucleotide cap analog can be modified at different phosphate positions with a boranophosphate group or a phophoroselenoate group such as the dinucleotide cap analogs described in US Patent No. US 8,519,110, the contents of which are herein incorporated by reference in its entirety.

[0512] In another embodiment, the cap is a cap analog is a N7-(4-chlorophenoxyethyl) substituted dicucleotide form of a cap analog known in the art and/or described herein. Non-limiting examples of a N7-(4-chlorophenoxyethyl) substituted dicucleotide form of a cap analog include a N7-(4-chlorophenoxyethyl)-G(5')ppp(5')G and a N7-(4-chlorophenoxyethyl)-$m^{3'-O}$G(5')ppp(5')G cap analog (*See, e.g.,* the various cap analogs and the methods of synthesizing cap analogs described in Kore et al. Bioorganic & Medicinal Chemistry 2013 21:4570-4574; the contents of which are herein incorporated by reference in its entirety). In another embodiment, a cap analog of the present disclosure is a 4-chloro/bromophenoxyethyl analog.

[0513] While cap analogs allow for the concomitant capping of a polynucleotide or a region thereof, in an *in vitro* transcription reaction, up to 20% of transcripts can remain uncapped. This, as well as the structural differences of a cap analog from an endogenous 5′-cap structures of nucleic acids produced by the endogenous, cellular transcription machinery, can lead to reduced translational competency and reduced cellular stability.

[0514] Polynucleotides of the disclosure can also be capped post-manufacture (whether IVT or chemical synthesis), using enzymes, in order to generate more authentic 5′-cap structures. As used herein, the phrase "more authentic" refers to a feature that closely mirrors or mimics, either structurally or functionally, an endogenous or wild type feature. That is, a "more authentic" feature is better representative of an endogenous, wild-type, natural or physiological cellular function and/or structure as compared to synthetic features or analogs, etc., of the prior art, or which outperforms the corresponding endogenous, wild-type, natural or physiological feature in one or more respects. Non-limiting examples of more authentic 5′cap structures of the present disclosure are those that, among other things, have enhanced binding of cap binding proteins, increased half-life, reduced susceptibility to 5′ endonucleases and/or reduced 5′decapping, as compared to synthetic 5′cap structures known in the art (or to a wild-type, natural or physiological 5′cap structure). For example, recombinant Vaccinia Virus Capping Enzyme and recombinant 2′-O-methyltransferase enzyme can create a canonical 5′-5′-triphosphate linkage between the 5′-terminal nucleotide of a polynucleotide and a guanine cap nucleotide wherein the

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cap guanine contains an N7 methylation and the 5′-terminal nucleotide of the mRNA contains a 2′-O-methyl. Such a structure is termed the Cap1 structure. This cap results in a higher translational-competency and cellular stability and a reduced activation of cellular pro-inflammatory cytokines, as compared, *e.g.,* to other 5′cap analog structures known in the art. Cap structures include, but are not limited to, 7mG(5')ppp(5')N,pN2p (cap 0), 7mG(5')ppp(5')NlmpNp (cap 1), and 7mG(5')-ppp(5')NlmpN2mp (cap 2).

[0515] As a non-limiting example, capping chimeric polynucleotides post-manufacture can be more efficient as nearly 100% of the chimeric polynucleotides can be capped. This is in contrast to ~80% when a cap analog is linked to a chimeric polynucleotide in the course of an *in vitro* transcription reaction.

[0516] According to the present disclosure, 5′ terminal caps can include endogenous caps or cap analogs. According to the present disclosure, a 5′ terminal cap can comprise a guanine analog. Useful guanine analogs include, but are not limited to, inosine, N1-methyl-guanosine, 2′fluoro-guanosine, 7-deaza-guanosine, 8-oxo-guanosine, 2-amino-guanosine, LNA-guanosine, and 2-azido-guanosine.

Poly-A tails

[0517] The disclosure also includes a polynucleotide that comprises both a poly-A tail and the polynucleotide described herein, *i.e.*, a polynucleotide comprising an ORF encoding an MCM polypeptide.

[0518] During RNA processing, a long chain of adenine nucleotides (poly-A tail) can be added to a polynucleotide such as an mRNA molecule in order to increase stability. Immediately after transcription, the 3' end of the transcript can be cleaved to free a 3' hydroxyl. Then poly-A polymerase adds a chain of adenine nucleotides to the RNA. The process, called polyadenylation, adds a poly-A tail that can be between, for example, approximately 80 to approximately 250 residues long, including approximately 80, 90, 100, 110, 120, 130, 140, 150, 160, 170, 180, 190, 200, 210, 220, 230, 240 or 250 residues long.

[0519] PolyA tails can also be added after the construct is exported from the nucleus.

[0520] According to the present disclosure, terminal groups on the poly A tail can be incorporated for stabilization. Polynucleotides of the present disclosure can include des-3' hydroxyl tails. They can also include structural moieties or 2'-Omethyl modifications as taught

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by Junjie Li, et al. (Current Biology, Vol. 15, 1501–1507, August 23, 2005, the contents of which are incorporated herein by reference in its entirety).

[0521] The polynucleotides of the present disclosure can be designed to encode transcripts with alternative polyA tail structures including histone mRNA. According to Norbury, "Terminal uridylation has also been detected on human replication-dependent histone mRNAs. The turnover of these mRNAs is thought to be important for the prevention of potentially toxic histone accumulation following the completion or inhibition of chromosomal DNA replication. These mRNAs are distinguished by their lack of a 3′ poly(A) tail, the function of which is instead assumed by a stable stem–loop structure and its cognate stem–loop binding protein (SLBP); the latter carries out the same functions as those of PABP on polyadenylated mRNAs" (Norbury, "Cytoplasmic RNA: a case of the tail wagging the dog," Nature Reviews Molecular Cell Biology; AOP, published online 29 August 2013; doi:10.1038/nrm3645) the contents of which are incorporated herein by reference in its entirety.

[0522] Unique poly-A tail lengths provide certain advantages to the polynucleotides of the present disclosure.

[0523] Generally, the length of a poly-A tail, when present, is greater than 30 nucleotides in length. In another embodiment, the poly-A tail is greater than 35 nucleotides in length (*e.g.,* at least or greater than about 35, 40, 45, 50, 55, 60, 70, 80, 90, 100, 120, 140, 160, 180, 200, 250, 300, 350, 400, 450, 500, 600, 700, 800, 900, 1,000, 1,100, 1,200, 1,300, 1,400, 1,500, 1,600, 1,700, 1,800, 1,900, 2,000, 2,500, and 3,000 nucleotides). In some embodiments, the polynucleotide or region thereof includes from about 30 to about 3,000 nucleotides (*e.g.,* from 30 to 50, from 30 to 100, from 30 to 250, from 30 to 500, from 30 to 750, from 30 to 1,000, from 30 to 1,500, from 30 to 2,000, from 30 to 2,500, from 50 to 100, from 50 to 250, from 50 to 500, from 50 to 750, from 50 to 1,000, from 50 to 1,500, from 50 to 2,000, from 50 to 2,500, from 50 to 3,000, from 100 to 500, from 100 to 750, from 100 to 1,000, from 100 to 1,500, from 100 to 2,000, from 100 to 2,500, from 100 to 3,000, from 500 to 750, from 500 to 1,000, from 500 to 1,500, from 500 to 2,000, from 500 to 2,500, from 500 to 3,000, from 1,000 to 1,500, from 1,000 to 2,000, from 1,000 to 2,500, from 1,000 to 3,000, from 1,500 to 2,000, from 1,500 to 2,500, from 1,500 to 3,000, from 2,000 to 3,000, from 2,000 to 2,500, and from 2,500 to 3,000).

[0524] In some embodiments, the poly-A tail is designed relative to the length of the overall polynucleotide or the length of a particular region of the polynucleotide. This design can be

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based on the length of a coding region, the length of a particular feature or region or based on the length of the ultimate product expressed from the polynucleotides.

[0525] In this context, the poly-A tail can be 10, 20, 30, 40, 50, 60, 70, 80, 90, or 100% greater in length than the polynucleotide or feature thereof. The poly-A tail can also be designed as a fraction of the polynucleotides to which it belongs. In this context, the poly-A tail can be 10, 20, 30, 40, 50, 60, 70, 80, or 90% or more of the total length of the construct, a construct region or the total length of the construct minus the poly-A tail. Further, engineered binding sites and conjugation of polynucleotides for Poly-A binding protein can enhance expression.

[0526] Additionally, multiple distinct polynucleotides can be linked together via the PABP (Poly-A binding protein) through the 3′-end using modified nucleotides at the 3′-terminus of the poly-A tail. Transfection experiments can be conducted in relevant cell lines at and protein production can be assayed by ELISA at 12hr, 24hr, 48hr, 72hr and day 7 post-transfection.

[0527] In some embodiments, the polynucleotides of the present disclosure are designed to include a polyA-G Quartet region. The G-quartet is a cyclic hydrogen bonded array of four guanine nucleotides that can be formed by G-rich sequences in both DNA and RNA. In this embodiment, the G-quartet is incorporated at the end of the poly-A tail. The resultant polynucleotide is assayed for stability, protein production and other parameters including half-life at various time points. It has been discovered that the polyA-G quartet results in protein production from an mRNA equivalent to at least 75% of that seen using a poly-A tail of 120 nucleotides alone.

Start codon region

[0528] The disclosure also includes a polynucleotide that comprises both a start codon region and the polynucleotide described herein, *i.e.*, a polynucleotide comprising an ORF encoding an MCM polypeptide. In some embodiments, the polynucleotides of the present disclosure can have regions that are analogous to or function like a start codon region.

[0529] In some embodiments, the translation of a polynucleotide can initiate on a codon that is not the start codon AUG. Translation of the polynucleotide can initiate on an alternative start codon such as, but not limited to, ACG, AGG, AAG, CTG/CUG, GTG/GUG, ATA/AUA, ATT/AUU, TTG/UUG (see Touriol et al. Biology of the Cell 95 (2003) 169-178 and Matsuda and Mauro PLoS ONE, 2010 5:11; the contents of each of which are herein incorporated by reference in its entirety). As a non-limiting example, the translation of a polynucleotide begins

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on the alternative start codon ACG. As another non-limiting example, polynucleotide translation begins on the alternative start codon CTG or CUG. As yet another non-limiting example, the translation of a polynucleotide begins on the alternative start codon GTG or GUG.

[0530] Nucleotides flanking a codon that initiates translation such as, but not limited to, a start codon or an alternative start codon, are known to affect the translation efficiency, the length and/or the structure of the polynucleotide. (*See, e.g.,* Matsuda and Mauro PLoS ONE, 2010 5:11; the contents of which are herein incorporated by reference in its entirety). Masking any of the nucleotides flanking a codon that initiates translation can be used to alter the position of translation initiation, translation efficiency, length and/or structure of a polynucleotide.

[0531] In some embodiments, a masking agent can be used near the start codon or alternative start codon in order to mask or hide the codon to reduce the probability of translation initiation at the masked start codon or alternative start codon. Non-limiting examples of masking agents include antisense locked nucleic acids (LNA) polynucleotides and exon-junction complexes (EJCs) (*See, e.g.,* Matsuda and Mauro describing masking agents LNA polynucleotides and EJCs (PLoS ONE, 2010 5:11); the contents of which are herein incorporated by reference in its entirety).

[0532] In another embodiment, a masking agent can be used to mask a start codon of a polynucleotide in order to increase the likelihood that translation will initiate on an alternative start codon.

[0533] In some embodiments, a masking agent can be used to mask a first start codon or alternative start codon in order to increase the chance that translation will initiate on a start codon or alternative start codon downstream to the masked start codon or alternative start codon.

[0534] In some embodiments, a start codon or alternative start codon can be located within a perfect complement for a miR binding site. The perfect complement of a miR binding site can help control the translation, length and/or structure of the polynucleotide similar to a masking agent. As a non-limiting example, the start codon or alternative start codon can be located in the middle of a perfect complement for a miR-122 binding site. The start codon or alternative start codon can be located after the first nucleotide, second nucleotide, third nucleotide, fourth nucleotide, fifth nucleotide, sixth nucleotide, seventh nucleotide, eighth nucleotide, ninth nucleotide, tenth nucleotide, eleventh nucleotide, twelfth nucleotide, thirteenth nucleotide, fourteenth nucleotide, fifteenth nucleotide, sixteenth nucleotide, seventeenth nucleotide, eighteenth nucleotide, nineteenth nucleotide, twentieth nucleotide or twenty-first nucleotide.

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[0535] In another embodiment, the start codon of a polynucleotide can be removed from the polynucleotide sequence in order to have the translation of the polynucleotide begin on a codon that is not the start codon. Translation of the polynucleotide can begin on the codon following the removed start codon or on a downstream start codon or an alternative start codon. In a non-limiting example, the start codon ATG or AUG is removed as the first 3 nucleotides of the polynucleotide sequence in order to have translation initiate on a downstream start codon or alternative start codon. The polynucleotide sequence where the start codon was removed can further comprise at least one masking agent for the downstream start codon and/or alternative start codons in order to control or attempt to control the initiation of translation, the length of the polynucleotide and/or the structure of the polynucleotide.

Stop Codon Region

[0536] The disclosure also includes a polynucleotide that comprises both a stop codon region and the polynucleotide described herein, *i.e.*, a polynucleotide comprising an ORF encoding an MCM polypeptide. In some embodiments, the polynucleotides of the present disclosure can include at least two stop codons before the 3' untranslated region (UTR). The stop codon can be selected from TGA, TAA and TAG. In some embodiments, the polynucleotides of the present disclosure include the stop codon TGA and one additional stop codon. In a further embodiment the addition stop codon can be TAA. In another embodiment, the polynucleotides of the present disclosure include three stop codons.

Insertions and Substitutions

[0537] The disclosure also includes a polynucleotide that comprises insertions and/or substitutions in the polynucleotide described herein, *i.e.*, a polynucleotide comprising an ORF encoding an MCM polypeptide.

[0538] In some embodiments, the 5'UTR of the polynucleotide can be replaced by the insertion of at least one region and/or string of nucleosides of the same base. The region and/or string of nucleotides can include, but is not limited to, at least 3, at least 4, at least 5, at least 6, at least 7 or at least 8 nucleotides and the nucleotides can be natural and/or unnatural. As a non-limiting example, the group of nucleotides can include 5-8 adenine, cytosine, thymine, a string of any of the other nucleotides disclosed herein and/or combinations thereof.

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[0539] In some embodiments, the 5'UTR of the polynucleotide can be replaced by the insertion of at least two regions and/or strings of nucleotides of two different bases such as, but not limited to, adenine, cytosine, thymine, any of the other nucleotides disclosed herein and/or combinations thereof. For example, the 5'UTR can be replaced by inserting 5-8 adenine bases followed by the insertion of 5-8 cytosine bases. In another example, the 5'UTR can be replaced by inserting 5-8 cytosine bases followed by the insertion of 5-8 adenine bases.

[0540] In some embodiments, the polynucleotide can include at least one substitution and/or insertion downstream of the transcription start site that can be recognized by an RNA polymerase. As a non-limiting example, at least one substitution and/or insertion can occur downstream of the transcription start site by substituting at least one nucleic acid in the region just downstream of the transcription start site (such as, but not limited to, +1 to +6). Changes to region of nucleotides just downstream of the transcription start site can affect initiation rates, increase apparent nucleotide triphosphate (NTP) reaction constant values, and increase the dissociation of short transcripts from the transcription complex curing initial transcription (Brieba et al, Biochemistry (2002) 41: 5144-5149; herein incorporated by reference in its entirety). The modification, substitution and/or insertion of at least one nucleoside can cause a silent mutation of the sequence or can cause a mutation in the amino acid sequence.

[0541] In some embodiments, the polynucleotide can include the substitution of at least 1, at least 2, at least 3, at least 4, at least 5, at least 6, at least 7, at least 8, at least 9, at least 10, at least 11, at least 12 or at least 13 guanine bases downstream of the transcription start site.

[0542] In some embodiments, the polynucleotide can include the substitution of at least 1, at least 2, at least 3, at least 4, at least 5 or at least 6 guanine bases in the region just downstream of the transcription start site. As a non-limiting example, if the nucleotides in the region are GGGAGA, the guanine bases can be substituted by at least 1, at least 2, at least 3 or at least 4 adenine nucleotides. In another non-limiting example, if the nucleotides in the region are GGGAGA the guanine bases can be substituted by at least 1, at least 2, at least 3 or at least 4 cytosine bases. In another non-limiting example, if the nucleotides in the region are GGGAGA the guanine bases can be substituted by at least 1, at least 2, at least 3 or at least 4 thymine, and/or any of the nucleotides described herein.

[0543] In some embodiments, the polynucleotide can include at least one substitution and/or insertion upstream of the start codon. For the purpose of clarity, one of skill in the art would appreciate that the start codon is the first codon of the protein coding region whereas the

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transcription start site is the site where transcription begins. The polynucleotide can include, but is not limited to, at least 1, at least 2, at least 3, at least 4, at least 5, at least 6, at least 7 or at least 8 substitutions and/or insertions of nucleotide bases. The nucleotide bases can be inserted or substituted at 1, at least 1, at least 2, at least 3, at least 4 or at least 5 locations upstream of the start codon. The nucleotides inserted and/or substituted can be the same base (*e.g.,* all A or all C or all T or all G), two different bases (*e.g.,* A and C, A and T, or C and T), three different bases (*e.g.,* A, C and T or A, C and T) or at least four different bases. As a non-limiting example, the guanine base upstream of the coding region in the polynucleotide can be substituted with adenine, cytosine, thymine, or any of the nucleotides described herein. In another non-limiting example the substitution of guanine bases in the polynucleotide can be designed so as to leave one guanine base in the region downstream of the transcription start site and before the start codon (see Esvelt *et al.* Nature (2011) 472(7344):499-503; the contents of which is herein incorporated by reference in its entirety). As a non-limiting example, at least 5 nucleotides can be inserted at 1 location downstream of the transcription start site but upstream of the start codon and the at least 5 nucleotides can be the same base type.

IV. Methods of Making Polynucleotides

[0544] The present disclosure also provides methods for making a polynucleotide disclosed herein or a complement thereof. In some aspects, a polynucleotide (*e.g.*, an mRNA) disclosed herein, and encoding an MCM polypeptide or a functional fragment thereof, can be constructed using *in vitro* transcription. In other aspects, a polynucleotide (e.g., an mRNA) disclosed herein, and encoding an MCM polypeptide or a functional fragment thereof, can be constructed by chemical synthesis using an oligonucleotide synthesizer. In other aspects, a polynucleotide (e.g., an mRNA) disclosed herein, and encoding an MCM polypeptide or a functional fragment thereof is made by using a host cell. In certain aspects, a polynucleotide (e.g., an mRNA) disclosed herein, and encoding an MCM polypeptide or a functional fragment thereof is made by one or more combination of the IVT, chemical synthesis, host cell expression, or any other methods known in the art.

[0545] Naturally occurring nucleosides, non-naturally occurring nucleosides, or combinations thereof, can totally or partially naturally replace occurring nucleosides present in the candidate nucleotide sequence and can be incorporated into a sequence-optimized nucleotide

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sequence (e.g., an mRNA) encoding an MCM polypeptide. The resultant mRNAs can then be examined for their ability to produce protein and/or produce a therapeutic outcome.

In Vitro Transcription-enzymatic synthesis

[0546] A polynucleotide disclosed herein can be transcribed using an *in vitro* transcription (IVT) system. The system typically comprises a transcription buffer, nucleotide triphosphates (NTPs), an RNase inhibitor and a polymerase. The NTPs can be selected from, but are not limited to, those described herein including natural and unnatural (modified) NTPs. The polymerase can be selected from, but is not limited to, T7 RNA polymerase, T3 RNA polymerase and mutant polymerases such as, but not limited to, polymerases able to incorporate modified nucleic acids. See U.S. Publ. No. US20130259923, which is herein incorporated by reference in its entirety.

[0547] The IVT system typically comprises a transcription buffer, nucleotide triphosphates (NTPs), an RNase inhibitor and a polymerase. The NTPs can be selected from, but are not limited to, those described herein including natural and unnatural (modified) NTPs. The polymerase can be selected from, but is not limited to, T7 RNA polymerase, T3 RNA polymerase and mutant polymerases such as, but not limited to, polymerases able to incorporate polynucleotides disclosed herein.

[0548] Any number of RNA polymerases or variants can be used in the synthesis of the polynucleotides of the present disclosure.

[0549] RNA polymerases can be modified by inserting or deleting amino acids of the RNA polymerase sequence. As a non-limiting example, the RNA polymerase can be modified to exhibit an increased ability to incorporate a 2´-modified nucleotide triphosphate compared to an unmodified RNA polymerase (see International Publication WO2008078180 and U.S. Patent 8,101,385; herein incorporated by reference in their entireties).

[0550] Variants can be obtained by evolving an RNA polymerase, optimizing the RNA polymerase amino acid and/or nucleic acid sequence and/or by using other methods known in the art. As a non-limiting example, T7 RNA polymerase variants can be evolved using the continuous directed evolution system set out by Esvelt et al. (Nature (2011) 472(7344):499-503; herein incorporated by reference in its entirety) where clones of T7 RNA polymerase can encode at least one mutation such as, but not limited to, lysine at position 93 substituted for threonine (K93T), I4M, A7T, E63V, V64D, A65E, D66Y, T76N, C125R, S128R, A136T, N165S, G175R,

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H176L, Y178H, F182L, L196F, G198V, D208Y, E222K, S228A, Q239R, T243N, G259D, M267I, G280C, H300R, D351A, A354S, E356D, L360P, A383V, Y385C, D388Y, S397R, M401T, N410S, K450R, P451T, G452V, E484A, H523L, H524N, G542V, E565K, K577E, K577M, N601S, S684Y, L699I, K713E, N748D, Q754R, E775K, A827V, D851N or L864F. As another non-limiting example, T7 RNA polymerase variants can encode at least mutation as described in U.S. Pub. Nos. 20100120024 and 20070117112; herein incorporated by reference in their entireties. Variants of RNA polymerase can also include, but are not limited to, substitutional variants, conservative amino acid substitution, insertional variants, deletional variants and/or covalent derivatives.

[0551] In one aspect, the polynucleotide can be designed to be recognized by the wild type or variant RNA polymerases. In doing so, the polynucleotide can be modified to contain sites or regions of sequence changes from the wild type or parent chimeric polynucleotide.

[0552] Polynucleotide or nucleic acid synthesis reactions can be carried out by enzymatic methods utilizing polymerases. Polymerases catalyze the creation of phosphodiester bonds between nucleotides in a polynucleotide or nucleic acid chain. Currently known DNA polymerases can be divided into different families based on amino acid sequence comparison and crystal structure analysis. DNA polymerase I (pol I) or A polymerase family, including the Klenow fragments of E. Coli, Bacillus DNA polymerase I, Thermus aquaticus (Taq) DNA polymerases, and the T7 RNA and DNA polymerases, is among the best studied of these families. Another large family is DNA polymerase α (pol α) or B polymerase family, including all eukaryotic replicating DNA polymerases and polymerases from phages T4 and RB69. Although they employ similar catalytic mechanism, these families of polymerases differ in substrate specificity, substrate analog-incorporating efficiency, degree and rate for primer extension, mode of DNA synthesis, exonuclease activity, and sensitivity against inhibitors.

[0553] DNA polymerases are also selected based on the optimum reaction conditions they require, such as reaction temperature, pH, and template and primer concentrations. Sometimes a combination of more than one DNA polymerases is employed to achieve the desired DNA fragment size and synthesis efficiency. For example, Cheng et al. increase pH, add glycerol and dimethyl sulfoxide, decrease denaturation times, increase extension times, and utilize a secondary thermostable DNA polymerase that possesses a 3′ to 5′ exonuclease activity to effectively amplify long targets from cloned inserts and human genomic DNA. (Cheng et al., PNAS, Vol. 91, 5695-5699 (1994), the contents of which are incorporated herein by reference in

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their entirety). RNA polymerases from bacteriophage T3, T7, and SP6 have been widely used to prepare RNAs for biochemical and biophysical studies. RNA polymerases, capping enzymes, and poly-A polymerases are disclosed in the co-pending International Publication No. WO2014028429, the contents of which are incorporated herein by reference in their entirety.

[0554] In one aspect, the RNA polymerase which can be used in the synthesis of the polynucleotides described herein is a Syn5 RNA polymerase. (see Zhu et al. Nucleic Acids Research 2013, the contents of which is herein incorporated by reference in its entirety). The Syn5 RNA polymerase was recently characterized from marine cyanophage Syn5 by Zhu et al. where they also identified the promoter sequence (see Zhu et al. Nucleic Acids Research 2013, the contents of which is herein incorporated by reference in its entirety). Zhu et al. found that Syn5 RNA polymerase catalyzed RNA synthesis over a wider range of temperatures and salinity as compared to T7 RNA polymerase. Additionally, the requirement for the initiating nucleotide at the promoter was found to be less stringent for Syn5 RNA polymerase as compared to the T7 RNA polymerase making Syn5 RNA polymerase promising for RNA synthesis.

[0555] In one aspect, a Syn5 RNA polymerase can be used in the synthesis of the polynucleotides described herein. As a non-limiting example, a Syn5 RNA polymerase can be used in the synthesis of the polynucleotide requiring a precise 3´-termini.

[0556] In one aspect, a Syn5 promoter can be used in the synthesis of the polynucleotides. As a non-limiting example, the Syn5 promoter can be 5´-ATTGGGCACCCGTAAGGG-3´ as described by Zhu et al. (Nucleic Acids Research 2013, the contents of which is herein incorporated by reference in its entirety).

[0557] In one aspect, a Syn5 RNA polymerase can be used in the synthesis of polynucleotides comprising at least one chemical modification described herein and/or known in the art. (see e.g., the incorporation of pseudo-UTP and 5Me-CTP described in Zhu et al. Nucleic Acids Research 2013, the contents of which is herein incorporated by reference in its entirety).

[0558] In one aspect, the polynucleotides described herein can be synthesized using a Syn5 RNA polymerase which has been purified using modified and improved purification procedure described by Zhu et al. (Nucleic Acids Research 2013, the contents of which is herein incorporated by reference in its entirety).

[0559] Various tools in genetic engineering are based on the enzymatic amplification of a target gene which acts as a template. For the study of sequences of individual genes or specific regions of interest and other research needs, it is necessary to generate multiple copies of a target

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gene from a small sample of polynucleotides or nucleic acids. Such methods can be applied in the manufacture of the polynucleotides of the disclosure.

[0560] Polymerase chain reaction (PCR) has wide applications in rapid amplification of a target gene, as well as genome mapping and sequencing. The key components for synthesizing DNA comprise target DNA molecules as a template, primers complementary to the ends of target DNA strands, deoxynucleoside triphosphates (dNTPs) as building blocks, and a DNA polymerase. As PCR progresses through denaturation, annealing and extension steps, the newly produced DNA molecules can act as a template for the next circle of replication, achieving exponentially amplification of the target DNA. PCR requires a cycle of heating and cooling for denaturation and annealing. Variations of the basic PCR include asymmetric PCR [Innis et al., PNAS, vol. 85, 9436-9440 (1988)], inverse PCR [Ochman et al., Genetics, vol. 120(3), 621-623, (1988)], reverse transcription PCR (RT-PCR) (Freeman et al., BioTechniques, vol. 26(1), 112-22, 124-5 (1999), the contents of which are incorporated herein by reference in their entirety and so on). In RT-PCR, a single stranded RNA is the desired target and is converted to a double stranded DNA first by reverse transcriptase.

[0561] A variety of isothermal in vitro nucleic acid amplification techniques have been developed as alternatives or complements of PCR. For example, strand displacement amplification (SDA) is based on the ability of a restriction enzyme to form a nick. (Walker et al., PNAS, vol. 89, 392-396 (1992), the contents of which are incorporated herein by reference in their entirety)). A restriction enzyme recognition sequence is inserted into an annealed primer sequence. Primers are extended by a DNA polymerase and dNTPs to form a duplex. Only one strand of the duplex is cleaved by the restriction enzyme. Each single strand chain is then available as a template for subsequent synthesis. SDA does not require the complicated temperature control cycle of PCR.

[0562] Nucleic acid sequence-based amplification (NASBA), also called transcription mediated amplification (TMA), is also an isothermal amplification method that utilizes a combination of DNA polymerase, reverse transcriptase, RNAse H, and T7 RNA polymerase. [Compton, Nature, vol. 350, 91-92 (1991)] the contents of which are incorporated herein by reference in their entirety. A target RNA is used as a template and a reverse transcriptase synthesizes its complementary DNA strand. RNAse H hydrolyzes the RNA template, making space for a DNA polymerase to synthesize a DNA strand complementary to the first DNA strand which is complementary to the RNA target, forming a DNA duplex. T7 RNA polymerase

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continuously generates complementary RNA strands of this DNA duplex. These RNA strands act as templates for new cycles of DNA synthesis, resulting in amplification of the target gene.

[0563] Rolling-circle amplification (RCA) amplifies a single stranded circular polynucleotide and involves numerous rounds of isothermal enzymatic synthesis where Φ29 DNA polymerase extends a primer by continuously progressing around the polynucleotide circle to replicate its sequence over and over again. Therefore, a linear copy of the circular template is achieved. A primer can then be annealed to this linear copy and its complementary chain can be synthesized. [See Lizardi et al., Nature Genetics, vol. 19, 225-232 (1998)] the contents of which are incorporated herein by reference in their entirety. A single stranded circular DNA can also serve as a template for RNA synthesis in the presence of an RNA polymerase. (Daubendiek et al., JACS, vol. 117, 7818-7819 (1995), the contents of which are incorporated herein by reference in their entirety). An inverse rapid amplification of cDNA ends (RACE) RCA is described by Polidoros et al. A messenger RNA (mRNA) is reverse transcribed into cDNA, followed by RNAse H treatment to separate the cDNA. The cDNA is then circularized by CircLigase into a circular DNA. The amplification of the resulting circular DNA is achieved with RCA. (Polidoros et al., BioTechniques, vol. 41, 35-42 (2006), the contents of which are incorporated herein by reference in their entirety).

[0564] Any of the foregoing methods can be utilized in the manufacture of one or more regions of the polynucleotides of the present disclosure.

[0565] Assembling polynucleotides or nucleic acids by a ligase is also widely used. DNA or RNA ligases promote intermolecular ligation of the 5′ and 3′ ends of polynucleotide chains through the formation of a phosphodiester bond. Ligase chain reaction (LCR) is a promising diagnosing technique based on the principle that two adjacent polynucleotide probes hybridize to one strand of a target gene and couple to each other by a ligase. If a target gene is not present, or if there is a mismatch at the target gene, such as a single-nucleotide polymorphism (SNP), the probes cannot ligase. (Wiedmann et al., PCR Methods and Application, vol.3 (4), s51-s64 (1994), the contents of which are incorporated herein by reference in their entirety). LCR can be combined with various amplification techniques to increase sensitivity of detection or to increase the amount of products if it is used in synthesizing polynucleotides and nucleic acids.

[0566] Several library preparation kits for nucleic acids are now commercially available. They include enzymes and buffers to convert a small amount of nucleic acid samples into an indexed library for downstream applications. For example, DNA fragments can be placed in a

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NEBNEXT® ULTRATM DNA Library Prep Kit by NEWENGLAND BIOLABS® for end preparation, ligation, size selection, clean-up, PCR amplification and final clean-up.

[0567] Continued development is going on to improvement the amplification techniques. For example, US Pat. 8,367,328 to Asada et al. the contents of which are incorporated herein by reference in their entirety, teaches utilizing a reaction enhancer to increase the efficiency of DNA synthesis reactions by DNA polymerases. The reaction enhancer comprises an acidic substance or cationic complexes of an acidic substance. US Pat. 7.384,739 to Kitabayashi et al. the contents of which are incorporated herein by reference in their entirety, teaches a carboxylate ion-supplying substance that promotes enzymatic DNA synthesis, wherein the carboxylate ion-supplying substance is selected from oxalic acid, malonic acid, esters of oxalic acid, esters of malonic acid, salts of malonic acid, and esters of maleic acid. US Pat. 7,378,262 to Sobek et al. the contents of which are incorporated herein by reference in their entirety, discloses an enzyme composition to increase fidelity of DNA amplifications. The composition comprises one enzyme with 3´ exonuclease activity but no polymerase activity and another enzyme that is a polymerase. Both of the enzymes are thermostable and are reversibly modified to be inactive at lower temperatures.

[0568] US Pat. No. 7,550,264 to Getts et al. teaches multiple round of synthesis of sense RNA molecules are performed by attaching oligodeoxynucleotides tails onto the 3´ end of cDNA molecules and initiating RNA transcription using RNA polymerase, the contents of which are incorporated herein by reference in their entirety. US Pat. Publication No. 2013/0183718 to Rohayem teaches RNA synthesis by RNA-dependent RNA polymerases (RdRp) displaying an RNA polymerase activity on single-stranded DNA templates, the contents of which are incorporated herein by reference in their entirety. Oligonucleotides with non-standard nucleotides can be synthesized with enzymatic polymerization by contacting a template comprising non-standard nucleotides with a mixture of nucleotides that are complementary to the nucleotides of the template as disclosed in US Pat. No. 6,617,106 to Benner, the contents of which are incorporated herein by reference in their entirety.

Chemical synthesis

[0569] Standard methods can be applied to synthesize an isolated polynucleotide sequence encoding an isolated polypeptide of interest. For example, a single DNA or RNA oligomer containing a codon-optimized nucleotide sequence coding for the particular isolated polypeptide

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can be synthesized. In other aspects, several small oligonucleotides coding for portions of the desired polypeptide can be synthesized and then ligated. In some aspects, the individual oligonucleotides typically contain 5' or 3' overhangs for complementary assembly.

[0570] A polynucleotide disclosed herein (e.g., mRNA) can be chemically synthesized using chemical synthesis methods and potential nucleobase substitutions known in the art. See, for example, International Publication Nos. WO2014093924, WO2013052523; WO2013039857, WO2012135805, WO2013151671; U.S. Publ. No. US20130115272; or U.S. Pat. Nos. US8999380, US8710200, all of which are herein incorporated by reference in their entireties.

V. Purification and Quantitation of Polynucleotides

Purification

[0571] Purification of the polynucleotides described herein (*i.e.*, a polynucleotide comprising an ORF encoding an MCM polypeptide) can include, but is not limited to, polynucleotide clean-up, quality assurance and quality control. Clean-up can be performed by methods known in the arts such as, but not limited to, AGENCOURT® beads (Beckman Coulter Genomics, Danvers, MA), poly-T beads, LNA™ oligo-T capture probes (EXIQON® Inc., Vedbaek, Denmark) or HPLC based purification methods such as, but not limited to, strong anion exchange HPLC, weak anion exchange HPLC, reverse phase HPLC (RP-HPLC), and hydrophobic interaction HPLC (HIC-HPLC). The term "purified" when used in relation to a polynucleotide such as a "purified polynucleotide" refers to one that is separated from at least one contaminant. As used herein, a "contaminant" is any substance that makes another unfit, impure or inferior. Thus, a purified polynucleotide (*e.g.,* DNA and RNA) is present in a form or setting different from that in which it is found in nature, or a form or setting different from that which existed prior to subjecting it to a treatment or purification method.

[0572] In some embodiments, purification of a polynucleotide of the disclosure removes impurities that can reduce or remove an unwanted immune response, *e.g.,* reducing cytokine activity.

[0573] In some embodiments, the polynucleotide of the disclosure is purified prior to administration using column chromatography (*e.g.*, strong anion exchange HPLC, weak anion exchange HPLC, reverse phase HPLC (RP-HPLC), and hydrophobic interaction HPLC (HIC-HPLC), or (LCMS)). In some embodiments, a column chromatography (*e.g.*, strong anion exchange HPLC, weak anion exchange HPLC, reverse phase HPLC (RP-HPLC), and

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hydrophobic interaction HPLC (HIC-HPLC), or (LCMS)) purified polynucleotide, that encodes an MCM polypeptide disclosed herein increases expression of MCM compared to polynucleotides encoding MCM purified by a different purification method. In some embodiments, a column chromatography (*e.g.*, strong anion exchange HPLC, weak anion exchange HPLC, reverse phase HPLC (RP-HPLC), and hydrophobic interaction HPLC (HIC-HPLC), or (LCMS)) purified polynucleotide encodes an MCM polypeptide or functional fragment thereof comprising one or more of the point mutations V69, T499, H532, A598, and V671. In some embodiments, the RP-HPLC purified polynucleotide increases MCM expression (*e.g.,* by 20-50%, at least 20%, at least 25%, at least 30%, at least 35%, at least 40%, at least 45%, or at least 50%).

[0574] A quality assurance and/or quality control check can be conducted using methods such as, but not limited to, gel electrophoresis, UV absorbance, or analytical HPLC.

[0575] In another embodiment, the polynucleotides can be sequenced by methods including, but not limited to reverse-transcriptase-PCR.

Quantification

[0576] In some embodiments, the polynucleotides of the present disclosure (*i.e.*, a polynucleotide comprising an ORF encoding an MCM polypeptide) can be quantified in exosomes or when derived from one or more bodily fluid. As used herein "bodily fluids" include peripheral blood, serum, plasma, ascites, urine, cerebrospinal fluid (CSF), sputum, saliva, bone marrow, synovial fluid, aqueous humor, amniotic fluid, cerumen, breast milk, broncheoalveolar lavage fluid, semen, prostatic fluid, cowper's fluid or pre-ejaculatory fluid, sweat, fecal matter, hair, tears, cyst fluid, pleural and peritoneal fluid, pericardial fluid, lymph, chyme, chyle, bile, interstitial fluid, menses, pus, sebum, vomit, vaginal secretions, mucosal secretion, stool water, pancreatic juice, lavage fluids from sinus cavities, bronchopulmonary aspirates, blastocyl cavity fluid, and umbilical cord blood. Alternatively, exosomes can be retrieved from an organ selected from the group consisting of lung, heart, pancreas, stomach, intestine, bladder, kidney, ovary, testis, skin, colon, breast, prostate, brain, esophagus, liver, and placenta.

[0577] In the exosome quantification method, a sample of not more than 2mL is obtained from the subject and the exosomes isolated by size exclusion chromatography, density gradient centrifugation, differential centrifugation, nanomembrane ultrafiltration, immunoabsorbent capture, affinity purification, microfluidic separation, or combinations thereof. In the analysis,

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the level or concentration of a polynucleotide can be an expression level, presence, absence, truncation or alteration of the administered construct. It is advantageous to correlate the level with one or more clinical phenotypes or with an assay for a human disease biomarker. The assay can be performed using construct specific probes, cytometry, qRT-PCR, real-time PCR, PCR, flow cytometry, electrophoresis, mass spectrometry, or combinations thereof while the exosomes can be isolated using immunohistochemical methods such as enzyme linked immunosorbent assay (ELISA) methods. Exosomes can also be isolated by size exclusion chromatography, density gradient centrifugation, differential centrifugation, nanomembrane ultrafiltration, immunoabsorbent capture, affinity purification, microfluidic separation, or combinations thereof.

[0578] These methods afford the investigator the ability to monitor, in real time, the level of polynucleotides remaining or delivered. This is possible because the polynucleotides of the present disclosure differ from the endogenous forms due to the structural or chemical modifications.

[0579] In some embodiments, the polynucleotide can be quantified using methods such as, but not limited to, ultraviolet visible spectroscopy (UV/Vis). A non-limiting example of a UV/Vis spectrometer is a NANODROP® spectrometer (ThermoFisher, Waltham, MA). The quantified polynucleotide can be analyzed in order to determine if the polynucleotide can be of proper size, check that no degradation of the polynucleotide has occurred. Degradation of the polynucleotide can be checked by methods such as, but not limited to, agarose gel electrophoresis, HPLC based purification methods such as, but not limited to, strong anion exchange HPLC, weak anion exchange HPLC, reverse phase HPLC (RP-HPLC), and hydrophobic interaction HPLC (HIC-HPLC), liquid chromatography-mass spectrometry (LCMS), capillary electrophoresis (CE) and capillary gel electrophoresis (CGE).

VI. Pharmaceutical Compositions

[0580] The disclosure includes pharmaceutical compositions that comprise the polynucleotide described herein, *i.e.*, a polynucleotide comprising an ORF encoding an MCM polypeptide. In some embodiments, the formulation can contain polynucleotide encoding wild type MCM or MCM comprising a nucleotide sequence having significant sequence similarity to a polynucleotide selected from the group of SEQ ID NOs: 1-207, 732-765, and 772, wherein the ORF encodes an MCM polypeptide.

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[0581] Pharmaceutical compositions can optionally comprise one or more additional active substances, *e.g.*, therapeutically and/or prophylactically active substances. Pharmaceutical compositions of the present disclosure can be sterile and/or pyrogen-free. General considerations in the formulation and/or manufacture of pharmaceutical agents can be found, for example, in *Remington: The Science and Practice of Pharmacy* 21st ed., Lippincott Williams & Wilkins, 2005 (incorporated herein by reference in its entirety). For the purposes of the present disclosure, the phrase "active ingredient" generally refers to polynucleotides to be delivered as described herein.

[0582] Formulations of the pharmaceutical compositions described herein can be prepared by any method known or hereafter developed in the art of pharmacology. In general, such preparatory methods include the step of associating the active ingredient with an excipient and/or one or more other accessory ingredients.

[0583] A pharmaceutical composition in accordance with the present disclosure can be prepared, packaged, and/or sold in bulk, as a single unit dose, and/or as a plurality of single unit doses. As used herein, a "unit dose" refers to a discrete amount of the pharmaceutical composition comprising a predetermined amount of the active ingredient. The amount of the active ingredient is generally equal to the dosage of the active ingredient that would be administered to a subject and/or a convenient fraction of such a dosage such as, for example, one-half or one-third of such a dosage.

[0584] Relative amounts of the active ingredient, the pharmaceutically acceptable excipient, and/or any additional ingredients in a pharmaceutical composition in accordance with the present disclosure can vary, depending upon the identity, size, and/or condition of the subject being treated and further depending upon the route by which the composition is to be administered. For example, the composition can comprise between 0.1% and 99% (w/w) of the active ingredient. By way of example, the composition can comprise between 0.1% and 100%, *e.g.*, between 0.5 and 50%, between 1-30%, between 5-80%, at least 80% (w/w) active ingredient.

[0585] In some embodiments, the formulations described herein can contain at least one polynucleotide. As a non-limiting example, the formulations can contain 1, 2, 3, 4 or 5 polynucleotides.

[0586] In some embodiments, the formulations described herein can comprise more than one type of polynucleotide. In some embodiments, the formulation can comprise a polynucleotide in linear and circular form. In another embodiment, the formulation can comprise a circular

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polynucleotide and an IVT polynucleotide. In yet another embodiment, the formulation can comprise an IVT polynucleotide, a chimeric polynucleotide and a circular polynucleotide.

[0587] In some embodiments, compositions are administered to humans, human patients or subjects. Although the descriptions of pharmaceutical compositions provided herein are principally directed to pharmaceutical compositions that are suitable for administration to humans, it will be understood by the skilled artisan that such compositions are generally suitable for administration to any other animal, *e.g.,* to non-human animals, *e.g.* non-human mammals. Modification of pharmaceutical compositions suitable for administration to humans in order to render the compositions suitable for administration to various animals is well understood, and the ordinarily skilled veterinary pharmacologist can design and/or perform such modification with merely ordinary, if any, experimentation. Subjects to which administration of the pharmaceutical compositions is contemplated include, but are not limited to, humans and/or other primates; mammals, including commercially relevant mammals such as cattle, pigs, horses, sheep, cats, dogs, mice, and/or rats; and/or birds, including commercially relevant birds such as poultry, chickens, ducks, geese, and/or turkeys.

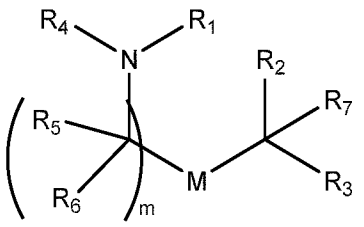
Delivery Agents

a. Lipid Compound

[0588] The present disclosure provides pharmaceutical compositions with advantageous properties. In particular, the present application provides pharmaceutical compositions comprising:

(a) a polynucleotide comprising an ORF encoding an MCM polypeptide; and

(b) a lipid compound having the formula (I)



(I),

wherein

R_1 is selected from the group consisting of C_{5-20} alkyl, C_{5-20} alkenyl, -R*YR", -YR", and -R"M'R';

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R_2 and R_3 are independently selected from the group consisting of H, C_{1-14} alkyl, C_{2-14} alkenyl, -R*YR", -YR", and -R*OR", or R_2 and R_3, together with the atom to which they are attached, form a heterocycle or carbocycle;

R_4 is selected from the group consisting of a C_{3-6} carbocycle, $-(CH_2)_nQ$, $-(CH_2)_nCHQR$, -CHQR, $-CQ(R)_2$, and unsubstituted C_{1-6} alkyl, where Q is selected from a carbocycle, heterocycle, -OR, $-O(CH_2)_nN(R)_2$, -C(O)OR, -OC(O)R, $-CX_3$, $-CX_2H$, $-CXH_2$, -CN, $-N(R)_2$, $-C(O)N(R)_2$, -N(R)C(O)R, $-N(R)S(O)_2R$, $-N(R)C(O)N(R)_2$, $-N(R)C(S)N(R)_2$, and $-C(R)N(R)_2C(O)OR$, and each n is independently selected from 1, 2, 3, 4, and 5;

each R_5 is independently selected from the group consisting of C_{1-3} alkyl, C_{2-3} alkenyl, and H;

each R_6 is independently selected from the group consisting of C_{1-3} alkyl, C_{2-3} alkenyl, and H;

M and M' are independently selected from -C(O)O-, -OC(O)-, -C(O)N(R')-, -N(R')C(O)-, -C(O)-, -C(S)-, -C(S)S-, -SC(S)-, -CH(OH)-, -P(O)(OR')O-, $-S(O)_2-$, an aryl group, and a heteroaryl group;

R_7 is selected from the group consisting of C_{1-3} alkyl, C_{2-3} alkenyl, and H;

each R is independently selected from the group consisting of C_{1-3} alkyl, C_{2-3} alkenyl, and H;

each R' is independently selected from the group consisting of C_{1-18} alkyl, C_{2-18} alkenyl, -R*YR", -YR", and H;

each R" is independently selected from the group consisting of C_{3-14} alkyl and C_{3-14} alkenyl;

each R* is independently selected from the group consisting of C_{1-12} alkyl and C_{2-12} alkenyl;

each Y is independently a C_{3-6} carbocycle;

each X is independently selected from the group consisting of F, Cl, Br, and I; and m is selected from 5, 6, 7, 8, 9, 10, 11, 12, and 13,

or salts or stereoisomers thereof, wherein alkyl and alkenyl groups can be linear or branched.

[0589] In some embodiments, a subset of compounds of Formula (I) includes those in which when R_4 is $-(CH_2)_nQ$, $-(CH_2)_nCHQR$, -CHQR, or $-CQ(R)_2$, then (i) Q is not $-N(R)_2$ when n is 1, 2, 3, 4 or 5, or (ii) Q is not 5, 6, or 7-membered heterocycloalkyl when n is 1 or 2.

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[0590] In another embodiments, another subset of compounds of Formula (I) includes those in which

R_1 is selected from the group consisting of C_{5-20} alkyl, C_{5-20} alkenyl, -R*YR", -YR", and -R"M'R';

R_2 and R_3 are independently selected from the group consisting of H, C_{1-14} alkyl, C_{2-14} alkenyl, -R*YR", -YR", and -R*OR", or R_2 and R_3, together with the atom to which they are attached, form a heterocycle or carbocycle;

R_4 is selected from the group consisting of a C_{3-6} carbocycle, $-(CH_2)_nQ$, $-(CH_2)_nCHQR$, -CHQR, $-CQ(R)_2$, and unsubstituted C_{1-6} alkyl, where Q is selected from a C_{3-6} carbocycle, a 5- to 14-membered heteroaryl having one or more heteroatoms selected from N, O, and S, -OR, $-O(CH_2)_nN(R)_2$, -C(O)OR, -OC(O)R, $-CX_3$, $-CX_2H$, $-CXH_2$, -CN, $-C(O)N(R)_2$, $-N(R)C(O)R$, $-N(R)S(O)_2R$, $-N(R)C(O)N(R)_2$, $-N(R)C(S)N(R)_2$, $-CRN(R)_2C(O)OR$, and a 5- to 14-membered heterocycloalkyl having one or more heteroatoms selected from N, O, and S which is substituted with one or more substituents selected from oxo (=O), OH, amino, and C_{1-3} alkyl, and each n is independently selected from 1, 2, 3, 4, and 5;

each R_5 is independently selected from the group consisting of C_{1-3} alkyl, C_{2-3} alkenyl, and H;

each R_6 is independently selected from the group consisting of C_{1-3} alkyl, C_{2-3} alkenyl, and H;

M and M' are independently selected from -C(O)O-, -OC(O)-, -C(O)N(R')-, -N(R')C(O)-, -C(O)-, -C(S)-, -C(S)S-, -SC(S)-, -CH(OH)-, -P(O)(OR')O-, $-S(O)_2-$, an aryl group, and a heteroaryl group;

R_7 is selected from the group consisting of C_{1-3} alkyl, C_{2-3} alkenyl, and H;

each R is independently selected from the group consisting of C_{1-3} alkyl, C_{2-3} alkenyl, and H;

each R' is independently selected from the group consisting of C_{1-18} alkyl, C_{2-18} alkenyl, -R*YR", -YR", and H;

each R" is independently selected from the group consisting of C_{3-14} alkyl and C_{3-14} alkenyl;

each R* is independently selected from the group consisting of C_{1-12} alkyl and C_{2-12} alkenyl;

each Y is independently a C_{3-6} carbocycle;

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each X is independently selected from the group consisting of F, Cl, Br, and I; and

m is selected from 5, 6, 7, 8, 9, 10, 11, 12, and 13,

or salts or stereoisomers thereof.

[0591] In yet another embodiments, another subset of compounds of Formula (I) includes those in which

R_1 is selected from the group consisting of C_{5-20} alkyl, C_{5-20} alkenyl, -R*YR", -YR", and -R"M'R';

R_2 and R_3 are independently selected from the group consisting of H, C_{1-14} alkyl, C_{2-14} alkenyl, -R*YR", -YR", and -R*OR", or R_2 and R_3, together with the atom to which they are attached, form a heterocycle or carbocycle;

R_4 is selected from the group consisting of a C_{3-6} carbocycle, $-(CH_2)_nQ$, $-(CH_2)_nCHQR$, -CHQR, $-CQ(R)_2$, and unsubstituted C_{1-6} alkyl, where Q is selected from a C_{3-6} carbocycle, a 5- to 14-membered heterocycle having one or more heteroatoms selected from N, O, and S, -OR, $-O(CH_2)_nN(R)_2$, -C(O)OR, -OC(O)R, $-CX_3$, $-CX_2H$, $-CXH_2$, -CN, $-C(O)N(R)_2$, $-N(R)C(O)R$, $-N(R)S(O)_2R$, $-N(R)C(O)N(R)_2$, $-N(R)C(S)N(R)_2$, $-CRN(R)_2C(O)OR$, and each n is independently selected from 1, 2, 3, 4, and 5; and when Q is a 5- to 14-membered heterocycle and (i) R_4 is $-(CH_2)_nQ$ in which n is 1 or 2, or (ii) R_4 is $-(CH_2)_nCHQR$ in which n is 1, or (iii) R_4 is -CHQR, and $-CQ(R)_2$, then Q is either a 5- to 14-membered heteroaryl or 8- to 14-membered heterocycloalkyl;

each R_5 is independently selected from the group consisting of C_{1-3} alkyl, C_{2-3} alkenyl, and H;

each R_6 is independently selected from the group consisting of C_{1-3} alkyl, C_{2-3} alkenyl, and H;

M and M' are independently selected from -C(O)O-, -OC(O)-, -C(O)N(R')-, -N(R')C(O)-, -C(O)-, -C(S)-, -C(S)S-, -SC(S)-, -CH(OH)-, -P(O)(OR')O-, $-S(O)_2-$, an aryl group, and a heteroaryl group;

R_7 is selected from the group consisting of C_{1-3} alkyl, C_{2-3} alkenyl, and H;

each R is independently selected from the group consisting of C_{1-3} alkyl, C_{2-3} alkenyl, and H;

each R' is independently selected from the group consisting of C_{1-18} alkyl, C_{2-18} alkenyl, -R*YR", -YR", and H;

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each R" is independently selected from the group consisting of C_{3-14} alkyl and C_{3-14} alkenyl;

each R* is independently selected from the group consisting of C_{1-12} alkyl and C_{2-12} alkenyl;

each Y is independently a C_{3-6} carbocycle;

each X is independently selected from the group consisting of F, Cl, Br, and I; and

m is selected from 5, 6, 7, 8, 9, 10, 11, 12, and 13,

or salts or stereoisomers thereof.

[0592] In still another embodiments, another subset of compounds of Formula (I) includes those in which

R_1 is selected from the group consisting of C_{5-20} alkyl, C_{5-20} alkenyl, -R*YR", -YR", and -R"M'R';

R_2 and R_3 are independently selected from the group consisting of H, C_{1-14} alkyl, C_{2-14} alkenyl, -R*YR", -YR", and -R*OR", or R_2 and R_3, together with the atom to which they are attached, form a heterocycle or carbocycle;

R_4 is selected from the group consisting of a C_{3-6} carbocycle, $-(CH_2)_nQ$, $-(CH_2)_nCHQR$, -CHQR, $-CQ(R)_2$, and unsubstituted C_{1-6} alkyl, where Q is selected from a C_{3-6} carbocycle, a 5- to 14-membered heteroaryl having one or more heteroatoms selected from N, O, and S, -OR, $-O(CH_2)_nN(R)_2$, -C(O)OR, -OC(O)R, $-CX_3$, $-CX_2H$, $-CXH_2$, -CN, $-C(O)N(R)_2$, -N(R)C(O)R, $-N(R)S(O)_2R$, $-N(R)C(O)N(R)_2$, $-N(R)C(S)N(R)_2$, $-CRN(R)_2C(O)OR$, and each n is independently selected from 1, 2, 3, 4, and 5;

each R_5 is independently selected from the group consisting of C_{1-3} alkyl, C_{2-3} alkenyl, and H;

each R_6 is independently selected from the group consisting of C_{1-3} alkyl, C_{2-3} alkenyl, and H;

M and M' are independently selected from -C(O)O-, -OC(O)-, -C(O)N(R')-, -N(R')C(O)-, -C(O)-, -C(S)-, -C(S)S-, -SC(S)-, -CH(OH)-, -P(O)(OR')O-, $-S(O)_2-$, an aryl group, and a heteroaryl group;

R_7 is selected from the group consisting of C_{1-3} alkyl, C_{2-3} alkenyl, and H;

each R is independently selected from the group consisting of C_{1-3} alkyl, C_{2-3} alkenyl, and H;

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each R' is independently selected from the group consisting of C_{1-18} alkyl, C_{2-18} alkenyl, -R*YR", -YR", and H;

each R" is independently selected from the group consisting of C_{3-14} alkyl and C_{3-14} alkenyl;

each R* is independently selected from the group consisting of C_{1-12} alkyl and C_{2-12} alkenyl;

each Y is independently a C_{3-6} carbocycle;

each X is independently selected from the group consisting of F, Cl, Br, and I; and

m is selected from 5, 6, 7, 8, 9, 10, 11, 12, and 13,

or salts or stereoisomers thereof.

In yet another embodiments, another subset of compounds of Formula (I) includes those in which

R_1 is selected from the group consisting of C_{5-20} alkyl, C_{5-20} alkenyl, -R*YR", -YR", and -R"M'R';

R_2 and R_3 are independently selected from the group consisting of H, C_{2-14} alkyl, C_{2-14} alkenyl, -R*YR", -YR", and -R*OR", or R_2 and R_3, together with the atom to which they are attached, form a heterocycle or carbocycle;

R_4 is $-(CH_2)_nQ$ or $-(CH_2)_nCHQR$, where Q is $-N(R)_2$, and n is selected from 3, 4, and 5;

each R_5 is independently selected from the group consisting of C_{1-3} alkyl, C_{2-3} alkenyl, and H;

each R_6 is independently selected from the group consisting of C_{1-3} alkyl, C_{2-3} alkenyl, and H;

M and M' are independently selected from -C(O)O-, -OC(O)-, -C(O)N(R')-, -N(R')C(O)-, -C(O)-, -C(S)-, -C(S)S-, -SC(S)-, -CH(OH)-, -P(O)(OR')O-, $-S(O)_2-$, an aryl group, and a heteroaryl group;

R_7 is selected from the group consisting of C_{1-3} alkyl, C_{2-3} alkenyl, and H;

each R is independently selected from the group consisting of C_{1-3} alkyl, C_{2-3} alkenyl, and H;

each R' is independently selected from the group consisting of C_{1-18} alkyl, C_{2-18} alkenyl, -R*YR", -YR", and H;

each R" is independently selected from the group consisting of C_{3-14} alkyl and C_{3-14} alkenyl;

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each R* is independently selected from the group consisting of C_{1-12} alkyl and C_{1-12} alkenyl;

each Y is independently a C_{3-6} carbocycle;

each X is independently selected from the group consisting of F, Cl, Br, and I; and

m is selected from 5, 6, 7, 8, 9, 10, 11, 12, and 13,

or salts or stereoisomers thereof.

[0593] In still another embodiments, another subset of compounds of Formula (I) includes those in which

R_1 is selected from the group consisting of C_{5-20} alkyl, C_{5-20} alkenyl, -R*YR", -YR", and -R"M'R';

R_2 and R_3 are independently selected from the group consisting of C_{1-14} alkyl, C_{2-14} alkenyl, -R*YR", -YR", and -R*OR", or R_2 and R_3, together with the atom to which they are attached, form a heterocycle or carbocycle;

R_4 is selected from the group consisting of $-(CH_2)_nQ$, $-(CH_2)_nCHQR$, -CHQR, and $-CQ(R)_2$, where Q is $-N(R)_2$, and n is selected from 1, 2, 3, 4, and 5;

each R_5 is independently selected from the group consisting of C_{1-3} alkyl, C_{2-3} alkenyl, and H;

each R_6 is independently selected from the group consisting of C_{1-3} alkyl, C_{2-3} alkenyl, and H;

M and M' are independently selected from -C(O)O-, -OC(O)-, -C(O)N(R')-, -N(R')C(O)-, -C(O)-, -C(S)-, -C(S)S-, -SC(S)-, -CH(OH)-, -P(O)(OR')O-, $-S(O)_2-$, an aryl group, and a heteroaryl group;

R_7 is selected from the group consisting of C_{1-3} alkyl, C_{2-3} alkenyl, and H;

each R is independently selected from the group consisting of C_{1-3} alkyl, C_{2-3} alkenyl, and H;

each R' is independently selected from the group consisting of C_{1-18} alkyl, C_{2-18} alkenyl, -R*YR", -YR", and H;

each R" is independently selected from the group consisting of C_{3-14} alkyl and C_{3-14} alkenyl;

each R* is independently selected from the group consisting of C_{1-12} alkyl and C_{1-12} alkenyl;

each Y is independently a C_{3-6} carbocycle;

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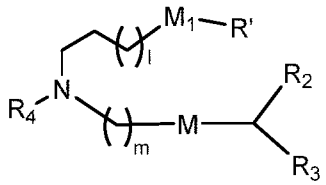
each X is independently selected from the group consisting of F, Cl, Br, and I; and

m is selected from 5, 6, 7, 8, 9, 10, 11, 12, and 13,

or salts or stereoisomers thereof.

[0594] In certain embodiments, a subset of compounds of Formula (I) includes those of Formula (IA):

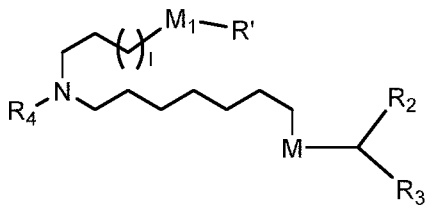


(IA),

or a salt or stereoisomer thereof, wherein l is selected from 1, 2, 3, 4, and 5; m is selected from 5, 6, 7, 8, and 9; M_1 is a bond or M'; R_4 is unsubstituted C_{1-3} alkyl, or $-(CH_2)_nQ$, in which Q is OH, $-NHC(S)N(R)_2$, or $-NHC(O)N(R)_2$; M and M' are independently selected from -C(O)O-, -OC(O)-, -C(O)N(R')-, -P(O)(OR')O-, an aryl group, and a heteroaryl group; and

R_2 and R_3 are independently selected from the group consisting of H, C_{1-14} alkyl, and C_{2-14} alkenyl.

[0595] In certain embodiments, a subset of compounds of Formula (I) includes those of Formula (II):

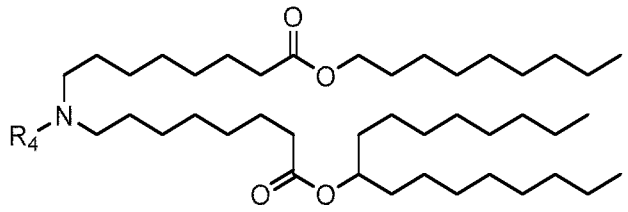


(II)

or a salt or stereoisomer thereof, wherein l is selected from 1, 2, 3, 4, and 5; M_1 is a bond or M'; R_4 is unsubstituted C_{1-3} alkyl, or $-(CH_2)_nQ$, in which n is 2, 3, or 4, and Q is OH, $-NHC(S)N(R)_2$, or $-NHC(O)N(R)_2$; M and M' are independently selected from -C(O)O-, -OC(O)-, -C(O)N(R')-, -P(O)(OR')O-, an aryl group, and a heteroaryl group; and

R_2 and R_3 are independently selected from the group consisting of H, C_{1-14} alkyl, and C_{2-14} alkenyl.

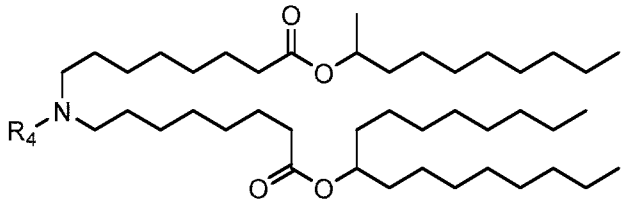
[0596] In some embodiments, the compound of formula (I) is of the formula (IIa),



(IIa),

or a salt thereof, wherein R_4 is as described above.

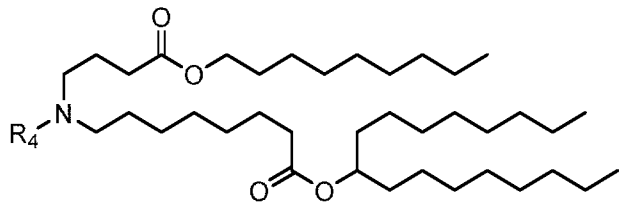
[0597] In some embodiments, the compound of formula (I) is of the formula (IIb),



(IIb),

or a salt thereof, wherein R_4 is as described above.

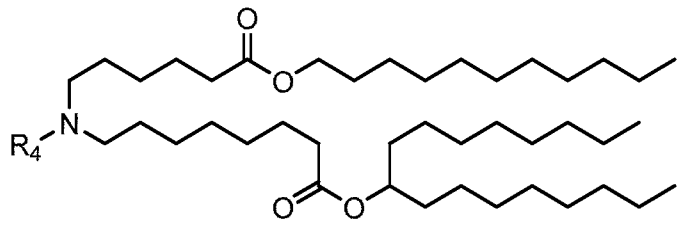
[0598] In some embodiments, the compound of formula (I) is of the formula (IIc),



(IIc),

or a salt thereof, wherein R_4 is as described above.

[0599] In some embodiments, the compound of formula (I) is of the formula (IIe):



(IIe),

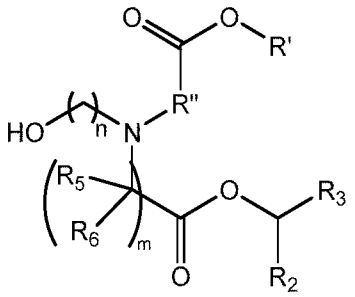
or a salt thereof, wherein R_4 is as described above.

[0600] In some embodiments, the compound of formula (IIa), (IIb), (IIc), or (IIe) comprises an R_4 which is selected from $-(CH_2)_nQ$ and $-(CH_2)_nCHQR$, wherein Q, R and n are as defined above.

[0601] In some embodiments, Q is selected from the group consisting of -OR, -OH, $-O(CH_2)_nN(R)_2$, -OC(O)R, $-CX_3$, -CN, -N(R)C(O)R, -N(H)C(O)R, $-N(R)S(O)_2R$, $-N(H)S(O)_2R$, $-N(R)C(O)N(R)_2$, $-N(H)C(O)N(R)_2$, -N(H)C(O)N(H)(R), $-N(R)C(S)N(R)_2$, $-N(H)C(S)N(R)_2$,

-N(H)C(S)N(H)(R), and a heterocycle, wherein R is as defined above. In some aspects, n is 1 or 2. In some embodiments, Q is OH, -NHC(S)N(R)$_2$, or -NHC(O)N(R)$_2$.

[0602] In some embodiments, the compound of formula (I) is of the formula (IId),



(IId),

or a salt thereof, wherein R_2 and R_3 are independently selected from the group consisting of C_{5-14} alkyl and C_{5-14} alkenyl, n is selected from 2, 3, and 4, and R', R'', R_5, R_6 and m are as defined above.

[0603] In some aspects of the compound of formula (IId), R_2 is C_8 alkyl. In some aspects of the compound of formula (IId), R_3 is C_5-C_9 alkyl. In some aspects of the compound of formula (IId), m is 5, 7, or 9. In some aspects of the compound of formula (IId), each R_5 is H. In some aspects of the compound of formula (IId), each R_6 is H.

[0604] In another aspect, the present application provides a lipid composition (e.g., a lipid nanoparticle (LNP)) comprising: (1) a compound having the formula (I); (2) optionally a helper lipid (e.g. a phospholipid); (3) optionally a structural lipid (e.g. a sterol); (4) optionally a lipid conjugate (e.g. a PEG-lipid); and (5) optionally a quaternary amine compound. In exemplary embodiments, the lipid composition (e.g., LNP) further comprises a polynucleotide encoding an MCM polypeptide, e.g., a polynucleotide encapsulated therein.

[0605] As used herein, the term "alkyl" or "alkyl group" means a linear or branched, saturated hydrocarbon including one or more carbon atoms (e.g., one, two, three, four, five, six, seven, eight, nine, ten, eleven, twelve, thirteen, fourteen, fifteen, sixteen, seventeen, eighteen, nineteen, twenty, or more carbon atoms).

[0606] The notation "C_{1-14} alkyl" means a linear or branched, saturated hydrocarbon including 1-14 carbon atoms. An alkyl group can be optionally substituted.

[0607] As used herein, the term "alkenyl" or "alkenyl group" means a linear or branched hydrocarbon including two or more carbon atoms (e.g., two, three, four, five, six, seven, eight, nine, ten, eleven, twelve, thirteen, fourteen, fifteen, sixteen, seventeen, eighteen, nineteen, twenty, or more carbon atoms) and at least one double bond.

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[0608] The notation "C_{2-14} alkenyl" means a linear or branched hydrocarbon including 2-14 carbon atoms and at least one double bond. An alkenyl group can include one, two, three, four, or more double bonds. For example, C_{18} alkenyl can include one or more double bonds. A C_{18} alkenyl group including two double bonds can be a linoleyl group. An alkenyl group can be optionally substituted.

[0609] As used herein, the term "carbocycle" or "carbocyclic group" means a mono- or multi-cyclic system including one or more rings of carbon atoms. Rings can be three, four, five, six, seven, eight, nine, ten, eleven, twelve, thirteen, fourteen, or fifteen membered rings.

[0610] The notation "C_{3-6} carbocycle" means a carbocycle including a single ring having 3-6 carbon atoms. Carbocycles can include one or more double bonds and can be aromatic (e.g., aryl groups). Examples of carbocycles include cyclopropyl, cyclopentyl, cyclohexyl, phenyl, naphthyl, and 1,2-dihydronaphthyl groups. Carbocycles can be optionally substituted.

[0611] As used herein, the term "heterocycle" or "heterocyclic group" means a mono- or multi-cyclic system including one or more rings, where at least one ring includes at least one heteroatom. Heteroatoms can be, for example, nitrogen, oxygen, or sulfur atoms. Rings can be three, four, five, six, seven, eight, nine, ten, eleven, or twelve membered rings. Heterocycles can include one or more double bonds and can be aromatic (e.g., heteroaryl groups). Examples of heterocycles include imidazolyl, imidazolidinyl, oxazolyl, oxazolidinyl, thiazolyl, thiazolidinyl, pyrazolidinyl, pyrazolyl, isoxazolidinyl, isoxazolyl, isothiazolidinyl, isothiazolyl, morpholinyl, pyrrolyl, pyrrolidinyl, furyl, tetrahydrofuryl, thiophenyl, pyridinyl, piperidinyl, quinolyl, and isoquinolyl groups. Heterocycles can be optionally substituted.

[0612] As used herein, a "biodegradable group" is a group that can facilitate faster metabolism of a lipid in a subject. A biodegradable group can be, but is not limited to, -C(O)O-, -OC(O)-, -C(O)N(R')-, -N(R')C(O)-, -C(O)-, -C(S)-, -C(S)S-, -SC(S)-, -CH(OH)-, -P(O)(OR')O-, $-S(O)_2-$, an aryl group, and a heteroaryl group.

[0613] As used herein, an "aryl group" is a carbocyclic group including one or more aromatic rings. Examples of aryl groups include phenyl and naphthyl groups.

[0614] As used herein, a "heteroaryl group" is a heterocyclic group including one or more aromatic rings. Examples of heteroaryl groups include pyrrolyl, furyl, thiophenyl, imidazolyl, oxazolyl, and thiazolyl. Both aryl and heteroaryl groups can be optionally substituted. For example, M and M' can be selected from the non-limiting group consisting of optionally

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substituted phenyl, oxazole, and thiazole. In the formulas herein, M and M' can be independently selected from the list of biodegradable groups above.

[0615] Alkyl, alkenyl, and cyclyl (e.g., carbocyclyl and heterocyclyl) groups can be optionally substituted unless otherwise specified. Optional substituents can be selected from the group consisting of, but are not limited to, a halogen atom (e.g., a chloride, bromide, fluoride, or iodide group), a carboxylic acid (e.g., -C(O)OH), an alcohol (e.g., a hydroxyl, -OH), an ester (e.g., -C(O)OR or -OC(O)R), an aldehyde (e.g., -C(O)H), a carbonyl (e.g., -C(O)R, alternatively represented by C=O), an acyl halide (e.g., -C(O)X, in which X is a halide selected from bromide, fluoride, chloride, and iodide), a carbonate (e.g., -OC(O)OR), an alkoxy (e.g., -OR), an acetal (e.g., $-C(OR)_2R''''$, in which each OR are alkoxy groups that can be the same or different and R"" is an alkyl or alkenyl group), a phosphate (e.g., $P(O)_4^{3-}$), a thiol (e.g., -SH), a sulfoxide (e.g., -S(O)R), a sulfinic acid (e.g., -S(O)OH), a sulfonic acid (e.g., $-S(O)_2OH$), a thial (e.g., -C(S)H), a sulfate (e.g., $S(O)_4^{2-}$), a sulfonyl (e.g., $-S(O)_2-$), an amide (e.g., $-C(O)NR_2$, or -N(R)C(O)R), an azido (e.g., $-N_3$), a nitro (e.g., $-NO_2$), a cyano (e.g., -CN), an isocyano (e.g., -NC), an acyloxy (e.g., -OC(O)R), an amino (e.g., $-NR_2$, -NRH, or $-NH_2$), a carbamoyl (e.g., $-OC(O)NR_2$, -OC(O)NRH, or $-OC(O)NH_2$), a sulfonamide (e.g., $-S(O)_2NR_2$, $-S(O)_2NRH$, $-S(O)_2NH_2$, $-N(R)S(O)_2R$, $-N(H)S(O)_2R$, $-N(R)S(O)_2H$, or $-N(H)S(O)_2H$), an alkyl group, an alkenyl group, and a cyclyl (e.g., carbocyclyl or heterocyclyl) group.

[0616] In any of the preceding, R is an alkyl or alkenyl group, as defined herein. In some embodiments, the substituent groups themselves can be further substituted with, for example, one, two, three, four, five, or six substituents as defined herein. For example, a C_{1-6} alkyl group can be further substituted with one, two, three, four, five, or six substituents as described herein.

[0617] The compounds of any one of formulae (I), (IA), (II), (IIa), (IIb), (IIc), (IId), and (IIe) include one or more of the following features when applicable.

[0618] In some embodiments, R_4 is selected from the group consisting of a C_{3-6} carbocycle, $-(CH_2)_nQ$, $-(CH_2)_nCHQR$, -CHQR, and $-CQ(R)_2$, where Q is selected from a C_{3-6} carbocycle, 5- to 14- membered aromatic or non-aromatic heterocycle having one or more heteroatoms selected from N, O, S, and P, -OR, $-O(CH_2)_nN(R)_2$, -C(O)OR, -OC(O)R, $-CX_3$, $-CX_2H$, $-CXH_2$, -CN, $-N(R)_2$, $-C(O)N(R)_2$, -N(R)C(O)R, $-N(R)S(O)_2R$, $-N(R)C(O)N(R)_2$, $-N(R)C(S)N(R)_2$, and $-C(R)N(R)_2C(O)OR$, and each n is independently selected from 1, 2, 3, 4, and 5.

[0619] In another embodiment, R_4 is selected from the group consisting of a C_{3-6} carbocycle, $-(CH_2)_nQ$, $-(CH_2)_nCHQR$, -CHQR, and $-CQ(R)_2$, where Q is selected from a C_{3-6} carbocycle, a 5-

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to 14-membered heteroaryl having one or more heteroatoms selected from N, O, and S, -OR, $-O(CH_2)_nN(R)_2$, -C(O)OR, -OC(O)R, $-CX_3$, $-CX_2H$, $-CXH_2$, -CN, $-C(O)N(R)_2$, $-N(R)C(O)R$, $-N(R)S(O)_2R$, $-N(R)C(O)N(R)_2$, $-N(R)C(S)N(R)_2$, $-C(R)N(R)_2C(O)OR$, and a 5- to 14-membered heterocycloalkyl having one or more heteroatoms selected from N, O, and S which is substituted with one or more substituents selected from oxo (=O), OH, amino, and C_{1-3} alkyl, and each n is independently selected from 1, 2, 3, 4, and 5.

[0620] In another embodiment, R_4 is selected from the group consisting of a C_{3-6} carbocycle, $-(CH_2)_nQ$, $-(CH_2)_nCHQR$, -CHQR, and $-CQ(R)_2$, where Q is selected from a C_{3-6} carbocycle, a 5- to 14-membered heterocycle having one or more heteroatoms selected from N, O, and S, -OR, $-O(CH_2)_nN(R)_2$, -C(O)OR, -OC(O)R, $-CX_3$, $-CX_2H$, $-CXH_2$, -CN, $-C(O)N(R)_2$, $-N(R)C(O)R$, $-N(R)S(O)_2R$, $-N(R)C(O)N(R)_2$, $-N(R)C(S)N(R)_2$, $-C(R)N(R)_2C(O)OR$, and each n is independently selected from 1, 2, 3, 4, and 5; and when Q is a 5- to 14-membered heterocycle and (i) R_4 is $-(CH_2)_nQ$ in which n is 1 or 2, or (ii) R_4 is $-(CH_2)_nCHQR$ in which n is 1, or (iii) R_4 is -CHQR, and $-CQ(R)_2$, then Q is either a 5- to 14-membered heteroaryl or 8- to 14-membered heterocycloalkyl.

[0621] In another embodiment, R_4 is selected from the group consisting of a C_{3-6} carbocycle, $-(CH_2)_nQ$, $-(CH_2)_nCHQR$, -CHQR, and $-CQ(R)_2$, where Q is selected from a C_{3-6} carbocycle, a 5- to 14-membered heteroaryl having one or more heteroatoms selected from N, O, and S, -OR, $-O(CH_2)_nN(R)_2$, -C(O)OR, -OC(O)R, $-CX_3$, $-CX_2H$, $-CXH_2$, -CN, $-C(O)N(R)_2$, $-N(R)C(O)R$, $-N(R)S(O)_2R$, $-N(R)C(O)N(R)_2$, $-N(R)C(S)N(R)_2$, $-C(R)N(R)_2C(O)OR$, and each n is independently selected from 1, 2, 3, 4, and 5.

[0622] In another embodiment, R_4 is unsubstituted C_{1-4} alkyl, e.g., unsubstituted methyl.

[0623] In certain embodiments, the disclosure provides a compound having the Formula (I), wherein R_4 is $-(CH_2)_nQ$ or $-(CH_2)_nCHQR$, where Q is $-N(R)_2$, and n is selected from 3, 4, and 5.

[0624] In certain embodiments, the disclosure provides a compound having the Formula (I), wherein R_4 is selected from the group consisting of $-(CH_2)_nQ$, $-(CH_2)_nCHQR$, -CHQR, and $-CQ(R)_2$, where Q is $-N(R)_2$, and n is selected from 1, 2, 3, 4, and 5.

[0625] In certain embodiments, the disclosure provides a compound having the Formula (I), wherein R_2 and R_3 are independently selected from the group consisting of C_{2-14} alkyl, C_{2-14} alkenyl, -R*YR", -YR", and -R*OR", or R_2 and R_3, together with the atom to which they are attached, form a heterocycle or carbocycle, and R_4 is $-(CH_2)_nQ$ or $-(CH_2)_nCHQR$, where Q is $-N(R)_2$, and n is selected from 3, 4, and 5.

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[0626] In certain embodiments, R_2 and R_3 are independently selected from the group consisting of C_{2-14} alkyl, C_{2-14} alkenyl, -R*YR", -YR", and -R*OR", or R_2 and R_3, together with the atom to which they are attached, form a heterocycle or carbocycle.

[0627] In some embodiments, R_1 is selected from the group consisting of C_{5-20} alkyl and C_{5-20} alkenyl.

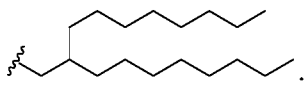
[0628] In other embodiments, R_1 is selected from the group consisting of -R*YR", -YR", and -R"M'R'.

[0629] In certain embodiments, R_1 is selected from -R*YR" and -YR". In some embodiments, Y is a cyclopropyl group. In some embodiments, R* is C_8 alkyl or C_8 alkenyl. In certain embodiments, R" is C_{3-12} alkyl. For example, R" can be C_3 alkyl. For example, R" can be C_{4-8} alkyl (e.g., C_4, C_5, C_6, C_7, or C_8 alkyl).

[0630] In some embodiments, R_1 is C_{5-20} alkyl. In some embodiments, R_1 is C_6 alkyl. In some embodiments, R_1 is C_8 alkyl. In other embodiments, R_1 is C_9 alkyl. In certain embodiments, R_1 is C_{14} alkyl. In other embodiments, R_1 is C_{18} alkyl.

[0631] In some embodiments, R_1 is C_{5-20} alkenyl. In certain embodiments, R_1 is C_{18} alkenyl. In some embodiments, R_1 is linoleyl.

[0632] In certain embodiments, R_1 is branched (*e.g.*, decan-2-yl, undecan-3-yl, dodecan-4-yl, tridecan-5-yl, tetradecan-6-yl, 2-methylundecan-3-yl, 2-methyldecan-2-yl, 3-methylundecan-3-yl, 4-methyldodecan-4-yl, or heptadeca-9-yl). In certain embodiments, R_1 is



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[0633] In certain embodiments, R_1 is unsubstituted C_{5-20} alkyl or C_{5-20} alkenyl. In certain embodiments, R' is substituted C_{5-20} alkyl or C_{5-20} alkenyl (*e.g.*, substituted with a C_{3-6} carbocycle such as 1-cyclopropylnonyl).

[0634] In other embodiments, R_1 is -R"M'R'.

[0635] In some embodiments, R' is selected from -R*YR" and -YR". In some embodiments, Y is C_{3-8} cycloalkyl. In some embodiments, Y is C_{6-10} aryl. In some embodiments, Y is a cyclopropyl group. In some embodiments, Y is a cyclohexyl group. In certain embodiments, R* is C_1 alkyl.

[0636] In some embodiments, R" is selected from the group consisting of C_{3-12} alkyl and C_{3-12} alkenyl. In some embodiments, R" adjacent to Y is C_1 alkyl. In some embodiments, R" adjacent to Y is C_{4-9} alkyl (*e.g.*, C_4, C_5, C_6, C_7 or C_8 or C_9 alkyl).

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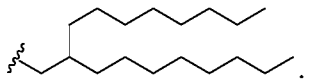
[0637] In some embodiments, R' is selected from C_4 alkyl and C_4 alkenyl. In certain embodiments, R' is selected from C_5 alkyl and C_5 alkenyl. In some embodiments, R' is selected from C_6 alkyl and C_6 alkenyl. In some embodiments, R' is selected from C_7 alkyl and C_7 alkenyl. In some embodiments, R' is selected from C_9 alkyl and C_9 alkenyl.

[0638] In other embodiments, R' is selected from C_{11} alkyl and C_{11} alkenyl. In other embodiments, R' is selected from C_{12} alkyl, C_{12} alkenyl, C_{13} alkyl, C_{13} alkenyl, C_{14} alkyl, C_{14} alkenyl, C_{15} alkyl, C_{15} alkenyl, C_{16} alkyl, C_{16} alkenyl, C_{17} alkyl, C_{17} alkenyl, C_{18} alkyl, and C_{18} alkenyl. In certain embodiments, R' is branched (*e.g.*, decan-2-yl, undecan-3-yl, dodecan-4-yl, tridecan-5-yl, tetradecan-6-yl, 2-methylundecan-3-yl, 2-methyldecan-2-yl, 3-methylundecan-3-yl, 4-methyldodecan-4-yl or heptadeca-9-yl). In certain embodiments, R' is



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[0639] In certain embodiments, R' is unsubstituted C_{1-18} alkyl. In certain embodiments, R' is substituted C_{1-18} alkyl (*e.g.*, C_{1-15} alkyl substituted with a C_{3-6} carbocycle such as 1-cyclopropylnonyl).

[0640] In some embodiments, R" is selected from the group consisting of C_{3-14} alkyl and C_{3-14} alkenyl. In some embodiments, R" is C_3 alkyl, C_4 alkyl, C_5 alkyl, C_6 alkyl, C_7 alkyl, or C_8 alkyl. In some embodiments, R" is C_9 alkyl, C_{10} alkyl, C_{11} alkyl, C_{12} alkyl, C_{13} alkyl, or C_{14} alkyl.

[0641] In some embodiments, M' is -C(O)O-. In some embodiments, M' is -OC(O)-.

[0642] In other embodiments, M' is an aryl group or heteroaryl group. For example, M' can be selected from the group consisting of phenyl, oxazole, and thiazole.

[0643] In some embodiments, M is -C(O)O- In some embodiments, M is -OC(O)-. In some embodiments, M is -C(O)N(R')-. In some embodiments, M is -P(O)(OR')O-.

[0644] In other embodiments, M is an aryl group or heteroaryl group. For example, M can be selected from the group consisting of phenyl, oxazole, and thiazole.

[0645] In some embodiments, M is the same as M'. In other embodiments, M is different from M'.

[0646] In some embodiments, each R_5 is H. In certain such embodiments, each R_6 is also H.

[0647] In some embodiments, R_7 is H. In other embodiments, R_7 is C_{1-3} alkyl (*e.g.*, methyl, ethyl, propyl, or i-propyl).

[0648] In some embodiments, R_2 and R_3 are independently C_{5-14} alkyl or C_{5-14} alkenyl.

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[0649] In some embodiments, R_2 and R_3 are the same. In some embodiments, R_2 and R_3 are C_8 alkyl. In certain embodiments, R_2 and R_3 are C_2 alkyl. In other embodiments, R_2 and R_3 are C_3 alkyl. In some embodiments, R_2 and R_3 are C_4 alkyl. In certain embodiments, R_2 and R_3 are C_5 alkyl. In other embodiments, R_2 and R_3 are C_6 alkyl. In some embodiments, R_2 and R_3 are C_7 alkyl.

[0650] In other embodiments, R_2 and R_3 are different. In certain embodiments, R_2 is C_8 alkyl. In some embodiments, R_3 is C_{1-7} (*e.g.*, C_1, C_2, C_3, C_4, C_5, C_6, or C_7 alkyl) or C_9 alkyl.

[0651] In some embodiments, R_7 and R_3 are H.

[0652] In certain embodiments, R_2 is H.

[0653] In some embodiments, m is 5, 7, or 9.

[0654] In some embodiments, R_4 is selected from $-(CH_2)_nQ$ and $-(CH_2)_nCHQR$.

[0655] In some embodiments, Q is selected from the group consisting of -OR, -OH, $-O(CH_2)_nN(R)_2$, -OC(O)R, $-CX_3$, -CN, -N(R)C(O)R, -N(H)C(O)R, $-N(R)S(O)_2R$, $-N(H)S(O)_2R$, $-N(R)C(O)N(R)_2$, $-N(H)C(O)N(R)_2$, -N(H)C(O)N(H)(R), $-N(R)C(S)N(R)_2$, $-N(H)C(S)N(R)_2$, -N(H)C(S)N(H)(R), $-C(R)N(R)_2C(O)OR$, a carbocycle, and a heterocycle.

[0656] In certain embodiments, Q is -OH.

[0657] In certain embodiments, Q is a substituted or unsubstituted 5- to 10- membered heteroaryl, *e.g.*, Q is an imidazole, a pyrimidine, a purine, 2-amino-1,9-dihydro-6*H*-purin-6-one-9-yl (or guanin-9-yl), adenin-9-yl, cytosin-1-yl, or uracil-1-yl. In certain embodiments, Q is a substituted 5- to 14-membered heterocycloalkyl, *e.g.*, substituted with one or more substituents selected from oxo (=O), OH, amino, and C_{1-3} alkyl. For example, Q is 4-methylpiperazinyl, 4-(4-methoxybenzyl)piperazinyl, or isoindolin-2-yl-1,3-dione.

[0658] In certain embodiments, Q is an unsubstituted or substituted C_{6-10} aryl (such as phenyl) or C_{3-6} cycloalkyl.

[0659] In some embodiments, n is 1. In other embodiments, n is 2. In further embodiments, n is 3. In certain other embodiments, n is 4. For example, R_4 can be $-(CH_2)_2OH$. For example, R_4 can be $-(CH_2)_3OH$. For example, R_4 can be $-(CH_2)_4OH$. For example, R_4 can be benzyl. For example, R_4 can be 4-methoxybenzyl.

[0660] In some embodiments, R_4 is a C_{3-6} carbocycle. In some embodiments, R_4 is a C_{3-6} cycloalkyl. For example, R_4 can be cyclohexyl optionally substituted with *e.g.*, OH, halo, C_{1-6} alkyl, etc. For example, R_4 can be 2-hydroxycyclohexyl.

[0661] In some embodiments, R is H.

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[0662] In some embodiments, R is unsubstituted C_{1-3} alkyl or unsubstituted C_{2-3} alkenyl. For example, R_4 can be $-CH_2CH(OH)CH_3$ or $-CH_2CH(OH)CH_2CH_3$.

[0663] In some embodiments, R is substituted C_{1-3} alkyl, *e.g.*, CH_2OH. For example, R_4 can be $-CH_2CH(OH)CH_2OH$.

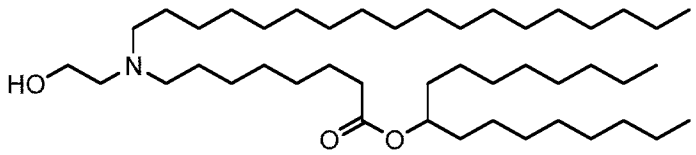
[0664] In some embodiments, R_2 and R_3, together with the atom to which they are attached, form a heterocycle or carbocycle. In some embodiments, R_2 and R_3, together with the atom to which they are attached, form a 5- to 14- membered aromatic or non-aromatic heterocycle having one or more heteroatoms selected from N, O, S, and P. In some embodiments, R_2 and R_3, together with the atom to which they are attached, form an optionally substituted C_{3-20} carbocycle (*e.g.*, C_{3-18} carbocycle, C_{3-15} carbocycle, C_{3-12} carbocycle, or C_{3-10} carbocycle), either aromatic or non-aromatic. In some embodiments, R_2 and R_3, together with the atom to which they are attached, form a C_{3-6} carbocycle. In other embodiments, R_2 and R_3, together with the atom to which they are attached, form a C_6 carbocycle, such as a cyclohexyl or phenyl group. In certain embodiments, the heterocycle or C_{3-6} carbocycle is substituted with one or more alkyl groups (*e.g.*, at the same ring atom or at adjacent or non-adjacent ring atoms). For example, R_2 and R_3, together with the atom to which they are attached, can form a cyclohexyl or phenyl group bearing one or more C_5 alkyl substitutions. In certain embodiments, the heterocycle or C_{3-6} carbocycle formed by R_2 and R_3, is substituted with a carbocycle groups. For example, R_2 and R_3, together with the atom to which they are attached, can form a cyclohexyl or phenyl group that is substituted with cyclohexyl. In some embodiments, R_2 and R_3, together with the atom to which they are attached, form a C_{7-15} carbocycle, such as a cycloheptyl, cyclopentadecanyl, or naphthyl group.

[0665] In some embodiments, R_4 is selected from $-(CH_2)_nQ$ and $-(CH_2)_nCHQR$. In some embodiments, Q is selected from the group consisting of -OR, -OH, $-O(CH_2)_nN(R)_2$, -OC(O)R, $-CX_3$, -CN, -N(R)C(O)R, -N(H)C(O)R, $-N(R)S(O)_2R$, $-N(H)S(O)_2R$, $-N(R)C(O)N(R)_2$, $-N(H)C(O)N(R)_2$, -N(H)C(O)N(H)(R), $-N(R)C(S)N(R)_2$, $-N(H)C(S)N(R)_2$, -N(H)C(S)N(H)(R), and a heterocycle. In other embodiments, Q is selected from the group consisting of an imidazole, a pyrimidine, and a purine.

[0666] In some embodiments, R_2 and R_3, together with the atom to which they are attached, form a heterocycle or carbocycle. In some embodiments, R_2 and R_3, together with the atom to which they are attached, form a C_{3-6} carbocycle, such as a phenyl group. In certain embodiments, the heterocycle or C_{3-6} carbocycle is substituted with one or more alkyl groups

(*e.g.*, at the same ring atom or at adjacent or non-adjacent ring atoms). For example, R_2 and R_3, together with the atom to which they are attached, can form a phenyl group bearing one or more C_5 alkyl substitutions.

[0667] In some embodiments, the pharmaceutical compositions of the present disclosure, the compound of formula (I) is selected from the group consisting of:



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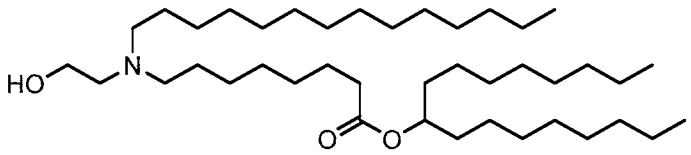

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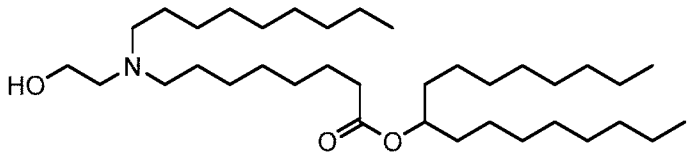

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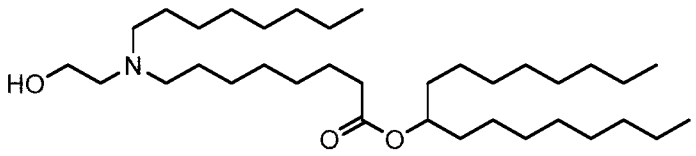

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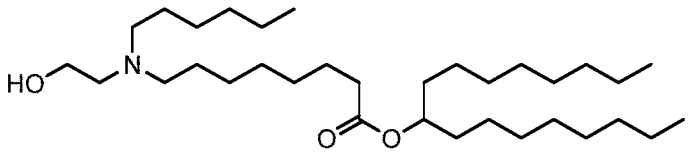

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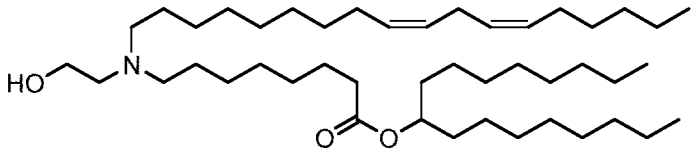

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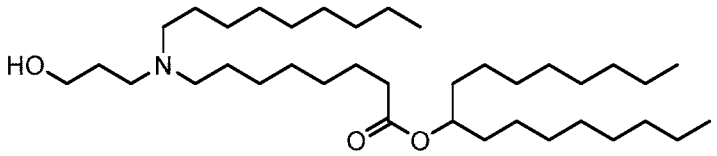

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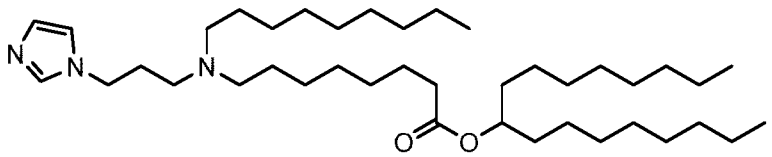

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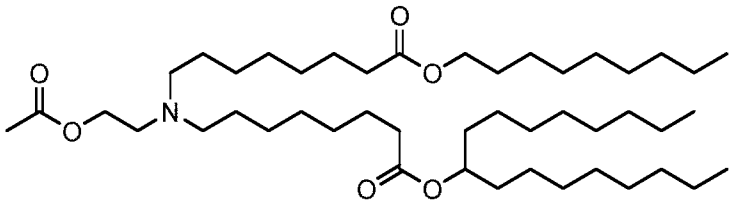

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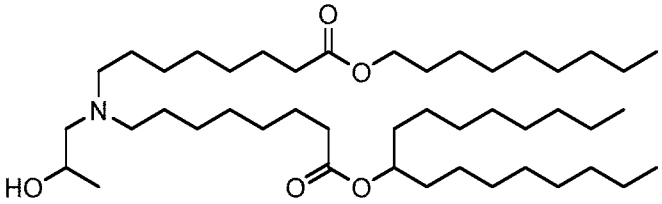

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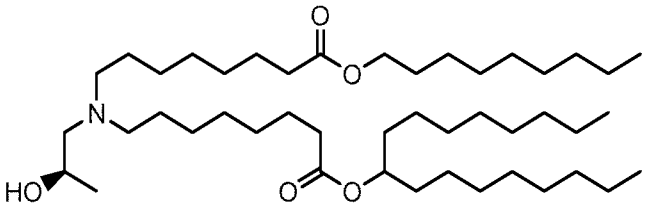

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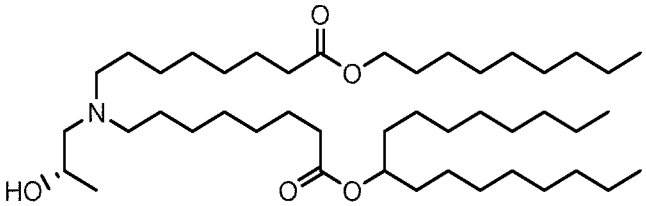

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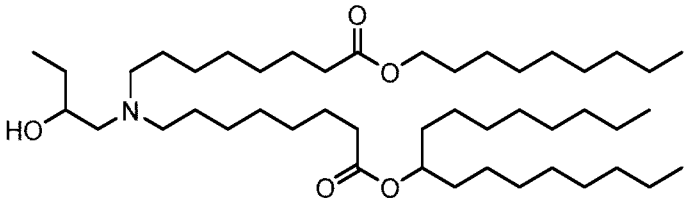

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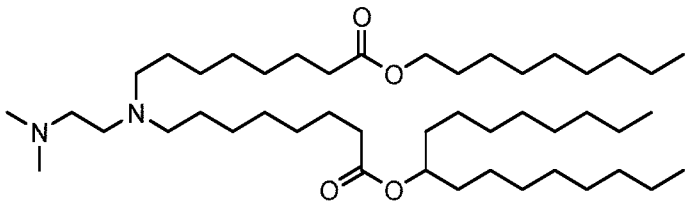

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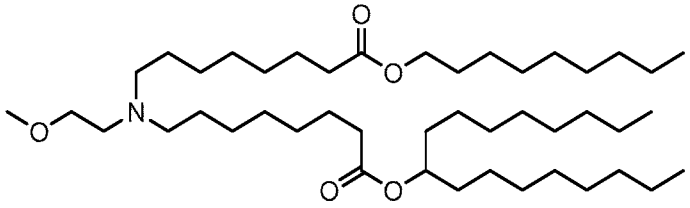

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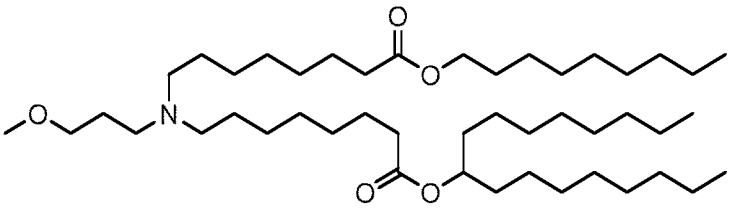

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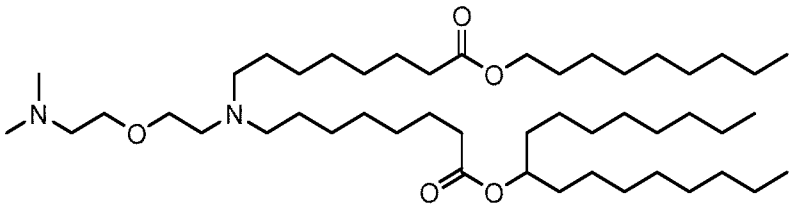

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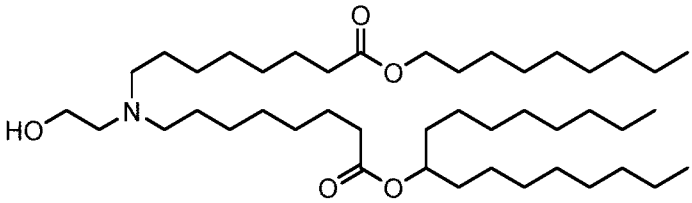

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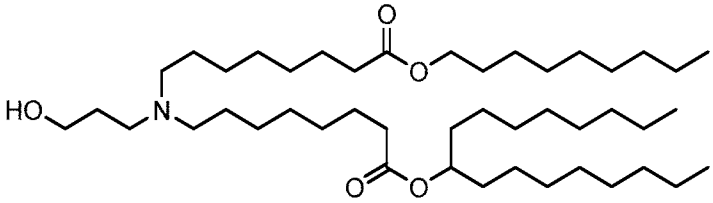

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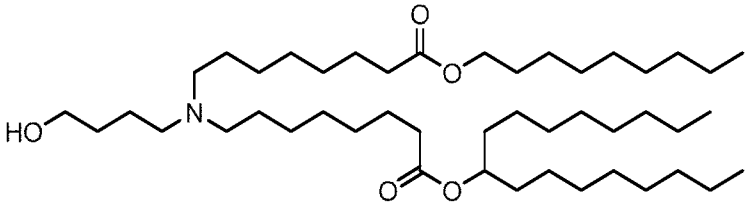

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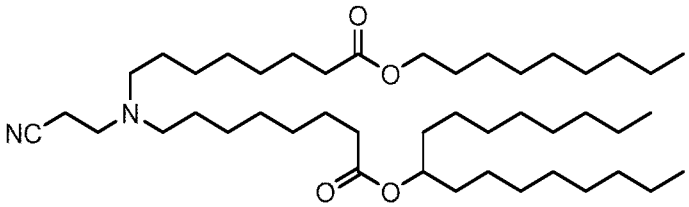

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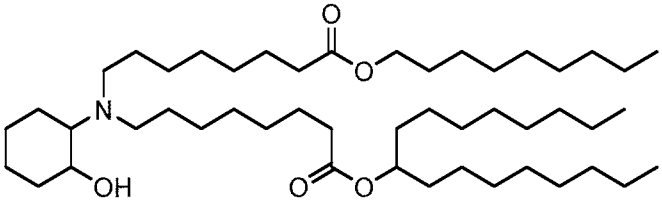

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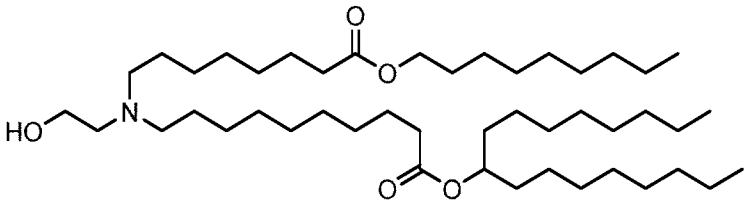

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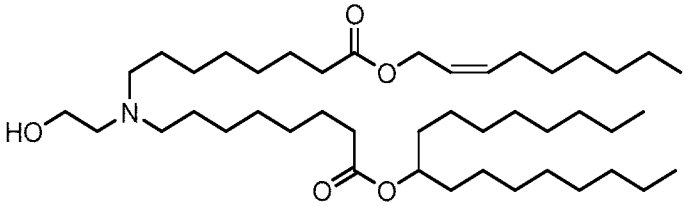

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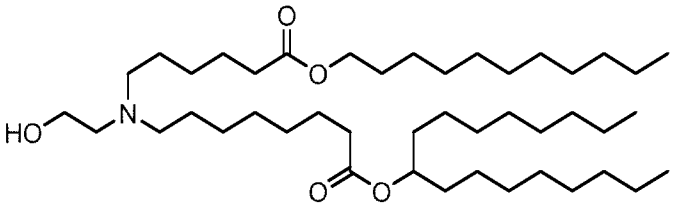

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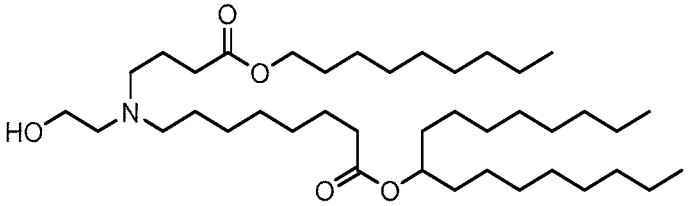

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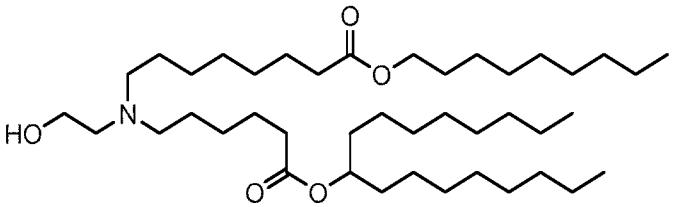

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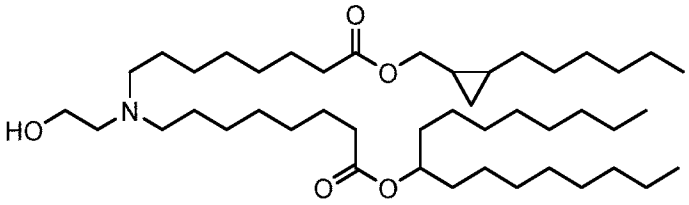

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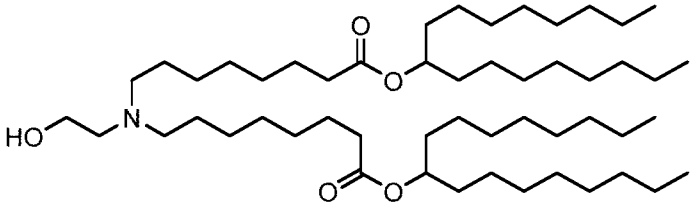

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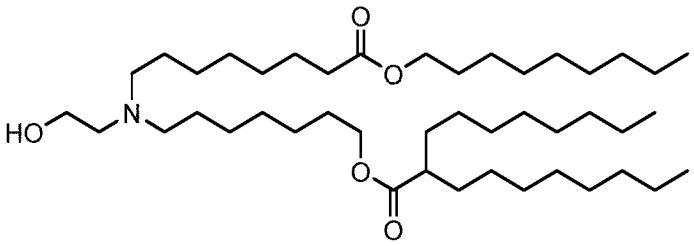

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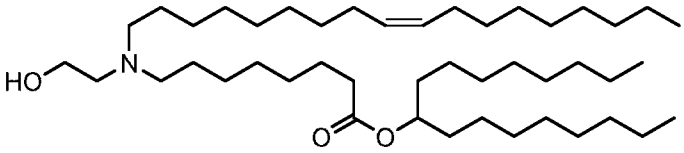

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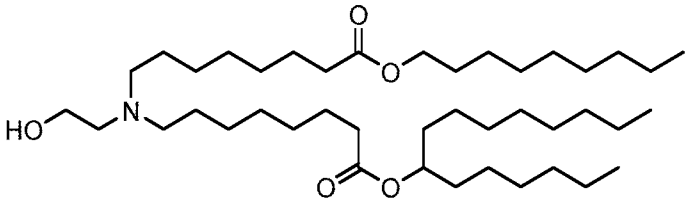

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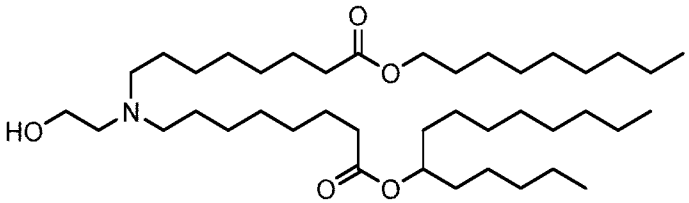

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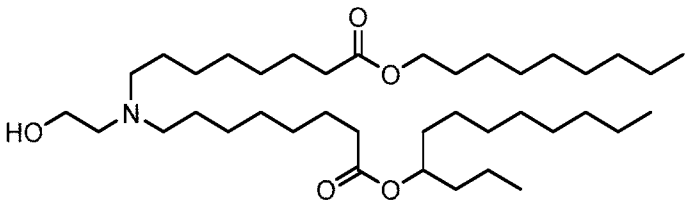

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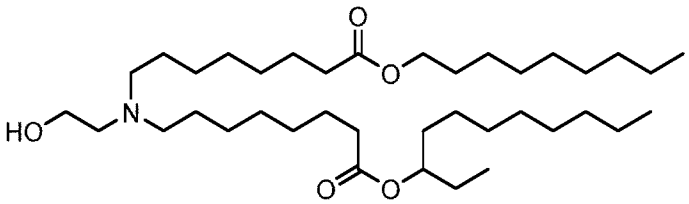

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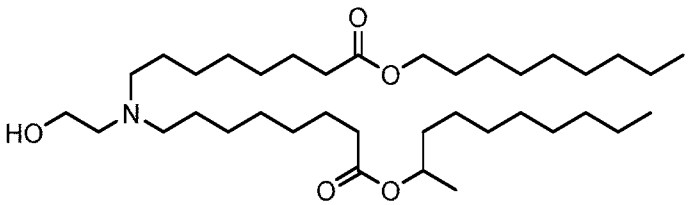

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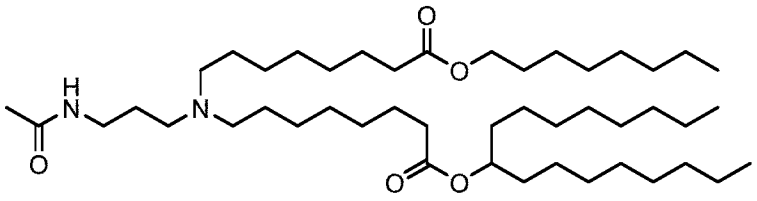

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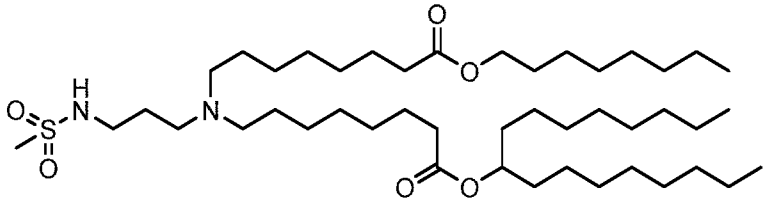

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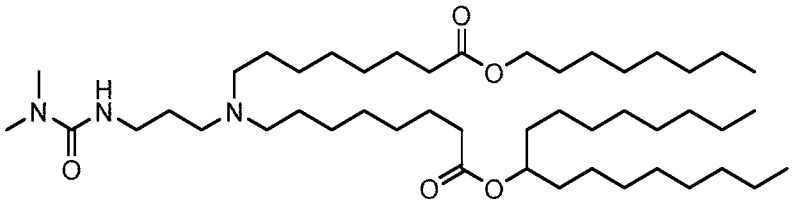

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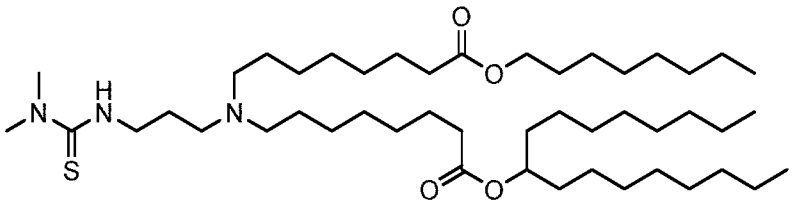

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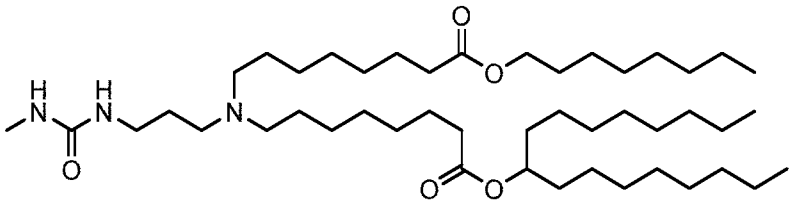

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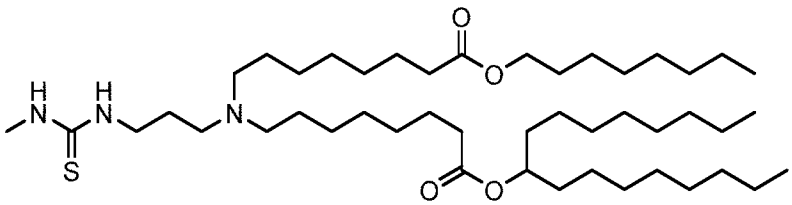

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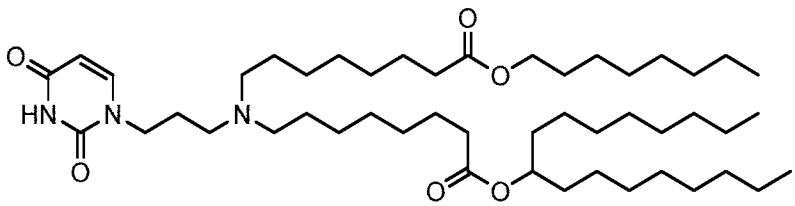

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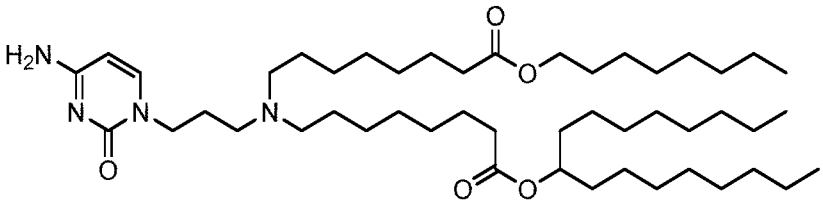

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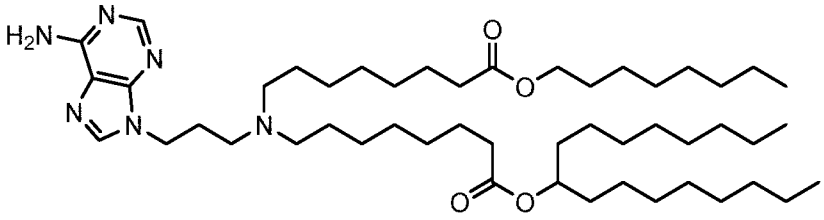

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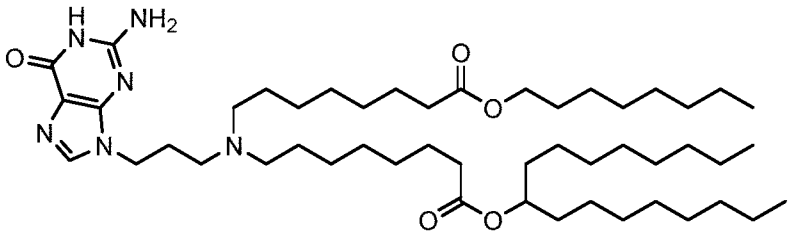

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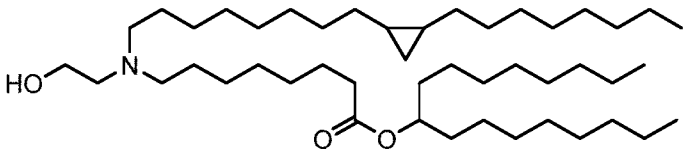

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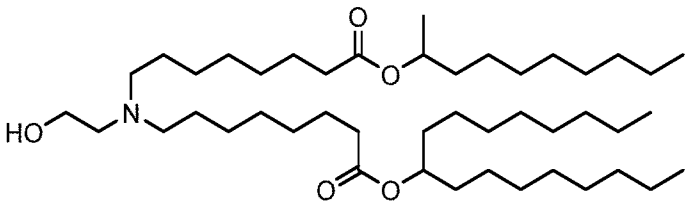

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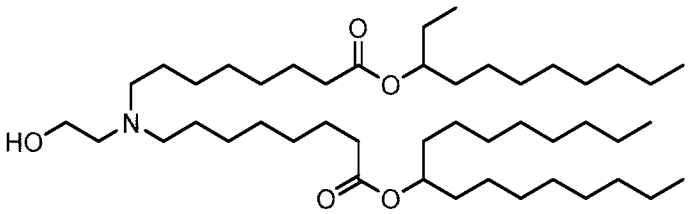

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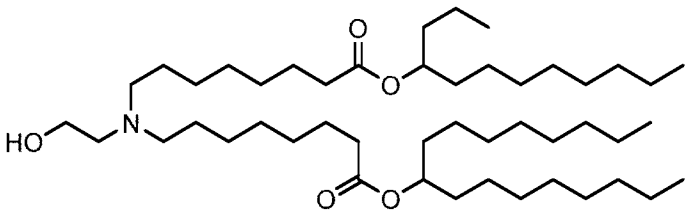

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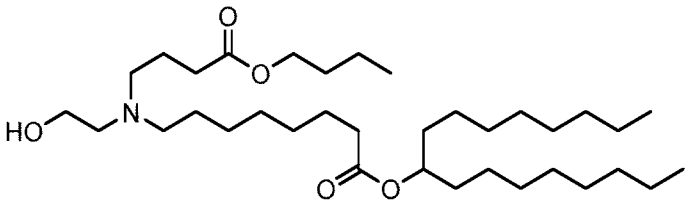

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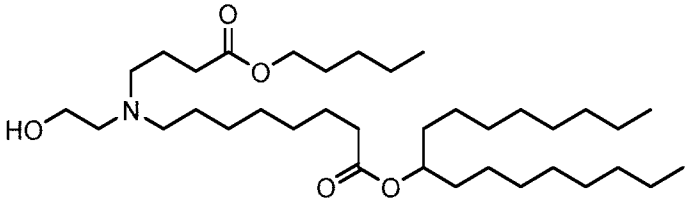

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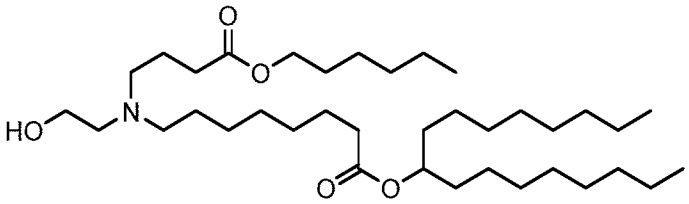

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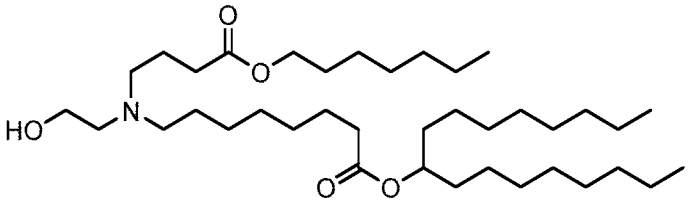

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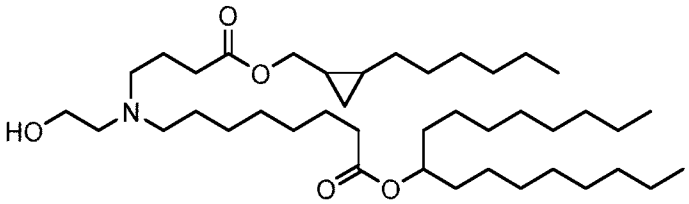

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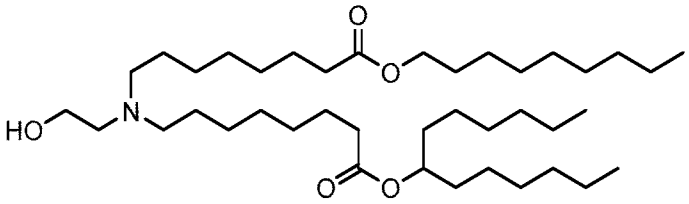

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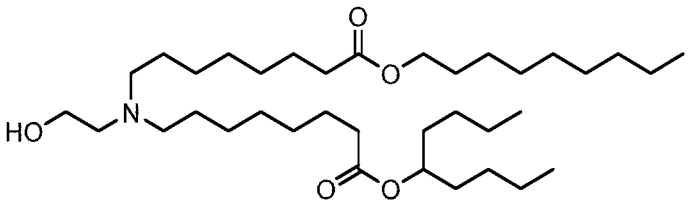

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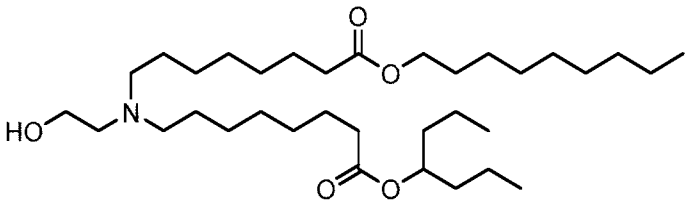

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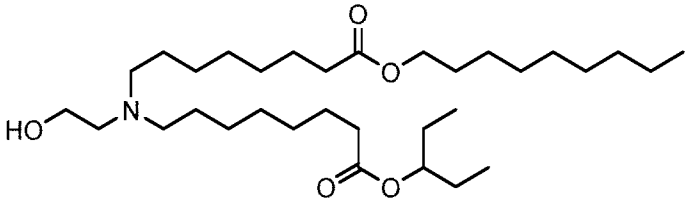

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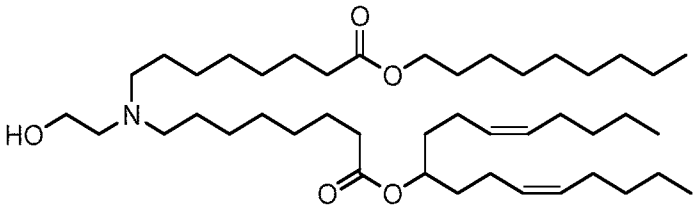

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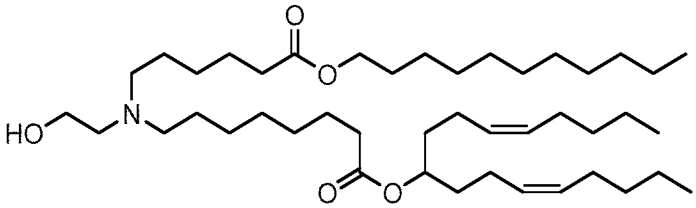

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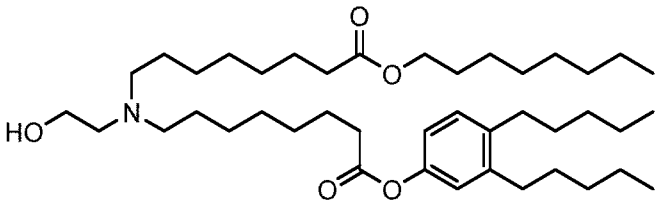

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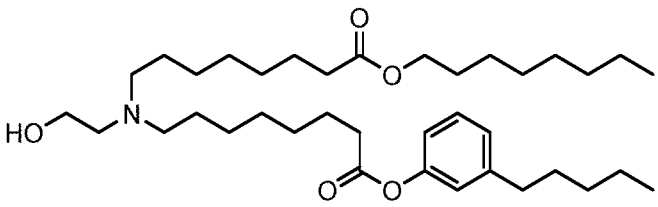

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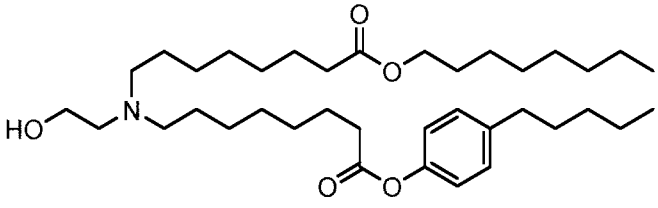

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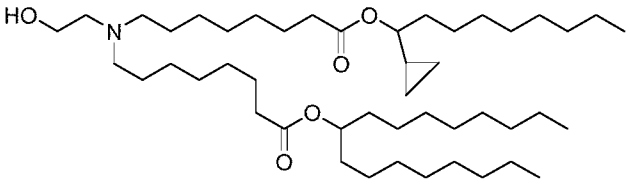

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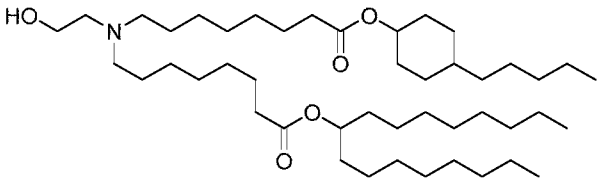

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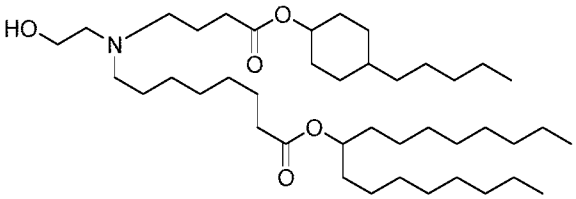

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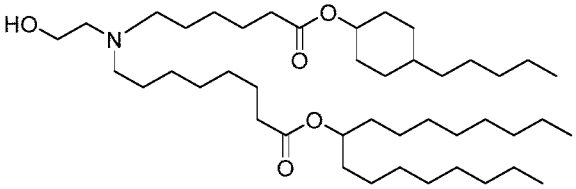

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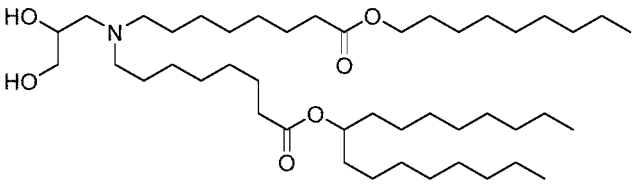

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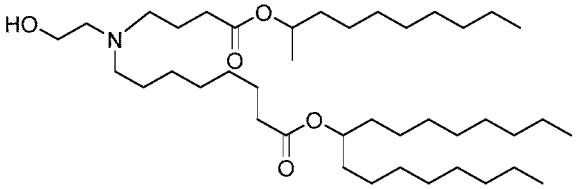

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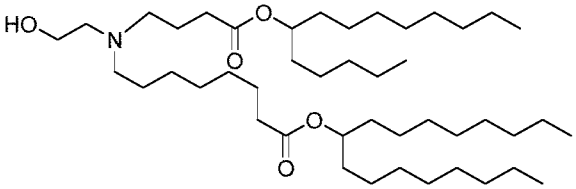

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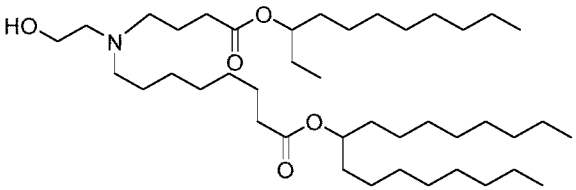

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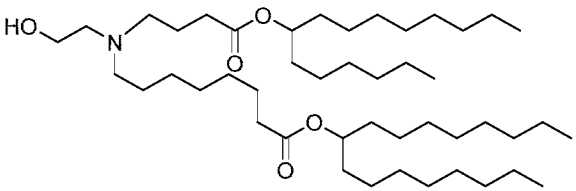

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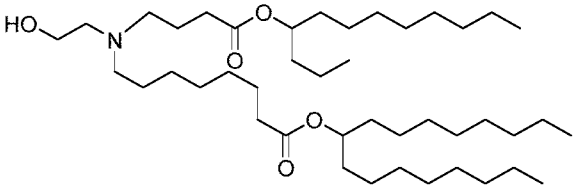

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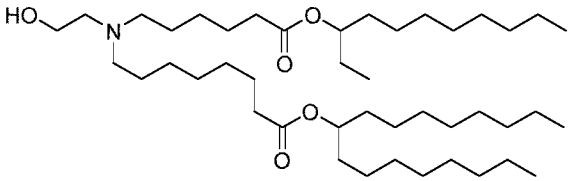

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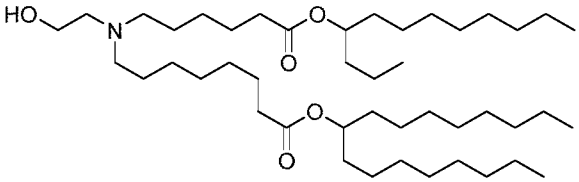

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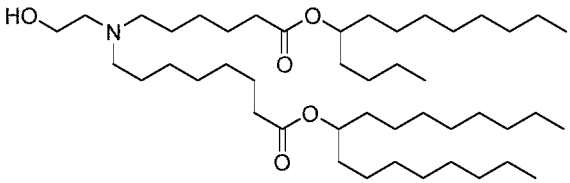

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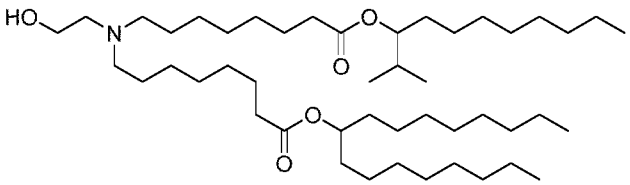

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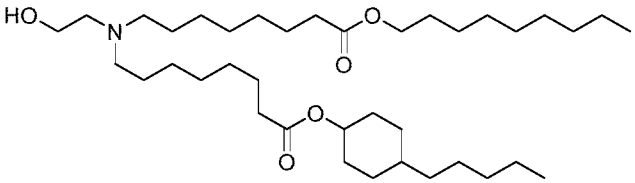

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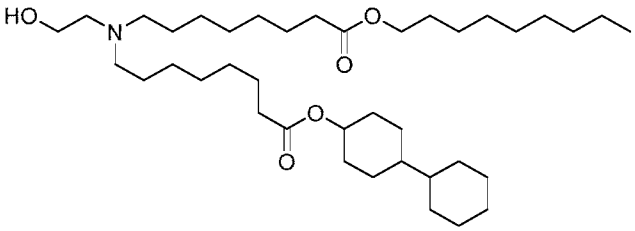

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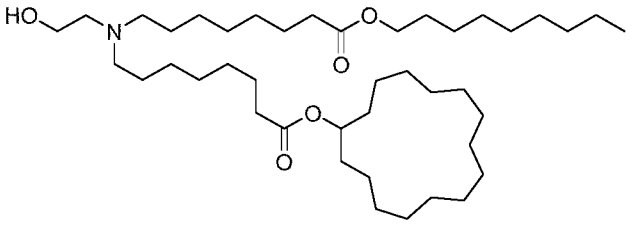

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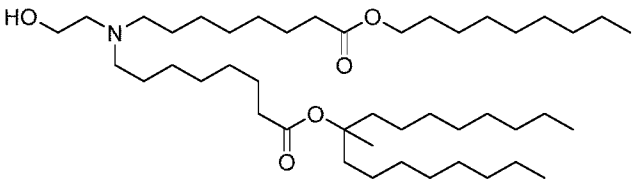

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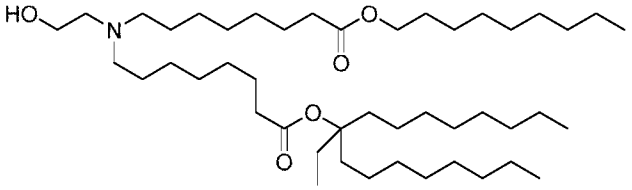

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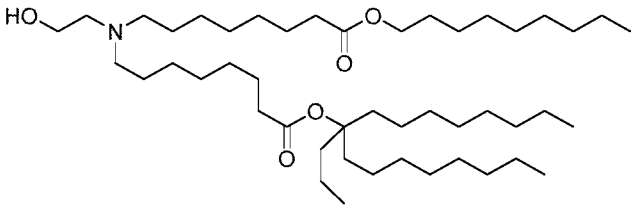

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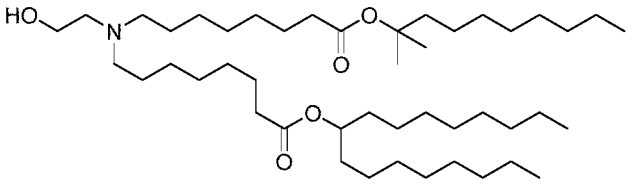

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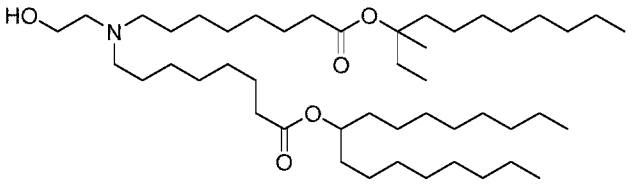

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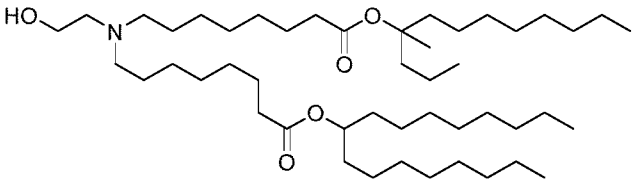

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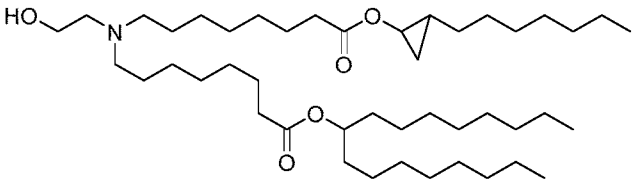

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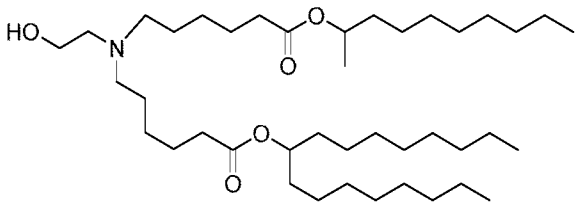

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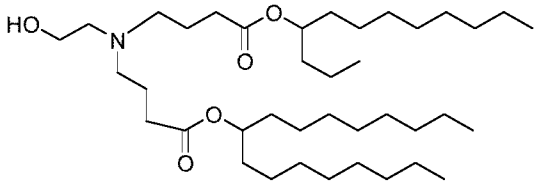

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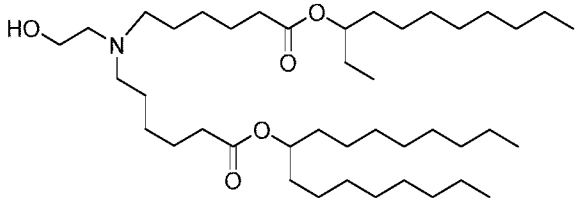

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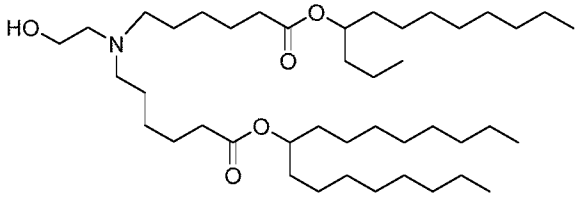

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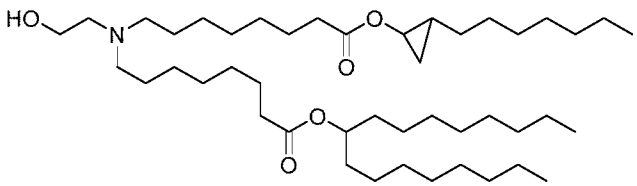

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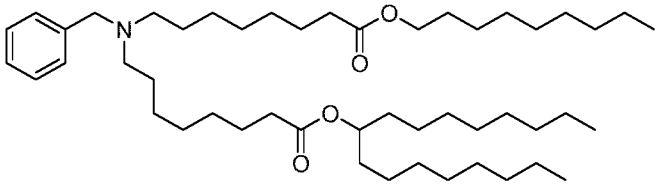

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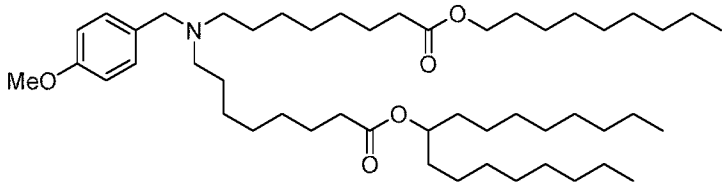

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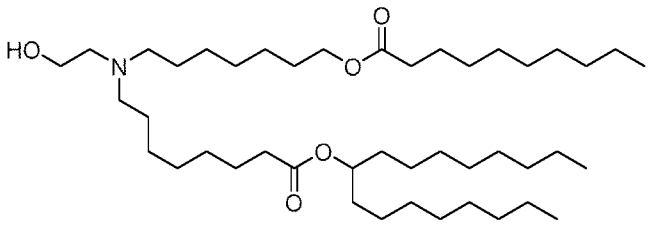

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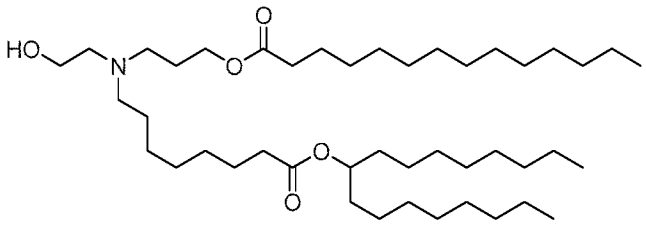

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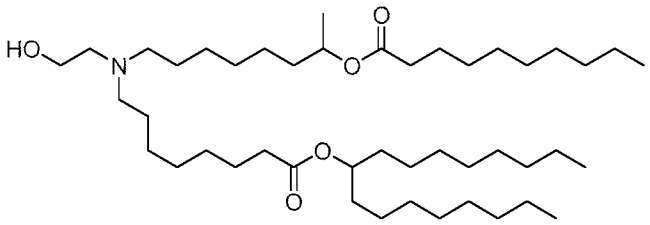

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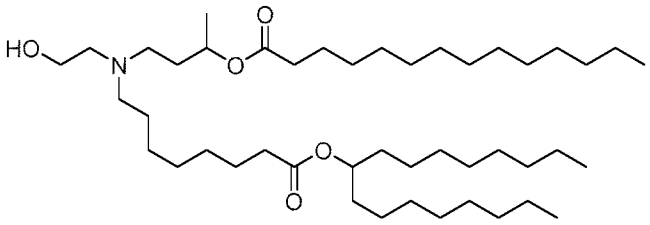

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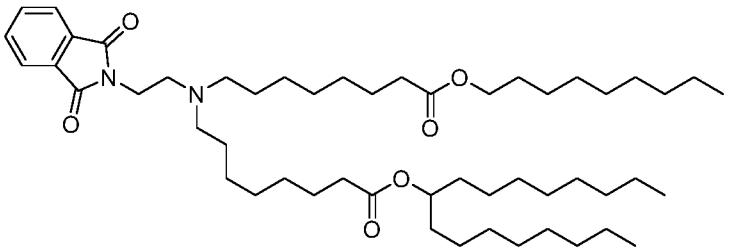

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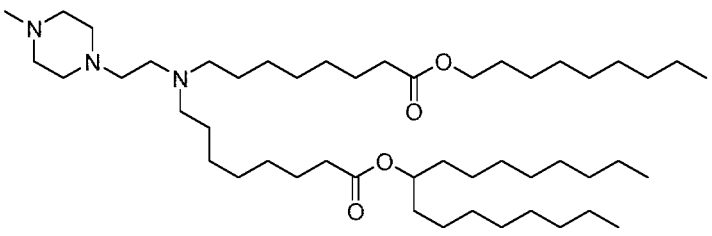

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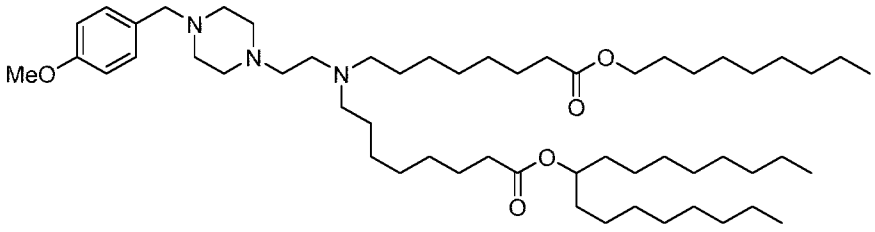

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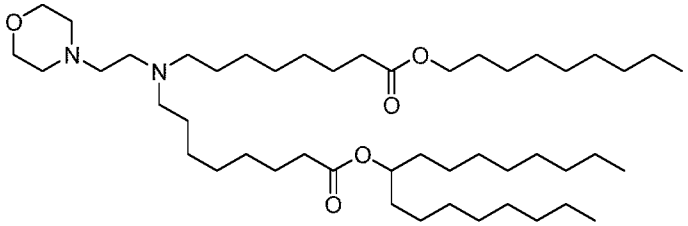

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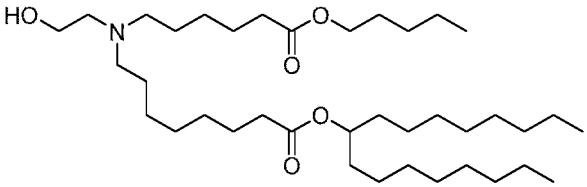

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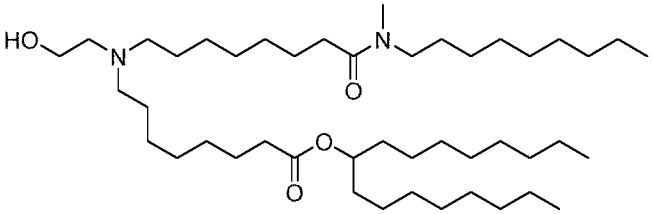

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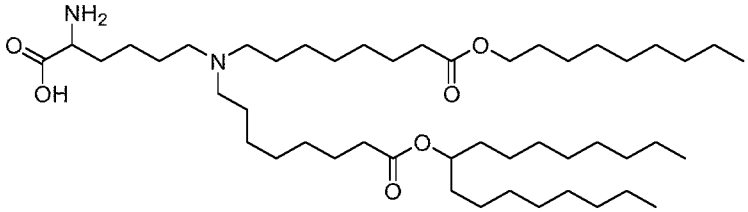

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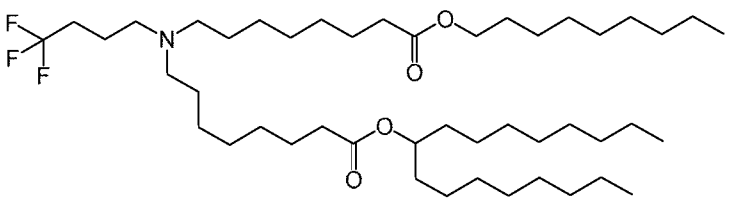

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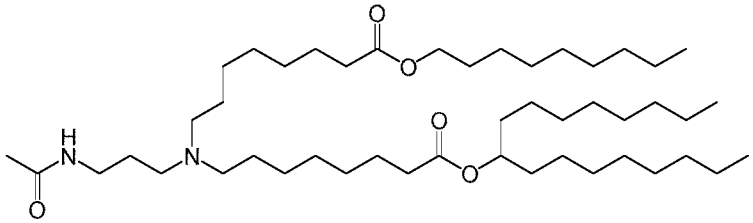

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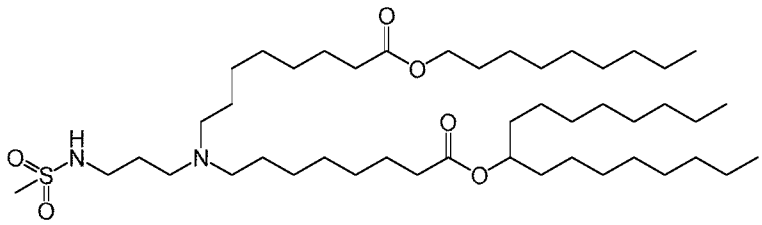

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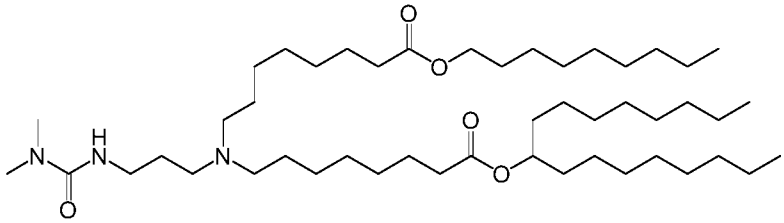

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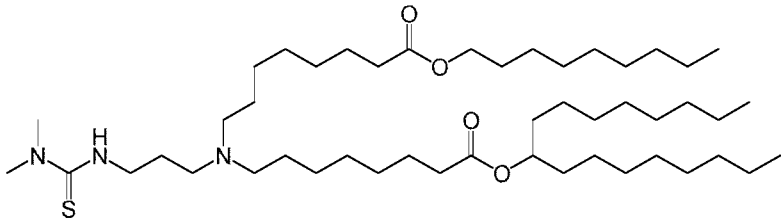

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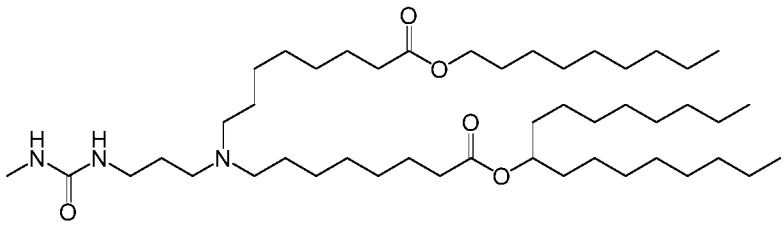

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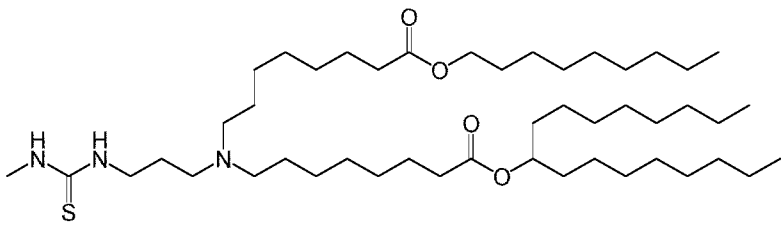

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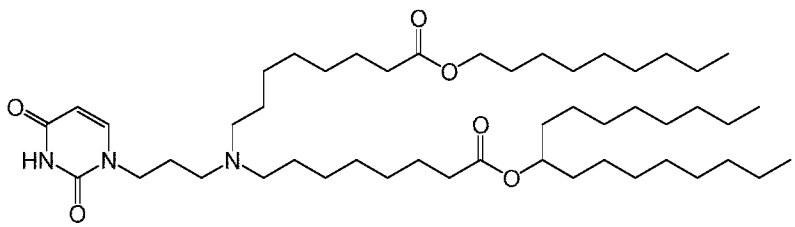

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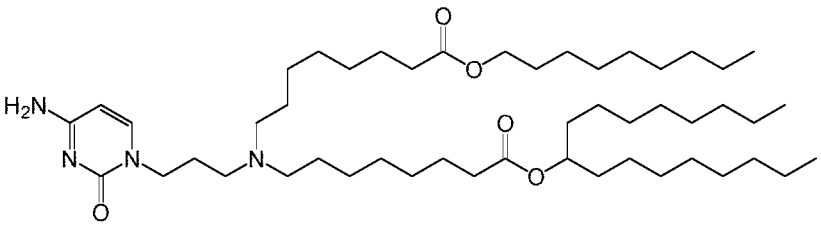

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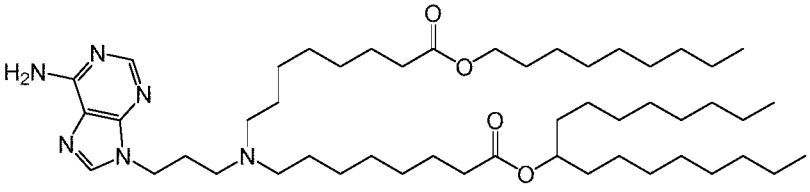

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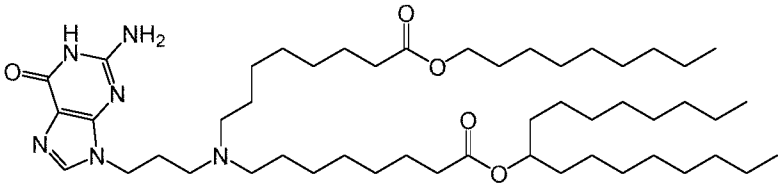

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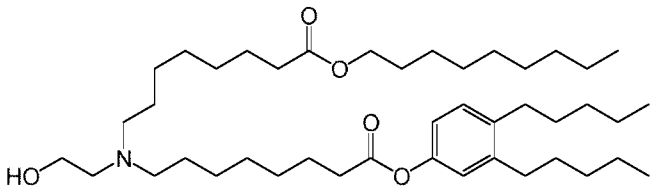

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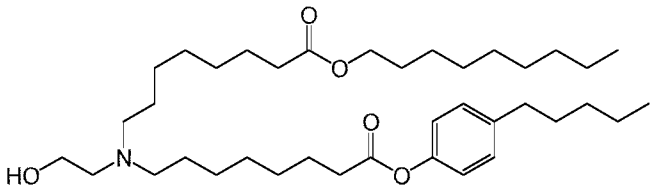

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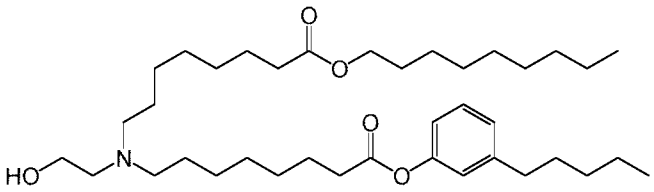

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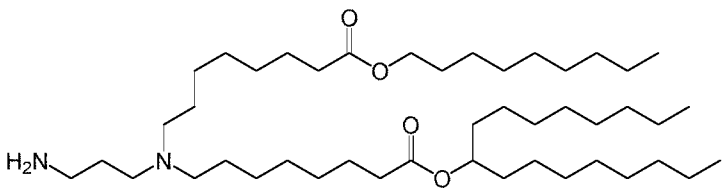

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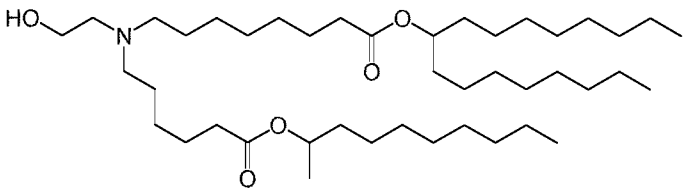

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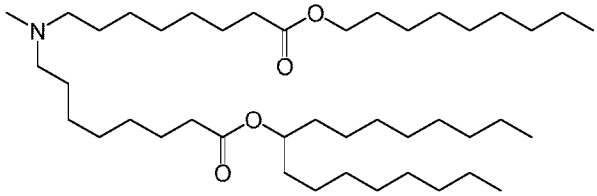

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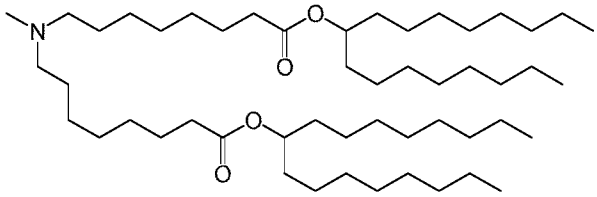

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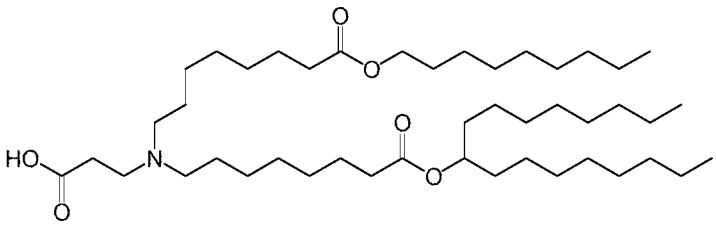

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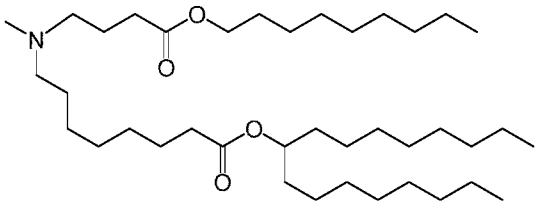

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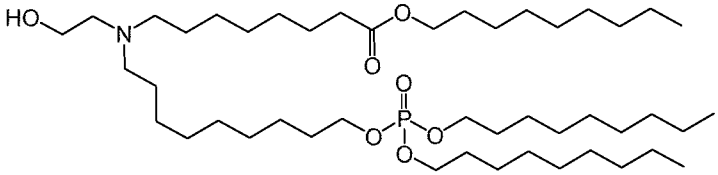

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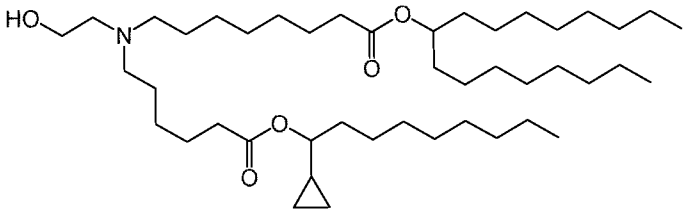

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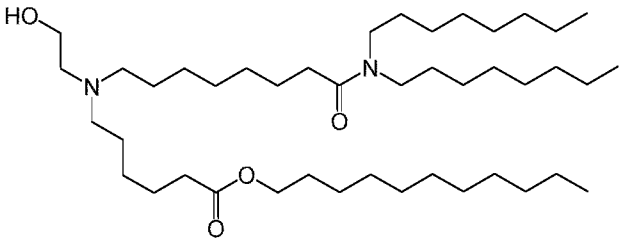

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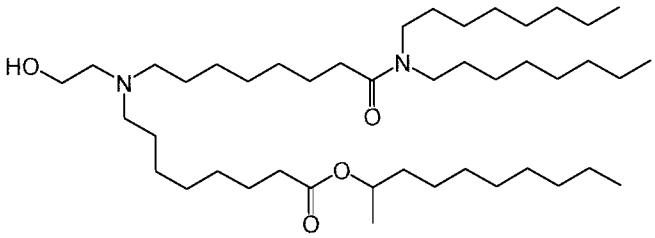

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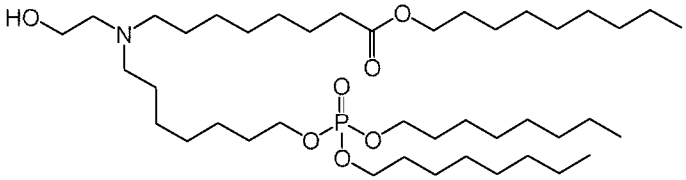

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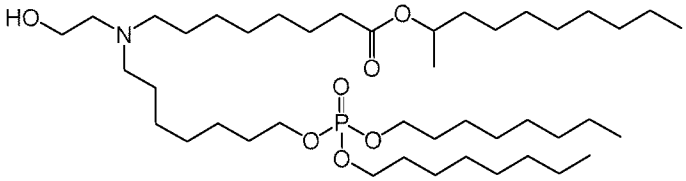

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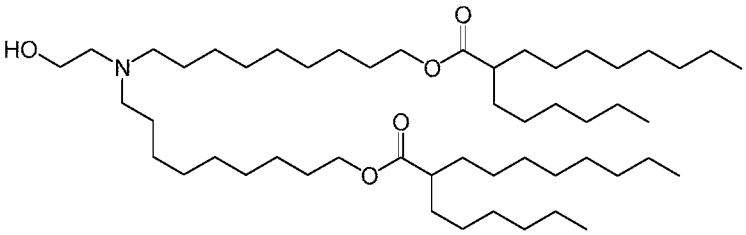

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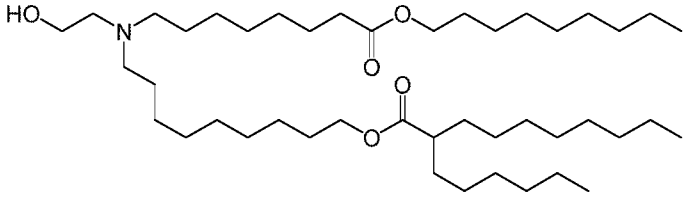

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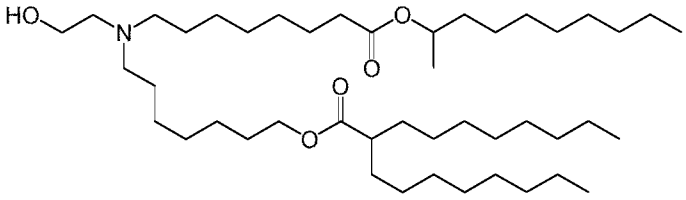

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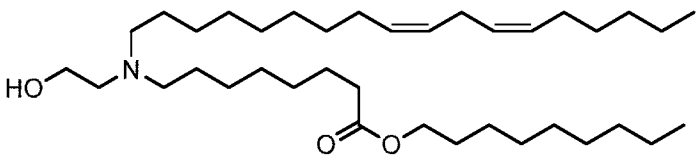

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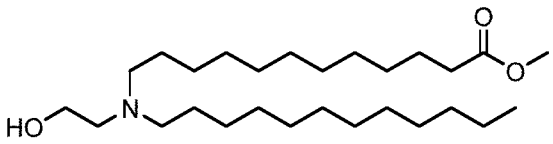

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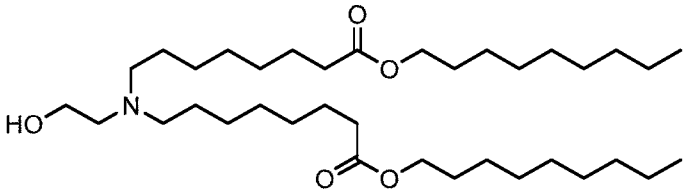

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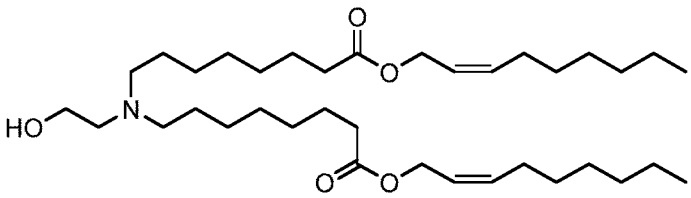

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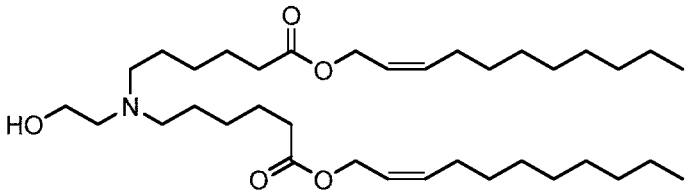

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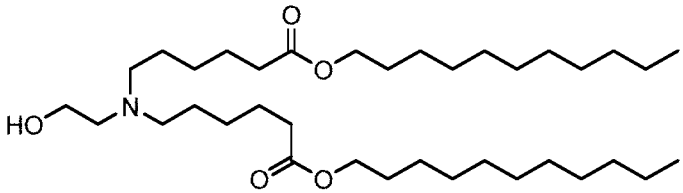

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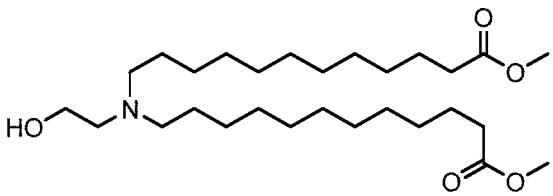

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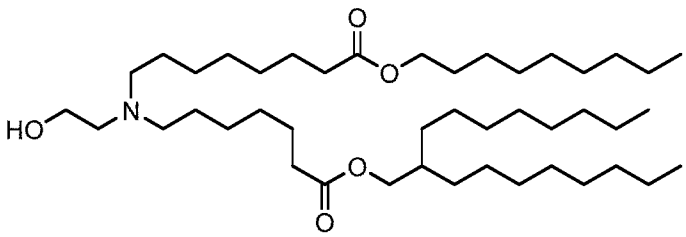

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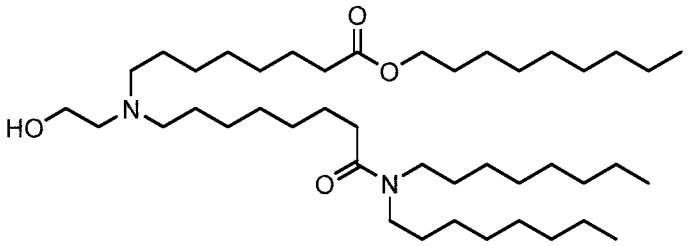

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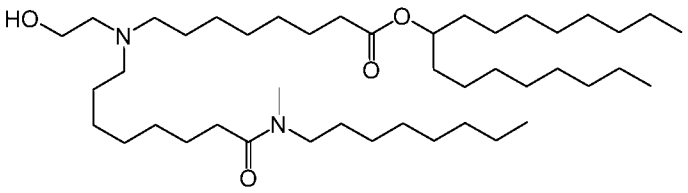

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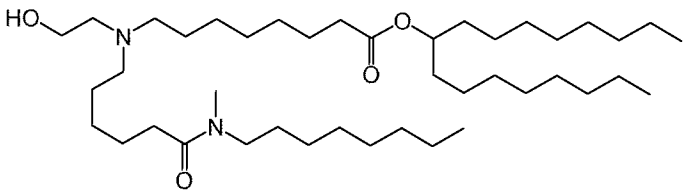

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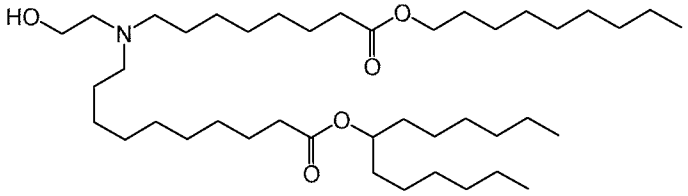


(Compound 147),

and salts or stereoisomers thereof.

[0668] The central amine moiety of a lipid according to formula (I) is typically protonated (i.e., positively charged) at a pH below the pKa of the amino moiety and is substantially not charged at a pH above the pKa. Such lipids can be referred to ionizable amino lipids.

[0669] In one specific embodiment, the compound of formula (I) is Compound 18.

[0670] In some embodiments, the amount of the compound of formula (I) ranges from about 1 mol % to 99 mol % in the lipid composition.

[0671] In one embodiment, the amount of the compound of formula (I) is at least about 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 26, 27, 28, 29, 30, 31, 32, 33, 34, 35, 36, 37, 38, 39, 40, 41, 42, 43, 44, 45, 46, 47, 48, 49, 50, 51, 52, 53, 54, 55, 56, 57, 58, 59, 60, 61, 62, 63, 64, 65, 66, 67, 68, 69, 70, 71, 72, 73, 74, 75, 76, 77, 78, 79, 80, 81, 82, 83, 84, 85, 86, 87, 88, 89, 90, 91, 92, 93, 94, 95, 96, 97, 98, or 99 mol % in the lipid composition.

[0672] In one embodiment, the amount of the compound of formula (I) ranges from about 30 mol % to about 70 mol %, from about 35 mol % to about 65 mol %, from about 40 mol % to about 60 mol %, and from about 45 mol % to about 55 mol % in the lipid composition.

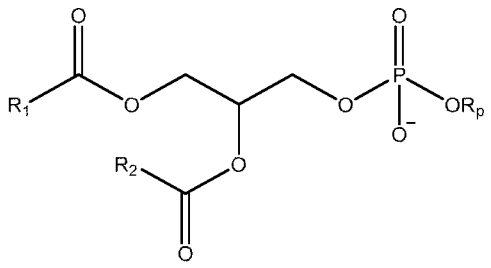
[0673] In one specific embodiment, the amount of the compound of formula (I) is about 50 mol % in the lipid composition.

[0674] In addition to the compound of formula (I), the lipid composition of the pharmaceutical compositions disclosed herein can comprise additional components such as phospholipids, structural lipids, quaternary amine compounds, PEG-lipids, and any combination thereof.

b. Additional Components in the Lipid Composition

(i) Phospholipids

[0675] The lipid composition of the pharmaceutical composition disclosed herein can comprise one or more phospholipids, for example, one or more saturated or (poly)unsaturated phospholipids or a combination thereof. In general, phospholipids comprise a phospholipid moiety and one or more fatty acid moieties. For example, a phospholipid can be a lipid according to formula (III):



(III)

in which R_p represents a phospholipid moiety and R_1 and R_2 represent fatty acid moieties with or without unsaturation that can be the same or different.

[0676] A phospholipid moiety can be selected, for example, from the non-limiting group consisting of phosphatidyl choline, phosphatidyl ethanolamine, phosphatidyl glycerol, phosphatidyl serine, phosphatidic acid, 2-lysophosphatidyl choline, and a sphingomyelin.

[0677] A fatty acid moiety can be selected, for example, from the non-limiting group consisting of lauric acid, myristic acid, myristoleic acid, palmitic acid, palmitoleic acid, stearic acid, oleic acid, linoleic acid, alpha-linolenic acid, erucic acid, phytanoic acid, arachidic acid, arachidonic acid, eicosapentaenoic acid, behenic acid, docosapentaenoic acid, and docosahexaenoic acid.

[0678] Particular phospholipids can facilitate fusion to a membrane. For example, a cationic phospholipid can interact with one or more negatively charged phospholipids of a membrane (e.g., a cellular or intracellular membrane). Fusion of a phospholipid to a membrane can allow

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one or more elements (e.g., a therapeutic agent) of a lipid-containing composition (e.g., LNPs) to pass through the membrane permitting, e.g., delivery of the one or more elements to a target tissue (e.g., tumoral tissue).

[0679] Non-natural phospholipid species including natural species with modifications and substitutions including branching, oxidation, cyclization, and alkynes are also contemplated. For example, a phospholipid can be functionalized with or cross-linked to one or more alkynes (e.g., an alkenyl group in which one or more double bonds is replaced with a triple bond). Under appropriate reaction conditions, an alkyne group can undergo a copper-catalyzed cycloaddition upon exposure to an azide. Such reactions can be useful in functionalizing a lipid bilayer of a nanoparticle composition to facilitate membrane permeation or cellular recognition or in conjugating a nanoparticle composition to a useful component such as a targeting or imaging moiety (e.g., a dye).

[0680] Phospholipids include, but are not limited to, glycerophospholipids such as phosphatidylcholines, phosphatidylethanolamines, phosphatidylserines, phosphatidylinositols, phosphatidy glycerols, and phosphatidic acids. Phospholipids also include phosphosphingolipid, such as sphingomyelin. In some embodiments, a pharmaceutical composition for intratumoral delivery disclosed herein can comprise more than one phospholipid. When more than one phospholipid is used, such phospholipids can belong to the same phospholipid class (e.g., MSPC and DSPC) or different classes (e.g., MSPC and MSPE).

[0681] Phospholipids can be of a symmetric or an asymmetric type. As used herein, the term "symmetric phospholipid" includes glycerophospholipids having matching fatty acid moieties and sphingolipids in which the variable fatty acid moiety and the hydrocarbon chain of the sphingosine backbone include a comparable number of carbon atoms. As used herein, the term "asymmetric phospholipid" includes lysolipids, glycerophospholipids having different fatty acid moieties (e.g., fatty acid moieties with different numbers of carbon atoms and/or unsaturations (e.g., double bonds)), and sphingolipids in which the variable fatty acid moiety and the hydrocarbon chain of the sphingosine backbone include a dissimilar number of carbon atoms (e.g., the variable fatty acid moiety include at least two more carbon atoms than the hydrocarbon chain or at least two fewer carbon atoms than the hydrocarbon chain).

[0682] In some embodiments, the lipid composition of a pharmaceutical composition disclosed herein comprises at least one symmetric phospholipid. Symmetric phospholipids can be selected from the non-limiting group consisting of

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1,2-dipropionyl-*sn*-glycero-3-phosphocholine (03:0 PC),
1,2-dibutyryl-*sn*-glycero-3-phosphocholine (04:0 PC),
1,2-dipentanoyl-*sn*-glycero-3-phosphocholine (05:0 PC),
1,2-dihexanoyl-*sn*-glycero-3-phosphocholine (06:0 PC),
1,2-diheptanoyl-*sn*-glycero-3-phosphocholine (07:0 PC),
1,2-dioctanoyl-*sn*-glycero-3-phosphocholine (08:0 PC),
1,2-dinonanoyl-*sn*-glycero-3-phosphocholine (09:0 PC),
1,2-didecanoyl-*sn*-glycero-3-phosphocholine (10:0 PC),
1,2-diundecanoyl-*sn*-glycero-3-phosphocholine (11:0 PC, DUPC),
1,2-dilauroyl-*sn*-glycero-3-phosphocholine (12:0 PC),
1,2-ditridecanoyl-*sn*-glycero-3-phosphocholine (13:0 PC),
1,2-dimyristoyl-*sn*-glycero-3-phosphocholine (14:0 PC, DMPC),
1,2-dipentadecanoyl-*sn*-glycero-3-phosphocholine (15:0 PC),
1,2-dipalmitoyl-*sn*-glycero-3-phosphocholine (16:0 PC, DPPC),
1,2-diphytanoyl-*sn*-glycero-3-phosphocholine (4ME 16:0 PC),
1,2-diheptadecanoyl-*sn*-glycero-3-phosphocholine (17:0 PC),
1,2-distearoyl-*sn*-glycero-3-phosphocholine (18:0 PC, DSPC),
1,2-dinonadecanoyl-*sn*-glycero-3-phosphocholine (19:0 PC),
1,2-diarachidoyl-*sn*-glycero-3-phosphocholine (20:0 PC),
1,2-dihenarachidoyl-*sn*-glycero-3-phosphocholine (21:0 PC),
1,2-dibehenoyl-*sn*-glycero-3-phosphocholine (22:0 PC),
1,2-ditricosanoyl-*sn*-glycero-3-phosphocholine (23:0 PC),
1,2-dilignoceroyl-*sn*-glycero-3-phosphocholine (24:0 PC),
1,2-dimyristoleoyl-*sn*-glycero-3-phosphocholine (14:1 (Δ9-Cis) PC),
1,2-dimyristelaidoyl-*sn*-glycero-3-phosphocholine (14:1 (Δ9-Trans) PC),
1,2-dipalmitoleoyl-*sn*-glycero-3-phosphocholine (16:1 (Δ9-Cis) PC),
1,2-dipalmitelaidoyl-*sn*-glycero-3-phosphocholine (16:1 (Δ9-Trans) PC),
1,2-dipetroselenoyl-*sn*-glycero-3-phosphocholine (18:1 (Δ6-Cis) PC),
1,2-dioleoyl-*sn*-glycero-3-phosphocholine (18:1 (Δ9-Cis) PC, DOPC),
1,2-dielaidoyl-*sn*-glycero-3-phosphocholine (18:1 (Δ9-Trans) PC),
1,2-dilinoleoyl-*sn*-glycero-3-phosphocholine (18:2 (Cis) PC, DLPC),
1,2-dilinolenoyl-*sn*-glycero-3-phosphocholine (18:3 (Cis) PC, DLnPC),

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1,2-dieicosenoyl-*sn*-glycero-3-phosphocholine (20:1 (Cis) PC),
1,2-diarachidonoyl-*sn*-glycero-3-phosphocholine (20:4 (Cis) PC, DAPC),
1,2-dierucoyl-*sn*-glycero-3-phosphocholine (22:1 (Cis) PC),
1,2-didocosahexaenoyl-*sn*-glycero-3-phosphocholine (22:6 (Cis) PC, DHAPC),
1,2-dinervonoyl-*sn*-glycero-3-phosphocholine (24:1 (Cis) PC),
1,2-dihexanoyl-*sn*-glycero-3-phosphoethanolamine (06:0 PE),
1,2-dioctanoyl-*sn*-glycero-3-phosphoethanolamine (08:0 PE),
1,2-didecanoyl-*sn*-glycero-3-phosphoethanolamine (10:0 PE),
1,2-dilauroyl-*sn*-glycero-3-phosphoethanolamine (12:0 PE),
1,2-dimyristoyl-*sn*-glycero-3-phosphoethanolamine (14:0 PE),
1,2-dipentadecanoyl-*sn*-glycero-3-phosphoethanolamine (15:0 PE),
1,2-dipalmitoyl-*sn*-glycero-3-phosphoethanolamine (16:0 PE),
1,2-diphytanoyl-*sn*-glycero-3-phosphoethanolamine (4ME 16:0 PE),
1,2-diheptadecanoyl-*sn*-glycero-3-phosphoethanolamine (17:0 PE),
1,2-distearoyl-*sn*-glycero-3-phosphoethanolamine (18:0 PE, DSPE),
1,2-dipalmitoleoyl-*sn*-glycero-3-phosphoethanolamine (16:1 PE),
1,2-dioleoyl-*sn*-glycero-3-phosphoethanolamine (18:1 (Δ9-Cis) PE, DOPE),
1,2-dielaidoyl-*sn*-glycero-3-phosphoethanolamine (18:1 (Δ9-Trans) PE),
1,2-dilinoleoyl-*sn*-glycero-3-phosphoethanolamine (18:2 PE, DLPE),
1,2-dilinolenoyl-*sn*-glycero-3-phosphoethanolamine (18:3 PE, DLnPE),
1,2-diarachidonoyl-*sn*-glycero-3-phosphoethanolamine (20:4 PE, DAPE),
1,2-didocosahexaenoyl-*sn*-glycero-3-phosphoethanolamine (22:6 PE, DHAPE),
1,2-di-O-octadecenyl-*sn*-glycero-3-phosphocholine (18:0 Diether PC),
1,2-dioleoyl-*sn*-glycero-3-phospho-rac-(1-glycerol) sodium salt (DOPG), and
any combination thereof.

[0683] In some embodiments, the lipid composition of a pharmaceutical composition disclosed herein comprises at least one symmetric phospholipid selected from the non-limiting group consisting of DLPC, DMPC, DOPC, DPPC, DSPC, DUPC, 18:0 Diether PC, DLnPC, DAPC, DHAPC, DOPE, 4ME 16:0 PE, DSPE, DLPE,DLnPE, DAPE, DHAPE, DOPG, and any combination thereof.

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[0684] In some embodiments, the lipid composition of a pharmaceutical composition disclosed herein comprises at least one asymmetric phospholipid. Asymmetric phospholipids can be selected from the non-limiting group consisting of

1-myristoyl-2-palmitoyl-*sn*-glycero-3-phosphocholine (14:0-16:0 PC, MPPC),
1-myristoyl-2-stearoyl-*sn*-glycero-3-phosphocholine (14:0-18:0 PC, MSPC),
1-palmitoyl-2-acetyl-*sn*-glycero-3-phosphocholine (16:0-02:0 PC),
1-palmitoyl-2-myristoyl-*sn*-glycero-3-phosphocholine (16:0-14:0 PC, PMPC),
1-palmitoyl-2-stearoyl-*sn*-glycero-3-phosphocholine (16:0-18:0 PC, PSPC),
1-palmitoyl-2-oleoyl-*sn*-glycero-3-phosphocholine (16:0-18:1 PC, POPC),
1-palmitoyl-2-linoleoyl-*sn*-glycero-3-phosphocholine (16:0-18:2 PC, PLPC),
1-palmitoyl-2-arachidonoyl-*sn*-glycero-3-phosphocholine (16:0-20:4 PC),
1-palmitoyl-2-docosahexaenoyl-*sn*-glycero-3-phosphocholine (14:0-22:6 PC),
1-stearoyl-2-myristoyl-*sn*-glycero-3-phosphocholine (18:0-14:0 PC, SMPC),
1-stearoyl-2-palmitoyl-*sn*-glycero-3-phosphocholine (18:0-16:0 PC, SPPC),
1-stearoyl-2-oleoyl-*sn*-glycero-3-phosphocholine (18:0-18:1 PC, SOPC),
1-stearoyl-2-linoleoyl-*sn*-glycero-3-phosphocholine (18:0-18:2 PC),
1-stearoyl-2-arachidonoyl-*sn*-glycero-3-phosphocholine (18:0-20:4 PC),
1-stearoyl-2-docosahexaenoyl-*sn*-glycero-3-phosphocholine (18:0-22:6 PC),
1-oleoyl-2-myristoyl-*sn*-glycero-3-phosphocholine (18:1-14:0 PC, OMPC),
1-oleoyl-2-palmitoyl-*sn*-glycero-3-phosphocholine (18:1-16:0 PC, OPPC),
1-oleoyl-2-stearoyl-*sn*-glycero-3-phosphocholine (18:1-18:0 PC, OSPC),
1-palmitoyl-2-oleoyl-*sn*-glycero-3-phosphoethanolamine (16:0-18:1 PE, POPE),
1-palmitoyl-2-linoleoyl-*sn*-glycero-3-phosphoethanolamine (16:0-18:2 PE),
1-palmitoyl-2-arachidonoyl-*sn*-glycero-3-phosphoethanolamine (16:0-20:4 PE),
1-palmitoyl-2-docosahexaenoyl-*sn*-glycero-3-phosphoethanolamine (16:0-22:6 PE),
1-stearoyl-2-oleoyl-*sn*-glycero-3-phosphoethanolamine (18:0-18:1 PE),
1-stearoyl-2-linoleoyl-*sn*-glycero-3-phosphoethanolamine (18:0-18:2 PE),
1-stearoyl-2-arachidonoyl-*sn*-glycero-3-phosphoethanolamine (18:0-20:4 PE),
1-stearoyl-2-docosahexaenoyl-*sn*-glycero-3-phosphoethanolamine (18:0-22:6 PE),
1-oleoyl-2-cholesterylhemisuccinoyl-*sn*-glycero-3-phosphocholine (OChemsPC), and any combination thereof.

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[0685] Asymmetric lipids useful in the lipid composition can also be lysolipids. Lysolipids can be selected from the non-limiting group consisting of

1-hexanoyl-2-hydroxy-*sn*-glycero-3-phosphocholine (06:0 Lyso PC),
1-heptanoyl-2-hydroxy-*sn*-glycero-3-phosphocholine (07:0 Lyso PC),
1-octanoyl-2-hydroxy-*sn*-glycero-3-phosphocholine (08:0 Lyso PC),
1-nonanoyl-2-hydroxy-*sn*-glycero-3-phosphocholine (09:0 Lyso PC),
1-decanoyl-2-hydroxy-*sn*-glycero-3-phosphocholine (10:0 Lyso PC),
1-undecanoyl-2-hydroxy-*sn*-glycero-3-phosphocholine (11:0 Lyso PC),
1-lauroyl-2-hydroxy-*sn*-glycero-3-phosphocholine (12:0 Lyso PC),
1-tridecanoyl-2-hydroxy-*sn*-glycero-3-phosphocholine (13:0 Lyso PC),
1-myristoyl-2-hydroxy-*sn*-glycero-3-phosphocholine (14:0 Lyso PC),
1-pentadecanoyl-2-hydroxy-*sn*-glycero-3-phosphocholine (15:0 Lyso PC),
1-palmitoyl-2-hydroxy-*sn*-glycero-3-phosphocholine (16:0 Lyso PC),
1-heptadecanoyl-2-hydroxy-*sn*-glycero-3-phosphocholine (17:0 Lyso PC),
1-stearoyl-2-hydroxy-*sn*-glycero-3-phosphocholine (18:0 Lyso PC),
1-oleoyl-2-hydroxy-*sn*-glycero-3-phosphocholine (18:1 Lyso PC),
1-nonadecanoyl-2-hydroxy-*sn*-glycero-3-phosphocholine (19:0 Lyso PC),
1-arachidoyl-2-hydroxy-*sn*-glycero-3-phosphocholine (20:0 Lyso PC),
1-behenoyl-2-hydroxy-*sn*-glycero-3-phosphocholine (22:0 Lyso PC),
1-lignoceroyl-2-hydroxy-*sn*-glycero-3-phosphocholine (24:0 Lyso PC),
1-hexacosanoyl-2-hydroxy-*sn*-glycero-3-phosphocholine (26:0 Lyso PC),
1-myristoyl-2-hydroxy-*sn*-glycero-3-phosphoethanolamine (14:0 Lyso PE),
1-palmitoyl-2-hydroxy-*sn*-glycero-3-phosphoethanolamine (16:0 Lyso PE),
1-stearoyl-2-hydroxy-*sn*-glycero-3-phosphoethanolamine (18:0 Lyso PE),
1-oleoyl-2-hydroxy-*sn*-glycero-3-phosphoethanolamine (18:1 Lyso PE),
1-hexadecyl-*sn*-glycero-3-phosphocholine (C16 Lyso PC), and
any combination thereof.

[0686] In some embodiment, the lipid composition of a pharmaceutical composition disclosed herein comprises at least one asymmetric phospholipid selected from the group consisting of MPPC, MSPC, PMPC, PSPC, SMPC, SPPC, and any combination thereof. In some embodiments, the asymmetric phospholipid is 1-myristoyl-2-stearoyl-sn-glycero-3-phosphocholine (MSPC).

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[0687] In some embodiments, the lipid compositions disclosed herein can contain one or more symmetric phospholipids, one or more asymmetric phospholipids, or a combination thereof. When multiple phospholipids are present, they can be present in equimolar ratios, or non-equimolar ratios.

[0688] In one embodiment, the lipid composition of a pharmaceutical composition disclosed herein comprises a total amount of phospholipid (e.g., MSPC) which ranges from about 1 mol % to about 20 mol %, from about 5 mol %to about 20 mol %, from about 10 mol % to about 20 mol %, from about 15 mol % to about 20 mol %, from about 1 mol % to about 15 mol %, from about 5 mol % to about 15 mol %, from about 10 mol % to about 15 mol %, from about 5 mol % to about 10 mol % in the lipid composition. In one embodiment, the amount of the phospholipid is from about 8 mol % to about 15 mol % in the lipid composition. In one embodiment, the amount of the phospholipid (e.g., MSPC) is about 10 mol % in the lipid composition.

[0689] In some aspects, the amount of a specific phospholipid (e.g., MSPC) is at least about 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19 or 20 mol % in the lipid composition.

(ii) Quaternary Amine Compounds

[0690] The lipid composition of a pharmaceutical composition disclosed herein can comprise one or more quaternary amine compounds (e.g., DOTAP). The term "quaternary amine compound" is used to include those compounds having one or more quaternary amine groups (*e.g.*, trialkylamino groups) and permanently carrying a positive charge and existing in a form of a salt. For example, the one or more quaternary amine groups can be present in a lipid or a polymer (*e.g.*, PEG). In some embodiments, the quaternary amine compound comprises (1) a quaternary amine group and (2) at least one hydrophobic tail group comprising (i) a hydrocarbon chain, linear or branched, and saturated or unsaturated, and (ii) optionally an ether, ester, carbonyl, or ketal linkage between the quaternary amine group and the hydrocarbon chain. In some embodiments, the quaternary amine group can be a trimethylammonium group. In some embodiments, the quaternary amine compound comprises two identical hydrocarbon chains. In some embodiments, the quaternary amine compound comprises two different hydrocarbon chains.

[0691] In some embodiments, the lipid composition of a pharmaceutical composition disclosed herein comprises at least one quaternary amine compound. Quaternary amine compound can be selected from the non-limiting group consisting of

1,2-dioleoyl-3-trimethylammonium-propane (DOTAP),
N-[1-(2,3-dioleoyloxy)propyl]-N,N,N-trimethylammonium chloride (DOTMA),
1-[2-(oleoyloxy)ethyl]-2-oleyl-3-(2-hydroxyethyl)imidazolinium chloride (DOTIM),
2,3-dioleyloxy-N-[2(sperminecarboxamido)ethyl]-N,N-dimethyl-1-propanaminium trifluoroacetate (DOSPA),
N,N-distearyl-N,N-dimethylammonium bromide (DDAB),
N-(1,2-dimyristyloxyprop-3-yl)-N,N-dimethyl-N-hydroxyethyl ammonium bromide (DMRIE),
N-(1,2-dioleoyloxyprop-3-yl)-N,N-dimethyl-N-hydroxyethyl ammonium bromide (DORIE),
N,N-dioleyl-N,N-dimethylammonium chloride (DODAC),
1,2-dilauroyl-sn-glycero-3-ethylphosphocholine (DLePC),
1,2-distearoyl-3-trimethylammonium-propane (DSTAP),
1,2-dipalmitoyl-3-trimethylammonium-propane (DPTAP),
1,2-dilinoleoyl-3-trimethylammonium-propane (DLTAP),
1,2-dimyristoyl-3-trimethylammonium-propane (DMTAP)
1,2-distearoyl -sn-glycero-3-ethylphosphocholine (DSePC)
1,2-dipalmitoyl-sn-glycero-3-ethylphosphocholine (DPePC),
1,2-dimyristoyl -sn-glycero-3-ethylphosphocholine (DMePC),
1,2-dioleoyl-sn-glycero-3-ethylphosphocholine (DOePC),
1,2-di-(9Z-tetradecenoyl)-sn-glycero-3-ethylphosphocholine (14:1 EPC),
1-palmitoyl-2-oleoyl-sn-glycero-3-ethylphosphocholine (16:0-18:1 EPC),
and any combination thereof.

[0692] In one embodiment, the quaternary amine compound is 1,2-dioleoyl-3-trimethylammonium-propane (DOTAP).

[0693] Quaternary amine compounds are known in the art, such as those described in US 2013/0245107 A1, US 2014/0363493 A1, US 8,158,601, WO 2015/123264 A1, and WO 2015/148247 A1, which are incorporated herein by reference in their entirety.

[0694] In one embodiment, the amount of the quaternary amine compound (e.g., DOTAP) in the lipid composition disclosed herein ranges from about 0.01 mol % to about 20 mol %.

[0695] In one embodiment, the amount of the quaternary amine compound (e.g., DOTAP) in the lipid composition disclosed herein ranges from about 0.5 mol % to about 20 mol %, from

about 0.5 mol % to about 15 mol %, from about 0.5 mol % to about 10 mol %, from about 1 mol % to about 20 mol %, from about 1 mol % to about 15 mol %, from about 1 mol % to about 10 mol %, from about 2 mol % to about 20 mol %, from about 2 mol % to about 15 mol %, from about 2 mol % to about 10 mol %, from about 3 mol % to about 20 mol %, from about 3 mol % to about 15 mol %, from about 3 mol % to about 10 mol %, from about 4 mol % to about 20 mol %, from about 4 mol % to about 15 mol %, from about 4 mol % to about 10 mol %, from about 5 mol % to about 20 mol %, from about 5 mol % to about 15 mol %, from about 5 mol % to about 10 mol %, from about 6 mol % to about 20 mol %, from about 6 mol % to about 15 mol %, from about 6 mol % to about 10 mol %, from about 7 mol % to about 20 mol %, from about 7 mol % to about 15 mol %, from about 7 mol % to about 10 mol %, from about 8 mol % to about 20 mol %, from about 8 mol % to about 15 mol %, from about 8 mol % to about 10 mol %, from about 9 mol % to about 20 mol %, from about 9 mol % to about 15 mol %, from about 9 mol % to about 10 mol %.

[0696] In one embodiment, the amount of the quaternary amine compound (e.g., DOTAP) in the lipid composition disclosed herein ranges from about 5 mol % to about 10 mol %.

[0697] In one embodiment, the amount of the quaternary amine compound (e.g., DOTAP) in the lipid composition disclosed herein is about 5 mol %. In one embodiment, the amount of the quaternary amine compound (e.g., DOTAP) in the lipid composition disclosed herein is about 10 mol %.

[0698] In some embodiments, the amount of the quaternary amine compound (e.g., DOTAP) is at least about 0.01, 0.02, 0.03, 0.04, 0.05, 0.06, 0.07, 0.08, 0.09, 0.1, 0.2, 0.3, 0.4, 0.5, 0.6, 0.7, 0.8, 0.9, 1, 1.5, 2, 2.5, 3, 3.5, 4, 4.5, 5, 5.5, 6, 6.5, 7, 7.5, 8, 8.5, 9, 9.5, 10, 10.5, 11, 11.5, 12, 12.5, 13, 13.5, 14, 14.5, 15, 15.5, 16, 16.5, 17, 17.5, 18, 18.5, 19, 19.5 or 20 mol % in the lipid composition disclosed herein.

[0699] In one embodiment, the mole ratio of the compound of formula (I) (e.g., Compounds 18, 25, 26 or 48) to the quaternary amine compound (e.g., DOTA) is about 100:1 to about 2.5:1. In one embodiment, the mole ratio of the compound of formula (I) (e.g., Compounds 18, 25, 26 or 48) to the quaternary amine compound (e.g., DOTAP) is about 90:1, about 80:1, about 70:1, about 60:1, about 50:1, about 40:1, about 30:1, about 20:1, about 15:1, about 10:1, about 9:1, about 8:1, about 7:1, about 6:1, about 5:1, or about 2.5:1. In one embodiment, the mole ratio of the compound of formula (I) (e.g., Compounds 18, 25, 26 or 48) to the quaternary amine compound (e.g., DOTAP) in the lipid composition disclosed herein is about 10:1.

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[0700] In some aspects, the lipid composition the pharmaceutical compositions disclosed herein does not comprise a quaternary amine compound. In some aspects, the lipid composition of the pharmaceutical compositions disclosed does not comprise DOTAP.

(iii) Structural Lipids

[0701] The lipid composition of a pharmaceutical composition disclosed herein can comprise one or more structural lipids. As used herein, the term "structural lipid" refers to sterols and also to lipids containing sterol moieties. In some embodiments, the structural lipid is selected from the group consisting of cholesterol, fecosterol, sitosterol, ergosterol, campesterol, stigmasterol, brassicasterol, tomatidine, tomatine, ursolic acid, alpha-tocopherol, and mixtures thereof. In some embodiments, the structural lipid is cholesterol.

[0702] In one embodiment, the amount of the structural lipid (e.g., an sterol such as cholesterol) in the lipid composition of a pharmaceutical composition disclosed herein ranges from about 20 mol % to about 60 mol %, from about 25 mol % to about 55 mol %, from about 30 mol % to about 50 mol %, or from about 35 mol % to about 45 mol %.

[0703] In one embodiment, the amount of the structural lipid (e.g., an sterol such as cholesterol) in the lipid composition disclosed herein ranges from about 25 mol % to about 30 mol %, from about 30 mol % to about 35 mol %, or from about 35 mol % to about 40 mol %.

[0704] In one embodiment, the amount of the structural lipid (e.g., a sterol such as cholesterol) in the lipid composition disclosed herein is about 23.5 mol %, about 28.5 mol %, about 33.5 mol %, or about 38.5 mol %.

[0705] In some embodiments, the amount of the structural lipid (e.g., an sterol such as cholesterol) in the lipid composition disclosed herein is at least about 20, 21, 22, 23, 24, 25, 26, 27, 28, 29, 30, 31, 32, 33, 34, 35, 36, 37, 38, 39, 40, 41, 42, 43, 44, 45, 46, 47, 48, 49, 50, 51, 52, 53, 54, 55, 56, 57, 58, 59, or 60 mol %.

[0706] In some aspects, the lipid composition component of the pharmaceutical compositions for intratumoral delivery disclosed does not comprise cholesterol.

(iv) Polyethylene Glycol (PEG)-Lipids

[0707] The lipid composition of a pharmaceutical composition disclosed herein can comprise one or more a polyethylene glycol (PEG) lipid.

[0708] As used herein, the term "PEG-lipid" refers to polyethylene glycol (PEG)-modified lipids. Non-limiting examples of PEG-lipids include PEG-modified phosphatidylethanolamine and phosphatidic acid, PEG-ceramide conjugates (e.g., PEG-CerC14 or PEG-CerC20), PEG-modified dialkylamines and PEG-modified 1,2-diacyloxypropan-3-amines. Such lipids are also referred to as PEGylated lipids. For example, a PEG lipid can be PEG-c-DOMG, PEG-DMG, PEG-DLPE, PEG-DMPE, PEG-DPPC, or a PEG-DSPE lipid.

[0709] In some embodiments, the PEG-lipid includes, but not limited to 1,2-dimyristoyl-sn-glycerol methoxypolyethylene glycol (PEG-DMG), 1,2-distearoyl-sn-glycero-3-phosphoethanolamine-N-[amino(polyethylene glycol)] (PEG-DSPE), PEG-disteryl glycerol (PEG-DSG), PEG-dipalmetoleyl, PEG-dioleyl, PEG-distearyl, PEG-diacylglycamide (PEG-DAG), PEG-dipalmitoyl phosphatidylethanolamine (PEG-DPPE), or PEG-l,2-dimyristyloxlpropyl-3-amine (PEG-c-DMA).

[0710] In one embodiment, the PEG-lipid is selected from the group consisting of a PEG-modified phosphatidylethanolamine, a PEG-modified phosphatidic acid, a PEG-modified ceramide, a PEG-modified dialkylamine, a PEG-modified diacylglycerol, a PEG-modified dialkylglycerol, and mixtures thereof.

[0711] In some embodiments, the lipid moiety of the PEG-lipids includes those having lengths of from about C_{14} to about C_{22}, preferably from about C_{14} to about C_{16}. In some embodiments, a PEG moiety, for example an mPEG-NH_2, has a size of about 1000, 2000, 5000, 10,000, 15,000 or 20,000 daltons. In one embodiment, the PEG-lipid is PEG_{2k}-DMG.

[0712] In one embodiment, the lipid nanoparticles described herein can comprise a PEG lipid which is a non-diffusible PEG. Non-limiting examples of non-diffusible PEGs include PEG-DSG and PEG-DSPE.

[0713] PEG-lipids are known in the art, such as those described in U.S. Patent No. 8158601 and International Publ. No. WO 2015/130584 A2, which are incorporated herein by reference in their entirety.

[0714] In one embodiment, the amount of PEG-lipid in the lipid composition of a pharmaceutical composition disclosed herein ranges from about 0.1 mol % to about 5 mol %, from about 0.5 mol % to about 5 mol %, from about 1 mol % to about 5 mol %, from about 1.5 mol % to about 5 mol %, from about 2 mol % to about 5 mol % mol %, from about 0.1 mol % to about 4 mol %, from about 0.5 mol % to about 4 mol %, from about 1 mol % to about 4 mol %, from about 1.5 mol % to about 4 mol %, from about 2 mol % to about 4 mol %, from about 0.1

mol % to about 3 mol %, from about 0.5 mol % to about 3 mol %, from about 1 mol % to about 3 mol %, from about 1.5 mol % to about 3 mol %, from about 2 mol % to about 3 mol %, from about 0.1 mol % to about 2 mol %, from about 0.5 mol % to about 2 mol %, from about 1 mol % to about 2 mol %, from about 1.5 mol % to about 2 mol %, from about 0.1 mol % to about 1.5 mol %, from about 0.5 mol % to about 1.5 mol %, or from about 1 mol % to about 1.5 mol %.

[0715] In one embodiment, the amount of PEG-lipid in the lipid composition disclosed herein is about 1.5 mol %.

[0716] In one embodiment, the amount of PEG-lipid in the lipid composition disclosed herein is at least about 0.1, 0.2, 0.3, 0.4, 0.5, 0.6, 0.7, 0.8, 0.9, 1, 1.1, 1.2, 1.3, 1.4, 1.5, 1.6, 1.7, 1.8, 1.9, 2, 2.1, 2.2, 2.3, 2.4, 2.5, 2.6, 2.7, 2.8, 2.9, 3, 3.1, 3.2, 3.3, 3.4, 3.5, 3.6, 3.7, 3.8, 3.9, 4, 4.1, 4.2, 4.3, 4.4, 4.5, 4.6, 4.7, 4.8, 4.9, or 5 mol %.

[0717] In some aspects, the lipid composition of the pharmaceutical compositions disclosed herein does not comprise a PEG-lipid.

[0718] In some embodiments, the lipid composition disclosed herein comprises a compound of formula (I) and an asymmetric phospholipid. In some embodiments, the lipid composition comprises compound 18 and MSPC.

[0719] In some embodiments, the lipid composition disclosed herein comprises a compound of formula (I) and a quaternary amine compound. In some embodiments, the lipid composition comprises compound 18 and DOTAP.

[0720] In some embodiments, the lipid composition disclosed herein comprises a compound of formula (I), an asymmetric phospholipid, and a quaternary amine compound. In some embodiments, the lipid composition comprises compound 18, MSPC and DOTAP.

[0721] In one embodiment, the lipid composition comprises about 50 mol % of a compound of formula (I) (e.g., Compounds 18, 25, 26 or 48), about 10 mol % of DSPC or MSPC, about 33.5 mol % of cholesterol, about 1.5 mol % of PEG-DMG, and about 5 mol % of DOTAP. In one embodiment, the lipid composition comprises about 50 mol % of a compound of formula (I) (e.g. Compounds 18, 25, 26 or 48), about 10 mol % of DSPC or MSPC, about 28.5 mol % of cholesterol, about 1.5 mol % of PEG-DMG, and about 10 mol % of DOTAP.

[0722] The components of the lipid nanoparticle can be tailored for optimal delivery of the polynucleotides based on the desired outcome. As a non-limiting example, the lipid nanoparticle can comprise 40-60 mol % a compound of formula (I), 8-16 mol % phospholipid, 30-45 mol % cholesterol, 1-5 mol % PEG lipid, and optionally 1-15 mol % quaternary amine compound.

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[0723] In some embodiments, the lipid nanoparticle can comprise 45-65 mol % of a compound of formula (I), 5-10 mol % phospholipid, 25-40 mol % cholesterol, 0.5-5 mol % PEG lipid, and optionally 1-15 mol % quaternary amine compound.

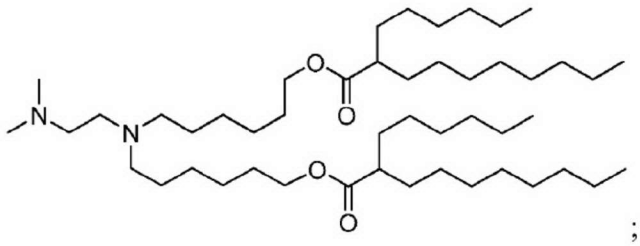
[0724] Non-limiting examples of nucleic acid lipid particles are disclosed in U.S. Patent Publication No. 20140121263, herein incorporated by reference in its entirety.

(v) Other Ionizable Amino Lipids

[0725] The lipid composition of the pharmaceutical composition disclosed herein can comprise one or more ionizable amino lipids in addition to a lipid according to formula (I).

[0726] Ionizable lipids can be selected from the non-limiting group consisting of 3-(didodecylamino)-N1,N1,4-tridodecyl-1-piperazineethanamine (KL10), N1-[2-(didodecylamino)ethyl]-N1,N4,N4-tridodecyl-1,4-piperazinediethanamine (KL22), 14,25-ditridecyl-15,18,21,24-tetraaza-octatriacontane (KL25), 1,2-dilinoleyloxy-N,N-dimethylaminopropane (DLin-DMA), 2,2-dilinoleyl-4-dimethylaminomethyl-[1,3]-dioxolane (DLin-K-DMA), heptatriaconta-6,9,28,31-tetraen-19-yl 4-(dimethylamino)butanoate (DLin-MC3-DMA), 2,2-dilinoleyl-4-(2-dimethylaminoethyl)-[1,3]-dioxolane (DLin-KC2-DMA), 1,2-dioleyloxy-N,N-dimethylaminopropane (DODMA), (13Z,165Z)-N,N-dimethyl-3-nonydocosa-13-16-dien-1-amine (L608), 2-({8-[(3β)-cholest-5-en-3-yloxy]octyl}oxy)-N,N-dimethyl-3-[(9Z,12Z)-octadeca-9,12-dien-1-yl oxy]propan-1-amine (Octyl-CLinDMA), (2R)-2-({8-[(3β)-cholest-5-en-3-yloxy]octyl}oxy)-N,N-dimethyl-3-[(9Z,12Z)-octadeca-9,12-die n-1-yloxy]propan-1-amine (Octyl-CLinDMA (2R)), and (2S)-2-({8-[(3β)-cholest-5-en-3-yloxy]octyl}oxy)-N,N-dimethyl-3-[(9Z,12Z)-octadeca-9,12-dien -1-yloxy]propan-1-amine (Octyl-CLinDMA (2S)). In addition to these, an ionizable amino lipid can also be a lipid including a cyclic amine group.

[0727] Ionizable lipids can also be the compounds disclosed in International Publication No. WO 2015/199952 A1, hereby incorporated by reference in its entirety. For example, the ionizable amino lipids include, but not limited to: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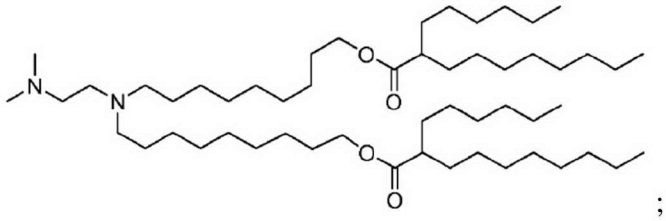
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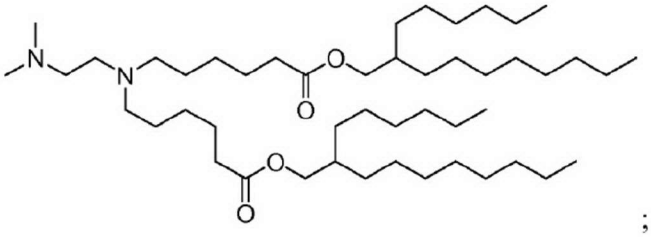
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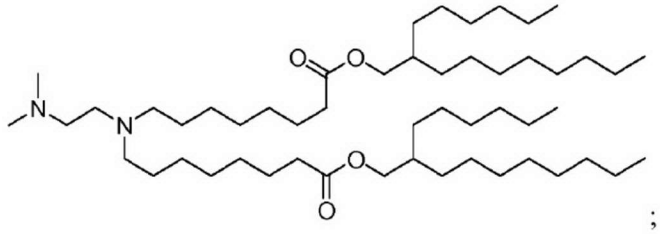
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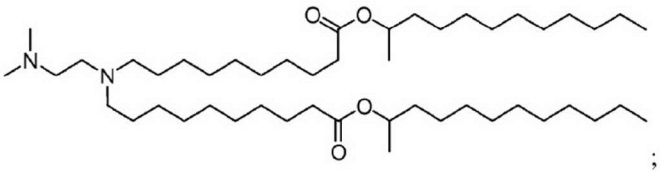
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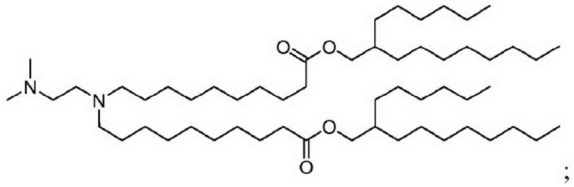
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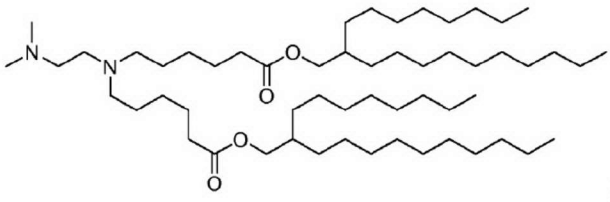
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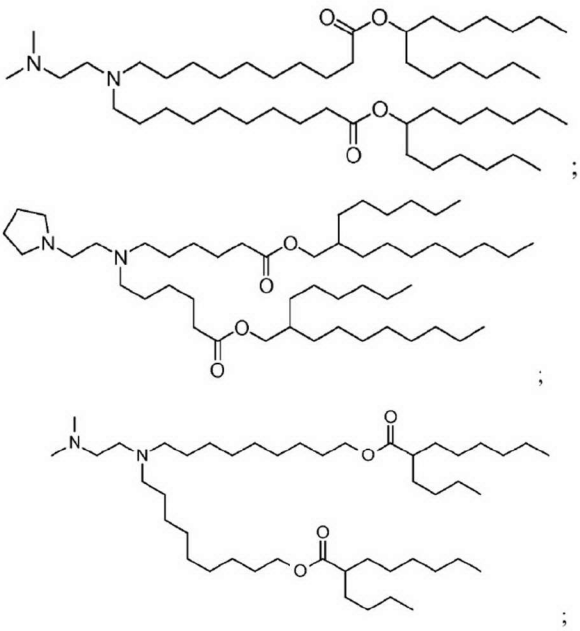

and any combination thereof.

(vi) Other Lipid Composition Components

[0728] The lipid composition of a pharmaceutical composition disclosed herein can include one or more components in addition to those described above. For example, the lipid composition can include one or more permeability enhancer molecules, carbohydrates, polymers, surface altering agents (e.g., surfactants), or other components. For example, a permeability enhancer molecule can be a molecule described by U.S. Patent Application Publication No. 2005/0222064. Carbohydrates can include simple sugars (e.g., glucose) and polysaccharides (e.g., glycogen and derivatives and analogs thereof). The lipid composition can include a buffer such as, but not limited to, citrate or phosphate at a pH of 7, salt and/or sugar. Salt and/or sugar can be included in the formulations described herein for isotonicity.

[0729] A polymer can be included in and/or used to encapsulate or partially encapsulate a pharmaceutical composition disclosed herein (e.g., a pharmaceutical composition in lipid nanoparticle form). A polymer can be biodegradable and/or biocompatible. A polymer can be selected from, but is not limited to, polyamines, polyethers, polyamides, polyesters, polycarbamates, polyureas, polycarbonates, polystyrenes, polyimides, polysulfones, polyurethanes, polyacetylenes, polyethylenes, polyethyleneimines, polyisocyanates, polyacrylates, polymethacrylates, polyacrylonitriles, and polyarylates.

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[0730] The ratio between the lipid composition and the polynucleotide range can be from about 10:1 to about 60:1 (wt/wt).

[0731] In some embodiments, the ratio between the lipid composition and the polynucleotide can be about 10:1, 11:1, 12:1, 13:1, 14:1, 15:1, 16:1, 17:1, 18:1, 19:1, 20:1, 21:1, 22:1, 23:1, 24:1, 25:1, 26:1, 27:1, 28:1, 29:1, 30:1, 31:1, 32:1, 33:1, 34:1, 35:1, 36:1, 37:1, 38:1, 39:1, 40:1, 41:1, 42:1, 43:1, 44:1, 45:1, 46:1, 47:1, 48:1, 49:1, 50:1, 51:1, 52:1, 53:1, 54:1, 55:1, 56:1, 57:1, 58:1, 59:1 or 60:1 (wt/wt). In some embodiments, the wt/wt ratio of the lipid composition to the polynucleotide encoding a therapeutic agent is about 20:1 or about 15:1.

[0732] In some embodiments, the pharmaceutical composition disclosed herein can contain more than one polypeptides. For example, a pharmaceutical composition disclosed herein can contain two or more polynucleotides (e.g., RNA, e.g., mRNA).

[0733] In one embodiment, the lipid nanoparticles described herein can comprise polynucleotides (e.g., mRNA) in a lipid:polynucleotide weight ratio of 5:1, 10:1, 15:1, 20:1, 25:1, 30:1, 35:1, 40:1, 45:1, 50:1, 55:1, 60:1 or 70:1, or a range or any of these ratios such as, but not limited to, 5:1 to about 10:1, from about 5:1 to about 15:1, from about 5:1 to about 20:1, from about 5:1 to about 25:1, from about 5:1 to about 30:1, from about 5:1 to about 35:1, from about 5:1 to about 40:1, from about 5:1 to about 45:1, from about 5:1 to about 50:1, from about 5:1 to about 55:1, from about 5:1 to about 60:1, from about 5:1 to about 70:1, from about 10:1 to about 15:1, from about 10:1 to about 20:1, from about 10:1 to about 25:1, from about 10:1 to about 30:1, from about 10:1 to about 35:1, from about 10:1 to about 40:1, from about 10:1 to about 45:1, from about 10:1 to about 50:1, from about 10:1 to about 55:1, from about 10:1 to about 60:1, from about 10:1 to about 70:1, from about 15:1 to about 20:1, from about 15:1 to about 25:1,from about 15:1 to about 30:1, from about 15:1 to about 35:1, from about 15:1 to about 40:1, from about 15:1 to about 45:1, from about 15:1 to about 50:1, from about 15:1 to about 55:1, from about 15:1 to about 60:1 or from about 15:1 to about 70:1.

[0734] In one embodiment, the lipid nanoparticles described herein can comprise the polynucleotide in a concentration from approximately 0.1 mg/ml to 2 mg/ml such as, but not limited to, 0.1 mg/ml, 0.2 mg/ml, 0.3 mg/ml, 0.4 mg/ml, 0.5 mg/ml, 0.6 mg/ml, 0.7 mg/ml, 0.8 mg/ml, 0.9 mg/ml, 1.0 mg/ml, 1.1 mg/ml, 1.2 mg/ml, 1.3 mg/ml, 1.4 mg/ml, 1.5 mg/ml, 1.6 mg/ml, 1.7 mg/ml, 1.8 mg/ml, 1.9 mg/ml, 2.0 mg/ml or greater than 2.0 mg/ml.

[0735] In one embodiment, formulations comprising the polynucleotides and lipid nanoparticles described herein can comprise 0.15 mg/ml to 2 mg/ml of the polynucleotide

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described herein (e.g., mRNA). In some embodiments, the formulation can further comprise 10 mM of citrate buffer and the formulation can additionally comprise up to 10% w/w of sucrose (e.g., at least 1% w/w, at least 2% w/w/, at least 3% w/w, at least 4% w/w, at least 5% w/w, at least 6% w/w, at least 7% w/w, at least 8% w/w, at least 9% w/w or 10% w/w).

(vii) Nanoparticle Compositions

[0736] In some embodiments, the pharmaceutical compositions disclosed herein are formulated as lipid nanoparticles (LNP). Accordingly, the present disclosure also provides nanoparticle compositions comprising (i) a lipid composition comprising a compound of formula (I) as described herein, and (ii) a polynucleotide encoding an MCM polypeptide. In such nanoparticle composition, the lipid composition disclosed herein can encapsulate the polynucleotide encoding an MCM polypeptide.

[0737] Nanoparticle compositions are typically sized on the order of micrometers or smaller and can include a lipid bilayer. Nanoparticle compositions encompass lipid nanoparticles (LNPs), liposomes (e.g., lipid vesicles), and lipoplexes. For example, a nanoparticle composition can be a liposome having a lipid bilayer with a diameter of 500 nm or less.

[0738] Nanoparticle compositions include, for example, lipid nanoparticles (LNPs), liposomes, and lipoplexes. In some embodiments, nanoparticle compositions are vesicles including one or more lipid bilayers. In certain embodiments, a nanoparticle composition includes two or more concentric bilayers separated by aqueous compartments. Lipid bilayers can be functionalized and/or crosslinked to one another. Lipid bilayers can include one or more ligands, proteins, or channels.

[0739] Nanoparticle compositions of the present disclosure comprise at least one compound according to formula (I). For example, the nanoparticle composition can include one or more of Compounds 1-147. Nanoparticle compositions can also include a variety of other components. For example, the nanoparticle composition can include one or more other lipids in addition to a lipid according to formula (I) or (II), for example (i) at least one phospholipid, (ii) at least one quaternary amine compound, (iii) at least one structural lipid, (iv) at least one PEG-lipid, or (v) any combination thereof.

[0740] In some embodiments, the nanoparticle composition comprises a compound of formula (I), (e.g., Compounds 18, 25, 26 or 48). In some embodiments, the nanoparticle composition comprises a compound of formula (I) (e.g., Compounds 18, 25, 26 or 48) and a

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phospholipid (e.g., DSPC or MSPC). In some embodiments, the nanoparticle composition comprises a compound of formula (I) (e.g., Compounds 18, 25, 26 or 48), a phospholipid (e.g., DSPC or MSPC), and a quaternary amine compound (e.g., DOTAP). In some embodiments, the nanoparticle composition comprises a compound of formula (I) (e.g., Compounds 18, 25, 26 or 48), and a quaternary amine compound (e.g., DOTAP).

[0741] In some embodiments, the nanoparticle composition comprises a lipid composition consisting or consisting essentially of compound of formula (I) (e.g., Compounds 18, 25, 26 or 48). In some embodiments, the nanoparticle composition comprises a lipid composition consisting or consisting essentially of a compound of formula (I) (e.g., Compounds 18, 25, 26 or 48) and a phospholipid (e.g., DSPC or MSPC). In some embodiments, the nanoparticle composition comprises a lipid composition consisting or consisting essentially of a compound of formula (I) (e.g., Compounds 18, 25, 26 or 48), a phospholipid (e.g., DSPC or MSPC), and a quaternary amine compound (e.g., DOTAP). In some embodiments, the nanoparticle composition comprises a lipid composition consisting or consisting essentially of a compound of formula (I) (e.g., Compounds 18, 25, 26 or 48), and a quaternary amine compound (e.g., DOTAP).

[0742] Nanoparticle compositions can be characterized by a variety of methods. For example, microscopy (e.g., transmission electron microscopy or scanning electron microscopy) can be used to examine the morphology and size distribution of a nanoparticle composition. Dynamic light scattering or potentiometry (e.g., potentiometric titrations) can be used to measure zeta potentials. Dynamic light scattering can also be utilized to determine particle sizes. Instruments such as the Zetasizer Nano ZS (Malvern Instruments Ltd, Malvern, Worcestershire, UK) can also be used to measure multiple characteristics of a nanoparticle composition, such as particle size, polydispersity index, and zeta potential.

[0743] The size of the nanoparticles can help counter biological reactions such as, but not limited to, inflammation, or can increase the biological effect of the polynucleotide.

[0744] As used herein, "size" or "mean size" in the context of nanoparticle compositions refers to the mean diameter of a nanoparticle composition.

[0745] In one embodiment, the polynucleotide encoding an MCM polypeptide are formulated in lipid nanoparticles having a diameter from about 10 to about 100 nm such as, but not limited to, about 10 to about 20 nm, about 10 to about 30 nm, about 10 to about 40 nm, about 10 to about 50 nm, about 10 to about 60 nm, about 10 to about 70 nm, about 10 to about 80 nm,

about 10 to about 90 nm, about 20 to about 30 nm, about 20 to about 40 nm, about 20 to about 50 nm, about 20 to about 60 nm, about 20 to about 70 nm, about 20 to about 80 nm, about 20 to about 90 nm, about 20 to about 100 nm, about 30 to about 40 nm, about 30 to about 50 nm, about 30 to about 60 nm, about 30 to about 70 nm, about 30 to about 80 nm, about 30 to about 90 nm, about 30 to about 100 nm, about 40 to about 50 nm, about 40 to about 60 nm, about 40 to about 70 nm, about 40 to about 80 nm, about 40 to about 90 nm, about 40 to about 100 nm, about 50 to about 60 nm, about 50 to about 70 nm, about 50 to about 80 nm, about 50 to about 90 nm, about 50 to about 100 nm, about 60 to about 70 nm, about 60 to about 80 nm, about 60 to about 90 nm, about 60 to about 100 nm, about 70 to about 80 nm, about 70 to about 90 nm, about 70 to about 100 nm, about 80 to about 90 nm, about 80 to about 100 nm and/or about 90 to about 100 nm.

[0746] In one embodiment, the nanoparticles have a diameter from about 10 to 500 nm. In one embodiment, the nanoparticle has a diameter greater than 100 nm, greater than 150 nm, greater than 200 nm, greater than 250 nm, greater than 300 nm, greater than 350 nm, greater than 400 nm, greater than 450 nm, greater than 500 nm, greater than 550 nm, greater than 600 nm, greater than 650 nm, greater than 700 nm, greater than 750 nm, greater than 800 nm, greater than 850 nm, greater than 900 nm, greater than 950 nm or greater than 1000 nm.

[0747] In some embodiments, the largest dimension of a nanoparticle composition is 1 μm or shorter (e.g., 1 μm, 900 nm, 800 nm, 700 nm, 600 nm, 500 nm, 400 nm, 300 nm, 200 nm, 175 nm, 150 nm, 125 nm, 100 nm, 75 nm, 50 nm, or shorter).

[0748] A nanoparticle composition can be relatively homogenous. A polydispersity index can be used to indicate the homogeneity of a nanoparticle composition, e.g., the particle size distribution of the nanoparticle composition. A small (e.g., less than 0.3) polydispersity index generally indicates a narrow particle size distribution. A nanoparticle composition can have a polydispersity index from about 0 to about 0.25, such as 0.01, 0.02, 0.03, 0.04, 0.05, 0.06, 0.07, 0.08, 0.09, 0.10, 0.11, 0.12, 0.13, 0.14, 0.15, 0.16, 0.17, 0.18, 0.19, 0.20, 0.21, 0.22, 0.23, 0.24, or 0.25. In some embodiments, the polydispersity index of a nanoparticle composition disclosed herein can be from about 0.10 to about 0.20.

[0749] The zeta potential of a nanoparticle composition can be used to indicate the electrokinetic potential of the composition. For example, the zeta potential can describe the surface charge of a nanoparticle composition. Nanoparticle compositions with relatively low charges, positive or negative, are generally desirable, as more highly charged species can interact undesirably with cells, tissues, and other elements in the body. In some embodiments, the zeta

potential of a nanoparticle composition disclosed herein can be from about -10 mV to about +20 mV, from about -10 mV to about +15 mV, from about 10 mV to about +10 mV, from about -10 mV to about +5 mV, from about -10 mV to about 0 mV, from about -10 mV to about -5 mV, from about -5 mV to about +20 mV, from about -5 mV to about +15 mV, from about -5 mV to about +10 mV, from about -5 mV to about +5 mV, from about -5 mV to about 0 mV, from about 0 mV to about +20 mV, from about 0 mV to about +15 mV, from about 0 mV to about +10 mV, from about 0 mV to about +5 mV, from about +5 mV to about +20 mV, from about +5 mV to about +15 mV, or from about +5 mV to about +10 mV.

[0750] In some embodiments, the zeta potential of the lipid nanoparticles can be from about 0 mV to about 100 mV, from about 0 mV to about 90 mV, from about 0 mV to about 80 mV, from about 0 mV to about 70 mV, from about 0 mV to about 60 mV, from about 0 mV to about 50 mV, from about 0 mV to about 40 mV, from about 0 mV to about 30 mV, from about 0 mV to about 20 mV, from about 0 mV to about 10 mV, from about 10 mV to about 100 mV, from about 10 mV to about 90 mV, from about 10 mV to about 80 mV, from about 10 mV to about 70 mV, from about 10 mV to about 60 mV, from about 10 mV to about 50 mV, from about 10 mV to about 40 mV, from about 10 mV to about 30 mV, from about 10 mV to about 20 mV, from about 20 mV to about 100 mV, from about 20 mV to about 90 mV, from about 20 mV to about 80 mV, from about 20 mV to about 70 mV, from about 20 mV to about 60 mV, from about 20 mV to about 50 mV, from about 20 mV to about 40 mV, from about 20 mV to about 30 mV, from about 30 mV to about 100 mV, from about 30 mV to about 90 mV, from about 30 mV to about 80 mV, from about 30 mV to about 70 mV, from about 30 mV to about 60 mV, from about 30 mV to about 50 mV, from about 30 mV to about 40 mV, from about 40 mV to about 100 mV, from about 40 mV to about 90 mV, from about 40 mV to about 80 mV, from about 40 mV to about 70 mV, from about 40 mV to about 60 mV, and from about 40 mV to about 50 mV. In some embodiments, the zeta potential of the lipid nanoparticles can be from about 10 mV to about 50 mV, from about 15 mV to about 45 mV, from about 20 mV to about 40 mV, and from about 25 mV to about 35 mV. In some embodiments, the zeta potential of the lipid nanoparticles can be about 10 mV, about 20 mV, about 30 mV, about 40 mV, about 50 mV, about 60 mV, about 70 mV, about 80 mV, about 90 mV, and about 100 mV.

[0751] The term "encapsulation efficiency" of a polynucleotide describes the amount of the polynucleotide that is encapsulated by or otherwise associated with a nanoparticle composition

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after preparation, relative to the initial amount provided. As used herein, "encapsulation" can refer to complete, substantial, or partial enclosure, confinement, surrounding, or encasement.

[0752] Encapsulation efficiency is desirably high (e.g., close to 100%). The encapsulation efficiency can be measured, for example, by comparing the amount of the polynucleotide in a solution containing the nanoparticle composition before and after breaking up the nanoparticle composition with one or more organic solvents or detergents.

[0753] Fluorescence can be used to measure the amount of free polynucleotide in a solution. For the nanoparticle compositions described herein, the encapsulation efficiency of a polynucleotide can be at least 50%, for example 50%, 55%, 60%, 65%, 70%, 75%, 80%, 85%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100%. In some embodiments, the encapsulation efficiency can be at least 80%. In certain embodiments, the encapsulation efficiency can be at least 90%.

[0754] The amount of a polynucleotide present in a pharmaceutical composition disclosed herein can depend on multiple factors such as the size of the polynucleotide, desired target and/or application, or other properties of the nanoparticle composition as well as on the properties of the polynucleotide.

[0755] For example, the amount of an mRNA useful in a nanoparticle composition can depend on the size (expressed as length, or molecular mass), sequence, and other characteristics of the mRNA. The relative amounts of a polynucleotide in a nanoparticle composition can also vary.

[0756] The relative amounts of the lipid composition and the polynucleotide present in a lipid nanoparticle composition of the present disclosure can be optimized according to considerations of efficacy and tolerability. For compositions including an mRNA as a polynucleotide, the N:P ratio can serve as a useful metric.

[0757] As the N:P ratio of a nanoparticle composition controls both expression and tolerability, nanoparticle compositions with low N:P ratios and strong expression are desirable. N:P ratios vary according to the ratio of lipids to RNA in a nanoparticle composition.

[0758] In general, a lower N:P ratio is preferred. The one or more RNA, lipids, and amounts thereof can be selected to provide an N:P ratio from about 2:1 to about 30:1, such as 2:1, 3:1, 4:1, 5:1, 6:1, 7:1, 8:1, 9:1, 10:1, 12:1, 14:1, 16:1, 18:1, 20:1, 22:1, 24:1, 26:1, 28:1, or 30:1. In certain embodiments, the N:P ratio can be from about 2:1 to about 8:1. In other embodiments,

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the N:P ratio is from about 5:1 to about 8:1. In certain embodiments, the N:P ratio is between 5:1 and 6:1. In one specific aspect, the N:P ratio is about is about 5.67:1.

[0759] In addition to providing nanoparticle compositions, the present disclosure also provides methods of producing lipid nanoparticles comprising encapsulating a polynucleotide. Such method comprises using any of the pharmaceutical compositions disclosed herein and producing lipid nanoparticles in accordance with methods of production of lipid nanoparticles known in the art. *See*, e.g., Wang et al. (2015) "Delivery of oligonucleotides with lipid nanoparticles" Adv. Drug Deliv. Rev. 87:68-80; Silva et al. (2015) "Delivery Systems for Biopharmaceuticals. Part I: Nanoparticles and Microparticles" Curr. Pharm. Technol. 16: 940-954; Naseri et al. (2015) "Solid Lipid Nanoparticles and Nanostructured Lipid Carriers: Structure, Preparation and Application" Adv. Pharm. Bull. 5:305-13; Silva et al. (2015) "Lipid nanoparticles for the delivery of biopharmaceuticals" Curr. Pharm. Biotechnol. 16:291-302, and references cited therein.

Excipients

[0760] The disclosure also includes pharmaceutical compositions that comprise a formulation of a polynucleotide described herein, *i.e.*, a polynucleotide comprising an ORF encoding an MCM polypeptide, with excipients. The polynucleotides of the disclosure can be formulated using one or more excipients to: (1) increase stability; (2) increase cell transfection; (3) permit the sustained or delayed release (*e.g.,* from a depot formulation of the polynucleotide); (4) alter the biodistribution (*e.g.,* target the polynucleotide to specific tissues or cell types); (5) increase the translation of encoded protein *in vivo*; and/or (6) alter the release profile of encoded protein *in vivo*. In addition to traditional excipients such as any and all solvents, dispersion media, diluents, or other liquid vehicles, dispersion or suspension aids, surface active agents, isotonic agents, thickening or emulsifying agents, preservatives, excipients of the present disclosure can include, without limitation, lipidoids, liposomes, lipid nanoparticles, polymers, lipoplexes, core-shell nanoparticles, peptides, proteins, cells transfected with polynucleotides (*e.g.,* for transplantation into a subject), hyaluronidase, nanoparticle mimics and combinations thereof. Accordingly, the formulations of the disclosure can include one or more excipients, each in an amount that together increases the stability of the polynucleotide, increases cell transfection by the polynucleotide, increases the expression of polynucleotides encoded protein, and/or alters

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the release profile of polynucleotide encoded proteins. Further, the polynucleotides of the present disclosure can be formulated using self-assembled nucleic acid nanoparticles.

[0761] A pharmaceutically acceptable excipient, as used herein, includes, but are not limited to, any and all solvents, dispersion media, diluents, or other liquid vehicles, dispersion or suspension aids, surface active agents, isotonic agents, thickening or emulsifying agents, preservatives, solid binders, lubricants, flavoring agents, stabilizers, antioxidants, osmolality adjusting agents, pH adjusting agents and the like, as suited to the particular dosage form desired. Various excipients for formulating pharmaceutical compositions and techniques for preparing the composition are known in the art (see *Remington*: *The Science and Practice of Pharmacy*, 21st Edition, A. R. Gennaro (Lippincott, Williams & Wilkins, Baltimore, MD, 2006; incorporated herein by reference in its entirety). The use of a conventional excipient medium can be contemplated within the scope of the present disclosure, except insofar as any conventional excipient medium is incompatible with a substance or its derivatives, such as by producing any undesirable biological effect or otherwise interacting in a deleterious manner with any other component(s) of the pharmaceutical composition, its use is contemplated to be within the scope of this disclosure.

[0762] In some embodiments, a pharmaceutically acceptable excipient can be at least 95%, at least 96%, at least 97%, at least 98%, at least 99%, or 100% pure. In some embodiments, an excipient is approved for use for humans and for veterinary use. In some embodiments, an excipient can be approved by United States Food and Drug Administration. In some embodiments, an excipient can be of pharmaceutical grade. In some embodiments, an excipient can meet the standards of the United States Pharmacopoeia (USP), the European Pharmacopoeia (EP), the British Pharmacopoeia, and/or the International Pharmacopoeia.

[0763] Pharmaceutically acceptable excipients used in the manufacture of pharmaceutical compositions include, but are not limited to, inert diluents, dispersing and/or granulating agents, surface active agents and/or emulsifiers, disintegrating agents, binding agents, preservatives, buffering agents, lubricating agents, and/or oils. Such excipients can optionally be included in pharmaceutical compositions. The composition can also include excipients such as cocoa butter and suppository waxes, coloring agents, coating agents, sweetening, flavoring, and/or perfuming agents.

[0764] Exemplary diluents include, but are not limited to, calcium carbonate, sodium carbonate, calcium phosphate, dicalcium phosphate, calcium sulfate, calcium hydrogen

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phosphate, sodium phosphate lactose, sucrose, cellulose, microcrystalline cellulose, kaolin, mannitol, sorbitol, inositol, sodium chloride, dry starch, cornstarch, powdered sugar, etc., and/or combinations thereof.

[0765] Exemplary granulating and/or dispersing agents include, but are not limited to, potato starch, corn starch, tapioca starch, sodium starch glycolate, clays, alginic acid, guar gum, citrus pulp, agar, bentonite, cellulose and wood products, natural sponge, cation-exchange resins, calcium carbonate, silicates, sodium carbonate, cross-linked poly(vinyl-pyrrolidone) (crospovidone), sodium carboxymethyl starch (sodium starch glycolate), carboxymethyl cellulose, cross-linked sodium carboxymethyl cellulose (croscarmellose), methylcellulose, pregelatinized starch (starch 1500), microcrystalline starch, water insoluble starch, calcium carboxymethyl cellulose, magnesium aluminum silicate (VEEGUM®), sodium lauryl sulfate, quaternary ammonium compounds, etc., and/or combinations thereof.

[0766] Exemplary surface active agents and/or emulsifiers include, but are not limited to, natural emulsifiers (*e.g.* acacia, agar, alginic acid, sodium alginate, tragacanth, chondrux, cholesterol, xanthan, pectin, gelatin, egg yolk, casein, wool fat, cholesterol, wax, and lecithin), colloidal clays (*e.g.,* bentonite [aluminum silicate] and VEEGUM® [magnesium aluminum silicate]), long chain amino acid derivatives, high molecular weight alcohols (*e.g.,* stearyl alcohol, cetyl alcohol, oleyl alcohol, triacetin monostearate, ethylene glycol distearate, glyceryl monostearate, and propylene glycol monostearate, polyvinyl alcohol), carbomers (*e.g.,* carboxy polymethylene, polyacrylic acid, acrylic acid polymer, and carboxyvinyl polymer), carrageenan, cellulosic derivatives (*e.g.,* carboxymethylcellulose sodium, powdered cellulose, hydroxymethyl cellulose, hydroxypropyl cellulose, hydroxypropyl methylcellulose, methylcellulose), sorbitan fatty acid esters (*e.g.,* polyoxyethylene sorbitan monolaurate [TWEEN®20], polyoxyethylene sorbitan [TWEEN®60], polyoxyethylene sorbitan monooleate [TWEEN®80], sorbitan monopalmitate [SPAN®40], sorbitan monostearate [SPAN®60], sorbitan tristearate [SPAN®65], glyceryl monooleate, sorbitan monooleate [SPAN®80]), polyoxyethylene esters (*e.g.,* polyoxyethylene monostearate [MYRJ®45], polyoxyethylene hydrogenated castor oil, polyethoxylated castor oil, polyoxymethylene stearate, and SOLUTOL®), sucrose fatty acid esters, polyethylene glycol fatty acid esters (*e.g.,* CREMOPHOR®), polyoxyethylene ethers, (*e.g.,* polyoxyethylene lauryl ether [BRIJ®30]), poly(vinyl-pyrrolidone), diethylene glycol monolaurate, triethanolamine oleate, sodium oleate, potassium oleate, ethyl oleate, oleic acid, ethyl laurate, sodium lauryl sulfate, PLUORINC®F 68, POLOXAMER®188, cetrimonium

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bromide, cetylpyridinium chloride, benzalkonium chloride, docusate sodium, etc. and/or combinations thereof.

[0767] Exemplary binding agents include, but are not limited to, starch (*e.g.*, cornstarch and starch paste); gelatin; sugars (*e.g.*, sucrose, glucose, dextrose, dextrin, molasses, lactose, lactitol, mannitol); amino acids (*e.g.*, glycine); natural and synthetic gums (*e.g.*, acacia, sodium alginate, extract of Irish moss, panwar gum, ghatti gum, mucilage of isapol husks, carboxymethylcellulose, methylcellulose, ethylcellulose, hydroxyethylcellulose, hydroxypropyl cellulose, hydroxypropyl methylcellulose, microcrystalline cellulose, cellulose acetate, poly(vinyl-pyrrolidone), magnesium aluminum silicate (VEEGUM®), and larch arabogalactan); alginates; polyethylene oxide; polyethylene glycol; inorganic calcium salts; silicic acid; polymethacrylates; waxes; water; alcohol; etc.; and combinations thereof.

[0768] Exemplary preservatives can include, but are not limited to, antioxidants, chelating agents, antimicrobial preservatives, antifungal preservatives, alcohol preservatives, acidic preservatives, and/or other preservatives. Oxidation is a potential degradation pathway for mRNA, especially for liquid mRNA formulations. In order to prevent oxidation, antioxidants can be added to the formulation. Exemplary antioxidants include, but are not limited to, alpha tocopherol, ascorbic acid, acorbyl palmitate, benzyl alcohol, butylated hydroxyanisole, EDTA, m-cresol, methionine, butylated hydroxytoluene, monothioglycerol, potassium metabisulfite, propionic acid, propyl gallate, sodium ascorbate, sodium bisulfite, sodium metabisulfite, thioglycerol and/or sodium sulfite. Exemplary chelating agents include ethylenediaminetetraacetic acid (EDTA), citric acid monohydrate, disodium edetate, dipotassium edetate, edetic acid, fumaric acid, malic acid, phosphoric acid, sodium edetate, tartaric acid, and/or trisodium edetate. Exemplary antimicrobial preservatives include, but are not limited to, benzalkonium chloride, benzethonium chloride, benzyl alcohol, bronopol, cetrimide, cetylpyridinium chloride, chlorhexidine, chlorobutanol, chlorocresol, chloroxylenol, cresol, ethyl alcohol, glycerin, hexetidine, imidurea, phenol, phenoxyethanol, phenylethyl alcohol, phenylmercuric nitrate, propylene glycol, and/or thimerosal. Exemplary antifungal preservatives include, but are not limited to, butyl paraben, methyl paraben, ethyl paraben, propyl paraben, benzoic acid, hydroxybenzoic acid, potassium benzoate, potassium sorbate, sodium benzoate, sodium propionate, and/or sorbic acid. Exemplary alcohol preservatives include, but are not limited to, ethanol, polyethylene glycol, phenol, phenolic compounds, bisphenol, chlorobutanol, hydroxybenzoate, and/or phenylethyl alcohol. Exemplary acidic preservatives include, but are

not limited to, vitamin A, vitamin C, vitamin E, beta-carotene, citric acid, acetic acid, dehydroacetic acid, ascorbic acid, sorbic acid, and/or phytic acid. Other preservatives include, but are not limited to, tocopherol, tocopherol acetate, deteroxime mesylate, cetrimide, butylated hydroxyanisol (BHA), butylated hydroxytoluened (BHT), ethylenediamine, sodium lauryl sulfate (SLS), sodium lauryl ether sulfate (SLES), sodium bisulfite, sodium metabisulfite, potassium sulfite, potassium metabisulfite, GLYDANT PLUS®, PHENONIP®, methylparaben, GERMALL®115, GERMABEN®II, NEOLONE™, KATHON™, and/or EUXYL®.

[0769] In some embodiments, the pH of polynucleotide solutions are maintained between pH 5 and pH 8 to improve stability. Exemplary buffers to control pH can include, but are not limited to sodium phosphate, sodium citrate, sodium succinate, histidine (or histidine-HCl), sodium carbonate, and/or sodium malate. In another embodiment, the exemplary buffers listed above can be used with additional monovalent counterions (including, but not limited to potassium). Divalent cations can also be used as buffer counterions; however, these are subject to complex formation and/or mRNA degradation.

[0770] Exemplary buffering agents can also include, but are not limited to, citrate buffer solutions, acetate buffer solutions, phosphate buffer solutions, ammonium chloride, calcium carbonate, calcium chloride, calcium citrate, calcium glubionate, calcium gluceptate, calcium gluconate, D-gluconic acid, calcium glycerophosphate, calcium lactate, propanoic acid, calcium levulinate, pentanoic acid, dibasic calcium phosphate, phosphoric acid, tribasic calcium phosphate, calcium hydroxide phosphate, potassium acetate, potassium chloride, potassium gluconate, potassium mixtures, dibasic potassium phosphate, monobasic potassium phosphate, potassium phosphate mixtures, sodium acetate, sodium bicarbonate, sodium chloride, sodium citrate, sodium lactate, dibasic sodium phosphate, monobasic sodium phosphate, sodium phosphate mixtures, tromethamine, magnesium hydroxide, aluminum hydroxide, alginic acid, pyrogen-free water, isotonic saline, Ringer's solution, ethyl alcohol, etc., and/or combinations thereof.

[0771] Exemplary lubricating agents include, but are not limited to, magnesium stearate, calcium stearate, stearic acid, silica, talc, malt, glyceryl behanate, hydrogenated vegetable oils, polyethylene glycol, sodium benzoate, sodium acetate, sodium chloride, leucine, magnesium lauryl sulfate, sodium lauryl sulfate, etc., and combinations thereof.

[0772] Exemplary oils include, but are not limited to, almond, apricot kernel, avocado, babassu, bergamot, black current seed, borage, cade, camomile, canola, caraway, carnauba,

castor, cinnamon, cocoa butter, coconut, cod liver, coffee, corn, cotton seed, emu, eucalyptus, evening primrose, fish, flaxseed, geraniol, gourd, grape seed, hazel nut, hyssop, isopropyl myristate, jojoba, kukui nut, lavandin, lavender, lemon, litsea cubeba, macademia nut, mallow, mango seed, meadowfoam seed, mink, nutmeg, olive, orange, orange roughy, palm, palm kernel, peach kernel, peanut, poppy seed, pumpkin seed, rapeseed, rice bran, rosemary, safflower, sandalwood, sasquana, savoury, sea buckthorn, sesame, shea butter, silicone, soybean, sunflower, tea tree, thistle, tsubaki, vetiver, walnut, and wheat germ oils. Exemplary oils include, but are not limited to, butyl stearate, caprylic triglyceride, capric triglyceride, cyclomethicone, diethyl sebacate, dimethicone 360, isopropyl myristate, mineral oil, octyldodecanol, oleyl alcohol, silicone oil, and/or combinations thereof.

[0773] Excipients such as cocoa butter and suppository waxes, coloring agents, coating agents, sweetening, flavoring, and/or perfuming agents can be present in the composition, according to the judgment of the formulator.

[0774] Exemplary additives include physiologically biocompatible buffers (*e.g.,* trimethylamine hydrochloride), addition of chelants (such as, for example, DTPA or DTPA-bisamide) or calcium chelate complexes (as for example calcium DTPA, CaNaDTPA-bisamide), or, optionally, additions of calcium or sodium salts (for example, calcium chloride, calcium ascorbate, calcium gluconate or calcium lactate). In addition, antioxidants and suspending agents can be used.

Lipidoids

[0775] The disclosure includes pharmaceutical compositions that comprise a lipidoid formulation of the polynucleotide described herein, *i.e.*, a polynucleotide comprising an ORF encoding an MCM polypeptide.

[0776] The synthesis of lipidoids has been extensively described and formulations containing these compounds are particularly suited for delivery of polynucleotides (*see* Mahon et al., Bioconjug. Chem. 2010 21:1448-1454; Schroeder et al., J Intern Med. 2010 267:9-21; Akinc et al., Nat Biotechnol. 2008 26:561-569; Love et al., Proc Natl Acad Sci U S A. 2010 107:1864-1869; Siegwart et al., Proc Natl Acad Sci U S A. 2011 108:12996-3001; all of which are incorporated herein in their entireties).

[0777] Lipidoids have been used to effectively deliver double stranded small interfering RNA molecules in rodents and non-human primates (see Akinc et al., Nat Biotechnol. 2008

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26:561-569; Frank-Kamenetsky et al., Proc Natl Acad Sci U S A. 2008 105:11915-11920; Akinc et al., Mol Ther. 2009 17:872-879; Love et al., Proc Natl Acad Sci U S A. 2010 107:1864-1869; Leuschner et al., Nat Biotechnol. 2011 29:1005-1010; all of which is incorporated herein in their entirety), and the present disclosure describes their formulation and use in delivering polynucleotides.

[0778] Complexes, micelles, liposomes or particles can be prepared containing these lipidoids and therefore, can result in an effective delivery of the polynucleotide, as judged by the production of an encoded protein, following the injection of a lipidoid formulation via localized and/or systemic routes of administration. Lipidoid complexes of polynucleotides can be administered by various means including, but not limited to, intravenous, intramuscular, or subcutaneous routes.

[0779] *In vivo* delivery of nucleic acids can be affected by many parameters, including, but not limited to, the formulation composition, nature of particle PEGylation, degree of loading, polynucleotide to lipid ratio, and biophysical parameters such as, but not limited to, particle size (Akinc et al., Mol Ther. 2009 17:872-879; herein incorporated by reference in its entirety). As an example, small changes in the anchor chain length of poly(ethylene glycol) (PEG) lipids can result in significant effects on *in vivo* efficacy. Formulations with the different lipidoids, including, but not limited to penta[3-(1-laurylaminopropionyl)]-triethylenetetramine hydrochloride (TETA–5LAP; aka 98N12-5, see Murugaiah et al., Analytical Biochemistry, 401:61 (2010); herein incorporated by reference in its entirety), C12-200 (including derivatives and variants), and MD1, can be tested for *in vivo* activity.

[0780] The lipidoid referred to herein as "98N12-5" is disclosed by Akinc et al., Mol Ther. 2009 17:872-879 and is incorporated by reference in its entirety.

[0781] The lipidoid referred to herein as "C12-200" is disclosed by Love et al., Proc Natl Acad Sci U S A. 2010 107:1864-1869 and Liu and Huang, Molecular Therapy. 2010 669-670; both of which are herein incorporated by reference in their entirety. The lipidoid formulations can include particles comprising either 3 or 4 or more components in addition to polynucleotides.

[0782] Lipidoids and polynucleotide formulations comprising lipidoids are described in International Patent Application No. PCT/US2014/097077, the contents of which are herein incorporated by reference in its entirety.

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Liposomes, Lipoplexes, and Lipid Nanoparticles

[0783] The disclosure also includes pharmaceutical compositions that comprise a formulation of the polynucleotide described herein, *i.e.*, a polynucleotide comprising an ORF encoding an MCM polypeptide, using one or more liposomes, lipoplexes, or lipid nanoparticles. In one embodiment, pharmaceutical compositions of the polynucleotides include liposomes. Liposomes are artificially-prepared vesicles that can primarily be composed of a lipid bilayer and can be used as a delivery vehicle for the administration of nutrients and pharmaceutical formulations. Liposomes can be of different sizes such as, but not limited to, a multilamellar vesicle (MLV)that can be hundreds of nanometers in diameter and can contain a series of concentric bilayers separated by narrow aqueous compartments, a small unicellular vesicle (SUV)that can be smaller than 50 nm in diameter, and a large unilamellar vesicle (LUV)that can be between 50 and 500 nm in diameter. Liposome design can include, but is not limited to, opsonins or ligands in order to improve the attachment of liposomes to unhealthy tissue or to activate events such as, but not limited to, endocytosis. Liposomes can contain a low or a high pH in order to improve the delivery of the pharmaceutical formulations.

[0784] The formation of liposomes can depend on the physicochemical characteristics such as, but not limited to, the pharmaceutical formulation entrapped and the liposomal ingredients , the nature of the medium in which the lipid vesicles are dispersed, the effective concentration of the entrapped substance and its potential toxicity, any additional processes involved during the application and/or delivery of the vesicles, the optimization size, polydispersity and the shelf-life of the vesicles for the intended application, and the batch-to-batch reproducibility and possibility of large-scale production of safe and efficient liposomal products.

[0785] As a non-limiting example, liposomes such as synthetic membrane vesicles can be prepared by the methods, apparatus and devices described in US Patent Publication No. US20130177638, US20130177637, US20130177636, US20130177635, US20130177634, US20130177633, US20130183375, US20130183373 and US20130183372, the contents of each of which are herein incorporated by reference in its entirety.

[0786] In one embodiment, pharmaceutical compositions described herein can include, without limitation, liposomes such as those formed from 1,2-dioleyloxy-N,N-dimethylaminopropane (DODMA) liposomes, DiLa2 liposomes from Marina Biotech (Bothell, WA), 1,2-dilinoleyloxy-3-dimethylaminopropane (DLin-DMA), 2,2-dilinoleyl-4-(2-dimethylaminoethyl)-[1,3]-dioxolane (DLin-KC2-DMA), and MC3 (US20100324120; herein

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incorporated by reference in its entirety) and liposomes that can deliver small molecule drugs such as, but not limited to, DOXIL® from Janssen Biotech, Inc. (Horsham, PA).

[0787] In one embodiment, pharmaceutical compositions described herein can include, without limitation, liposomes such as those formed from the synthesis of stabilized plasmid-lipid particles (SPLP) or stabilized nucleic acid lipid particle (SNALP) that have been previously described and shown to be suitable for oligonucleotide delivery *in vitro* and *in vivo* (see Wheeler et al. Gene Therapy. 1999 6:271-281; Zhang et al. Gene Therapy. 1999 6:1438-1447; Jeffs et al. Pharm Res. 2005 22:362-372; Morrissey et al., Nat Biotechnol. 2005 2:1002-1007; Zimmermann et al., Nature. 2006 441:111-114; Heyes et al. J Contr Rel. 2005 107:276-287; Semple et al. Nature Biotech. 2010 28:172-176; Judge et al. J Clin Invest. 2009 119:661-673; deFougerolles Hum Gene Ther. 2008 19:125-132; U.S. Patent Publication No US20130122104; all of which are incorporated herein in their entireties). The original manufacture method by Wheeler et al. was a detergent dialysis method, which was later improved by Jeffs et al. and is referred to as the spontaneous vesicle formation method. The liposome formulations are composed of 3 to 4 lipid components in addition to the polynucleotide. As an example a liposome can contain, but is not limited to, 55% cholesterol, 20% disteroylphosphatidyl choline (DSPC), 10% PEG-S-DSG, and 15% 1,2-dioleyloxy-N,N-dimethylaminopropane (DODMA), as described by Jeffs et al. As another example, certain liposome formulations can contain, but are not limited to, 48% cholesterol, 20% DSPC, 2% PEG-c-DMA, and 30% cationic lipid, where the cationic lipid can be 1,2-distearloxy-N,N-dimethylaminopropane (DSDMA), DODMA, DLin-DMA, or 1,2-dilinolenyloxy-3-dimethylaminopropane (DLenDMA), as described by Heyes et al.

[0788] In some embodiments, liposome formulations can comprise from about 25.0% cholesterol to about 40.0% cholesterol, from about 30.0% cholesterol to about 45.0% cholesterol, from about 35.0% cholesterol to about 50.0% cholesterol and/or from about 48.5% cholesterol to about 60% cholesterol. For example, formulations can comprise a percentage of cholesterol selected from the group consisting of 28.5%, 31.5%, 33.5%, 36.5%, 37.0%, 38.5%, 39.0% and 43.5%. In some embodiments, formulations can comprise from about 5.0% to about 10.0% DSPC and/or from about 7.0% to about 15.0% DSPC.

[0789] In one embodiment, pharmaceutical compositions can include liposomes that can be formed to deliver polynucleotides that can encode at least one polypeptide of interest. The polynucleotides can be encapsulated by the liposome and/or it can be contained in an aqueous core that can then be encapsulated by the liposome (see International Pub. Nos. WO2012031046,

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WO2012031043, WO2012030901 and WO2012006378 and US Patent Publication No. US20130189351, US20130195969 and US20130202684; the contents of each of which are herein incorporated by reference in their entirety).

[0790] In another embodiment, liposomes can be formulated for targeted delivery. As a non-limiting example, the liposome can be formulated for targeted delivery to the liver. The liposome used for targeted delivery can include, but is not limited to, the liposomes described in and methods of making liposomes described in US Patent Publication No. US20130195967, the contents of which are herein incorporated by reference in its entirety.

[0791] In another embodiment, the polynucleotide can be formulated in a cationic oil-in-water emulsion where the emulsion particle comprises an oil core and a cationic lipid that can interact with the polynucleotide anchoring the molecule to the emulsion particle (see International Pub. No. WO2012006380; herein incorporated by reference in its entirety).

[0792] In one embodiment, the polynucleotides can be formulated in a water-in-oil emulsion comprising a continuous hydrophobic phase in which the hydrophilic phase is dispersed. As a non-limiting example, the emulsion can be made by the methods described in International Publication No. WO201087791, the contents of which are herein incorporated by reference in its entirety.

[0793] In another embodiment, the lipid formulation can include at least cationic lipid, a lipid that can enhance transfection and a least one lipid that contains a hydrophilic head group linked to a lipid moiety (International Pub. No. WO2011076807 and U.S. Pub. No. 20110200582; the contents of each of which is herein incorporated by reference in their entirety). In another embodiment, the polynucleotides can be formulated in a lipid vesicle that can have crosslinks between functionalized lipid bilayers (see U.S. Pub. No. 20120177724, the contents of which is herein incorporated by reference in its entirety).

[0794] In one embodiment, the polynucleotides can be formulated in a liposome as described in International Patent Publication No. WO2013086526, the contents of which is herein incorporated by reference in its entirety. The polynucleotides can be encapsulated in a liposome using reverse pH gradients and/or optimized internal buffer compositions as described in International Patent Publication No. WO2013086526, the contents of which is herein incorporated by reference in its entirety.

[0795] In one embodiment, the polynucleotides pharmaceutical compositions can be formulated in liposomes such as, but not limited to, DiLa2 liposomes (Marina Biotech, Bothell,

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WA), SMARTICLES® (Marina Biotech, Bothell, WA), neutral DOPC (1,2-dioleoyl-sn-glycero-3-phosphocholine) based liposomes (*e.g.*, siRNA delivery for ovarian cancer (Landen et al. Cancer Biology & Therapy 2006 5(12)1708-1713); herein incorporated by reference in its entirety) and hyaluronan-coated liposomes (Quiet Therapeutics, Israel).

[0796] In one embodiment, the cationic lipid can be a low molecular weight cationic lipid such as those described in US Patent Application No. 20130090372, the contents of which are herein incorporated by reference in its entirety.

[0797] In one embodiment, the polynucleotides can be formulated in a lipid vesicle that can have crosslinks between functionalized lipid bilayers.

[0798] In one embodiment, the polynucleotides can be formulated in a liposome comprising a cationic lipid. The liposome can have a molar ratio of nitrogen atoms in the cationic lipid to the phosphates in the RNA (N:P ratio) of between 1:1 and 20:1 as described in International Publication No. WO2013006825, herein incorporated by reference in its entirety. In another embodiment, the liposome can have a N:P ratio of greater than 20:1 or less than 1:1.

[0799] In one embodiment, the polynucleotides can be formulated in a lipid-polycation complex. The formation of the lipid-polycation complex can be accomplished by methods known in the art and/or as described in U.S. Pub. No. 20120178702, herein incorporated by reference in its entirety. As a non-limiting example, the polycation can include a cationic peptide or a polypeptide such as, but not limited to, polylysine, polyornithine and/or polyarginine and the cationic peptides described in International Pub. No. WO2012013326 or US Patent Pub. No. US20130142818; each of which is herein incorporated by reference in its entirety. In another embodiment, the polynucleotides can be formulated in a lipid-polycation complex that can further include a non-cationic lipid such as, but not limited to, cholesterol or dioleoyl phosphatidylethanolamine (DOPE).

[0800] In one embodiment, the polynucleotides can be formulated in an aminoalcohol lipidoid. Aminoalcohol lipidoids that can be used in the present disclosure can be prepared by the methods described in U.S. Patent No. 8,450,298, herein incorporated by reference in its entirety.

[0801] The liposome formulation can be influenced by, but not limited to, the selection of the cationic lipid component, the degree of cationic lipid saturation, the nature of the PEGylation, ratio of all components and biophysical parameters such as size. In one example by Semple et al. (Semple et al. Nature Biotech. 2010 28:172-176; herein incorporated by reference in its entirety), the liposome formulation was composed of 57.1 % cationic lipid, 7.1%

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dipalmitoylphosphatidylcholine, 34.3 % cholesterol, and 1.4% PEG-c-DMA. As another example, changing the composition of the cationic lipid could more effectively deliver siRNA to various antigen presenting cells (Basha et al. Mol Ther. 2011 19:2186-2200; herein incorporated by reference in its entirety). In some embodiments, liposome formulations can comprise from about 35 to about 45% cationic lipid, from about 40% to about 50% cationic lipid, from about 50% to about 60% cationic lipid and/or from about 55% to about 65% cationic lipid. In some embodiments, the ratio of lipid to mRNA in liposomes can be from about 5:1 to about 20:1, from about 10:1 to about 25:1, from about 15:1 to about 30:1 and/or at least 30:1.

[0802] In some embodiments, the ratio of PEG in the lipid nanoparticle (LNP) formulations can be increased or decreased and/or the carbon chain length of the PEG lipid can be modified from C14 to C18 to alter the pharmacokinetics and/or biodistribution of the LNP formulations. As a non-limiting example, LNP formulations can contain from about 0.5% to about 3.0%, from about 1.0% to about 3.5%, from about 1.5% to about 4.0%, from about 2.0% to about 4.5%, from about 2.5% to about 5.0% and/or from about 3.0% to about 6.0% of the lipid molar ratio of PEG-c-DOMG (R-3-[(ω-methoxy-poly(ethyleneglycol)2000)carbamoyl)]-1,2-dimyristyloxypropyl-3-amine) (also referred to herein as PEG-DOMG) as compared to the cationic lipid, DSPC and cholesterol. In another embodiment the PEG-c-DOMG can be replaced with a PEG lipid such as, but not limited to, PEG- DSG (1,2-Distearoyl-sn-glycerol, methoxypolyethylene glycol), PEG-DMG (1,2-Dimyristoyl-sn-glycerol) and/or PEG-DPG (1,2-Dipalmitoyl-sn-glycerol, methoxypolyethylene glycol). The cationic lipid can be selected from any lipid known in the art such as, but not limited to, DLin-MC3-DMA, DLin-DMA, C12-200 and DLin-KC2-DMA.

[0803] In one embodiment, the polynucleotides can be formulated in a lipid nanoparticle such as those described in International Publication No. WO2012170930, the contents of which is herein incorporated by reference in its entirety.

[0804] In one embodiment, the formulation comprising the polynucleotide is a nanoparticle that can comprise at least one lipid. The lipid can be selected from, but is not limited to, DLin-DMA, DLin-K-DMA, 98N12-5, C12-200, DLin-MC3-DMA, DLin-KC2-DMA, DODMA, PLGA, PEG, PEG-DMG, PEGylated lipids and amino alcohol lipids. In another aspect, the lipid can be a cationic lipid such as, but not limited to, DLin-DMA, DLin-D-DMA, DLin-MC3-DMA, DLin-KC2-DMA, DODMA and amino alcohol lipids. The amino alcohol cationic lipid can be the lipids described in and/or made by the methods described in US Patent Publication No. US20130150625, herein incorporated by reference in its entirety. As a non-limiting example, the

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cationic lipid can be 2-amino-3-[(9Z,12Z)-octadeca-9,12-dien-1-yloxy]-2-{[(9Z,2Z)-octadeca-9,12-dien-1-yloxy]methyl}propan-1-ol (Compound 1 in US20130150625); 2-amino-3-[(9Z)-octadec-9-en-1-yloxy]-2-{[(9Z)-octadec-9-en-1-yloxy]methyl}propan-1-ol (Compound 2 in US20130150625); 2-amino-3-[(9Z,12Z)-octadeca-9,12-dien-1-yloxy]-2-[(octyloxy)methyl]propan-1-ol (Compound 3 in US20130150625); and 2-(dimethylamino)-3-[(9Z,12Z)-octadeca-9,12-dien-1-yloxy]-2-{[(9Z,12Z)-octadeca-9,12-dien-1-yloxy]methyl}propan-1-ol (Compound 4 in US20130150625); or any pharmaceutically acceptable salt or stereoisomer thereof.

[0805] Lipid nanoparticle formulations typically comprise a lipid, in particular, an ionizable cationic lipid, for example, 2,2-dilinoleyl-4-dimethylaminoethyl-[1,3]-dioxolane (DLin-KC2-DMA), dilinoleyl-methyl-4-dimethylaminobutyrate (DLin-MC3-DMA), or di((Z)-non-2-en-1-yl) 9-((4-(dimethylamino)butanoyl)oxy)heptadecanedioate (L319), and further comprise a neutral lipid, a sterol and a molecule capable of reducing particle aggregation, for example a PEG or PEG-modified lipid.

[0806] In one embodiment, the lipid nanoparticle formulation consists essentially of (i) at least one lipid selected from the group consisting of 2,2-dilinoleyl-4-dimethylaminoethyl-[1,3]-dioxolane (DLin-KC2-DMA), dilinoleyl-methyl-4-dimethylaminobutyrate (DLin-MC3-DMA), and di((Z)-non-2-en-1-yl) 9-((4-(dimethylamino)butanoyl)oxy)heptadecanedioate (L319); (ii) a neutral lipid selected from DSPC, DPPC, POPC, DOPE and SM; (iii) a sterol, *e.g.*, cholesterol; and (iv) a PEG-lipid, *e.g.*, PEG-DMG or PEG-cDMA, in a molar ratio of about 20-60% cationic lipid: 5-25% neutral lipid: 25-55% sterol; 0.5-15% PEG-lipid.

[0807] In one embodiment, the formulation includes from about 25% to about 75% on a molar basis of a cationic lipid selected from 2,2-dilinoleyl-4-dimethylaminoethyl-[1,3]-dioxolane (DLin-KC2-DMA), dilinoleyl-methyl-4-dimethylaminobutyrate (DLin-MC3-DMA), and di((Z)-non-2-en-1-yl) 9-((4-(dimethylamino)butanoyl)oxy)heptadecanedioate (L319), *e.g.*, from about 35 to about 65%, from about 45 to about 65%, about 60%, about 57.5%, about 50% or about 40% on a molar basis.

[0808] In one embodiment, the formulation includes from about 0.5% to about 15% on a molar basis of the neutral lipid *e.g.*, from about 3 to about 12%, from about 5 to about 10% or about 15%, about 10%, or about 7.5% on a molar basis. Exemplary neutral lipids include, but are not limited to, DSPC, POPC, DPPC, DOPE and SM. In one embodiment, the formulation includes from about 5% to about 50% on a molar basis of the sterol (*e.g.*, about 15 to about 45%,

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about 20 to about 40%, about 40%, about 38.5%, about 35%, or about 31% on a molar basis. An exemplary sterol is cholesterol. In one embodiment, the formulation includes from about 0.5% to about 20% on a molar basis of the PEG or PEG-modified lipid (*e.g.*, about 0.5 to about 10%, about 0.5 to about 5%, about 1.5%, about 0.5%, about 1.5%, about 3.5%, or about 5% on a molar basis. In one embodiment, the PEG or PEG modified lipid comprises a PEG molecule of an average molecular weight of 2,000 Da. In other embodiments, the PEG or PEG modified lipid comprises a PEG molecule of an average molecular weight of less than 2,000, for example around 1,500 Da, around 1,000 Da, or around 500 Da. Exemplary PEG-modified lipids include, but are not limited to, PEG-distearoyl glycerol (PEG-DMG) (also referred herein as PEG-C14 or C14-PEG), PEG-cDMA (further discussed in Reyes et al. J. Controlled Release, 107, 276-287 (2005) the contents of which are herein incorporated by reference in its entirety)

[0809] In one embodiment, the formulations of the disclosure include 25-75% of a cationic lipid selected from 2,2-dilinoleyl-4-dimethylaminoethyl-[1,3]-dioxolane (DLin-KC2-DMA), dilinoleyl-methyl-4-dimethylaminobutyrate (DLin-MC3-DMA), and di((Z)-non-2-en-1-yl) 9-((4-(dimethylamino)butanoyl)oxy)heptadecanedioate (L319), 0.5-15% of the neutral lipid, 5-50% of the sterol, and 0.5-20% of the PEG or PEG-modified lipid on a molar basis.

[0810] In one embodiment, the formulations of the disclosure include 35-65% of a cationic lipid selected from 2,2-dilinoleyl-4-dimethylaminoethyl-[1,3]-dioxolane (DLin-KC2-DMA), dilinoleyl-methyl-4-dimethylaminobutyrate (DLin-MC3-DMA), and di((Z)-non-2-en-1-yl) 9-((4-(dimethylamino)butanoyl)oxy)heptadecanedioate (L319), 3-12% of the neutral lipid, 15-45% of the sterol, and 0.5-10% of the PEG or PEG-modified lipid on a molar basis.

[0811] In one embodiment, the formulations of the disclosure include 45-65% of a cationic lipid selected from 2,2-dilinoleyl-4-dimethylaminoethyl-[1,3]-dioxolane (DLin-KC2-DMA), dilinoleyl-methyl-4-dimethylaminobutyrate (DLin-MC3-DMA), and di((Z)-non-2-en-1-yl) 9-((4-(dimethylamino)butanoyl)oxy)heptadecanedioate (L319), 5-10% of the neutral lipid, 25-40% of the sterol, and 0.5-10% of the PEG or PEG-modified lipid on a molar basis.

[0812] In one embodiment, the formulations of the disclosure include about 60% of a cationic lipid selected from 2,2-dilinoleyl-4-dimethylaminoethyl-[1,3]-dioxolane (DLin-KC2-DMA), dilinoleyl-methyl-4-dimethylaminobutyrate (DLin-MC3-DMA), and di((Z)-non-2-en-1-yl) 9-((4-(dimethylamino)butanoyl)oxy)heptadecanedioate (L319), about 7.5% of the neutral lipid, about 31 % of the sterol, and about 1.5% of the PEG or PEG-modified lipid on a molar basis.

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[0813] In one embodiment, the formulations of the disclosure include about 50% of a cationic lipid selected from 2,2-dilinoleyl-4-dimethylaminoethyl-[1,3]-dioxolane (DLin-KC2-DMA), dilinoleyl-methyl-4-dimethylaminobutyrate (DLin-MC3-DMA), and di((Z)-non-2-en-1-yl) 9-((4-(dimethylamino)butanoyl)oxy)heptadecanedioate (L319), about 10% of the neutral lipid, about 38.5 % of the sterol, and about 1.5% of the PEG or PEG-modified lipid on a molar basis.

[0814] In one embodiment, the formulations of the disclosure include about 50% of a cationic lipid selected from 2,2-dilinoleyl-4-dimethylaminoethyl-[1,3]-dioxolane (DLin-KC2-DMA), dilinoleyl-methyl-4-dimethylaminobutyrate (DLin-MC3-DMA), and di((Z)-non-2-en-1-yl) 9-((4-(dimethylamino)butanoyl)oxy)heptadecanedioate (L319), about 10% of the neutral lipid, about 35 % of the sterol, about 4.5% or about 5% of the PEG or PEG-modified lipid, and about 0.5% of the targeting lipid on a molar basis.

[0815] In one embodiment, the formulations of the disclosure include about 40% of a cationic lipid selected from 2,2-dilinoleyl-4-dimethylaminoethyl-[1,3]-dioxolane (DLin-KC2-DMA), dilinoleyl-methyl-4-dimethylaminobutyrate (DLin-MC3-DMA), and di((Z)-non-2-en-1-yl) 9-((4-(dimethylamino)butanoyl)oxy)heptadecanedioate (L319), about 15% of the neutral lipid, about 40% of the sterol, and about 5% of the PEG or PEG-modified lipid on a molar basis.

[0816] In one embodiment, the formulations of the disclosure include about 57.2% of a cationic lipid selected from 2,2-dilinoleyl-4-dimethylaminoethyl-[1,3]-dioxolane (DLin-KC2-DMA), dilinoleyl-methyl-4-dimethylaminobutyrate (DLin-MC3-DMA), and di((Z)-non-2-en-1-yl) 9-((4-(dimethylamino)butanoyl)oxy)heptadecanedioate (L319), about 7.1% of the neutral lipid, about 34.3% of the sterol, and about 1.4% of the PEG or PEG-modified lipid on a molar basis.

[0817] In one embodiment, the formulations of the disclosure include about 57.5% of a cationic lipid selected from the PEG lipid is PEG-cDMA (PEG-cDMA is further discussed in Reyes et al. (J. Controlled Release, 107, 276-287 (2005), the contents of which are herein incorporated by reference in its entirety), about 7.5% of the neutral lipid, about 31.5 % of the sterol, and about 3.5% of the PEG or PEG-modified lipid on a molar basis.

[0818] In some embodiments, lipid nanoparticle formulation consists essentially of a lipid mixture in molar ratios of about 20-70% cationic lipid: 5-45% neutral lipid: 20-55% cholesterol: 0.5-15% PEG-modified lipid. In some embodiments, lipid nanoparticle formulation consists

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essentially of a lipid mixture in molar ratios of about 20-60% cationic lipid: 5-25% neutral lipid: 25-55% cholesterol: 0.5-15% PEG-modified lipid.

[0819] In particular embodiments, the molar lipid ratio is approximately 50/10/38.5/1.5 (mol% cationic lipid/neutral lipid, *e.g.*, DSPC/Chol/PEG-modified lipid, *e.g.*, PEG-DMG, PEG-DSG or PEG-DPG), 57.2/7.1134.3/1.4 (mol% cationic lipid/ neutral lipid, *e.g.*, DPPC/Chol/ PEG-modified lipid, *e.g.*, PEG-cDMA), 40/15/40/5 (mol% cationic lipid/ neutral lipid, *e.g.*, DSPC/Chol/ PEG-modified lipid, *e.g.*, PEG-DMG), 50/10/35/4.5/0.5 (mol% cationic lipid/ neutral lipid, *e.g.*, DSPC/Chol/ PEG-modified lipid, *e.g.*, PEG-DSG), 50/10/35/5 (cationic lipid/ neutral lipid, *e.g.*, DSPC/Chol/ PEG-modified lipid, *e.g.*, PEG-DMG), 40/10/40/10 (mol% cationic lipid/ neutral lipid, *e.g.*, DSPC/Chol/ PEG-modified lipid, *e.g.*, PEG-DMG or PEG-cDMA), 35/15/40/10 (mol% cationic lipid/ neutral lipid, *e.g.*, DSPC/Chol/ PEG-modified lipid, *e.g.*, PEG-DMG or PEG-cDMA) or 52/13/30/5 (mol% cationic lipid/ neutral lipid, *e.g.*, DSPC/Chol/ PEG-modified lipid, *e.g.*, PEG-DMG or PEG-cDMA).

[0820] Exemplary lipid nanoparticle compositions and methods of making same are described, for example, in Semple et al. (2010) Nat. Biotechnol. 28:172-176; Jayarama et al. (2012), Angew. Chem. Int. Ed., 51: 8529–8533; and Maier et al. (2013) Molecular Therapy 21, 1570-1578 (the contents of each of which are incorporated herein by reference in their entirety).

[0821] In one embodiment, the lipid nanoparticle formulations described herein can comprise a cationic lipid, a PEG lipid and a structural lipid and optionally comprise a non-cationic lipid. As a non-limiting example, the lipid nanoparticle can comprise about 40-60% of cationic lipid, about 5-15% of a non-cationic lipid, about 1-2% of a PEG lipid and about 30-50% of a structural lipid. As another non-limiting example, the lipid nanoparticle can comprise about 50% cationic lipid, about 10% non-cationic lipid, about 1.5% PEG lipid and about 38.5% structural lipid. As yet another non-limiting example, the lipid nanoparticle can comprise about 55% cationic lipid, about 10% non-cationic lipid, about 2.5% PEG lipid and about 32.5% structural lipid. In one embodiment, the cationic lipid can be any cationic lipid described herein such as, but not limited to, DLin-KC2-DMA, DLin-MC3-DMA and L319.

[0822] In one embodiment, the lipid nanoparticle formulations described herein can be 4 component lipid nanoparticles. The lipid nanoparticle can comprise a cationic lipid, a non-cationic lipid, a PEG lipid and a structural lipid. As a non-limiting example, the lipid nanoparticle can comprise about 40-60% of cationic lipid, about 5-15% of a non-cationic lipid, about 1-2% of a PEG lipid and about 30-50% of a structural lipid. As another non-limiting

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example, the lipid nanoparticle can comprise about 50% cationic lipid, about 10% non-cationic lipid, about 1.5% PEG lipid and about 38.5% structural lipid. As yet another non-limiting example, the lipid nanoparticle can comprise about 55% cationic lipid, about 10% non-cationic lipid, about 2.5% PEG lipid and about 32.5% structural lipid. In one embodiment, the cationic lipid can be any cationic lipid described herein such as, but not limited to, DLin-KC2-DMA, DLin-MC3-DMA and L319.

[0823] In one embodiment, the lipid nanoparticle formulations described herein can comprise a cationic lipid, a non-cationic lipid, a PEG lipid and a structural lipid. As a non-limiting example, the lipid nanoparticle comprise about 50% of the cationic lipid DLin-KC2-DMA, about 10% of the non-cationic lipid DSPC, about 1.5% of the PEG lipid PEG-DOMG and about 38.5% of the structural lipid cholesterol. As a non-limiting example, the lipid nanoparticle comprise about 50% of the cationic lipid DLin-MC3-DMA, about 10% of the non-cationic lipid DSPC, about 1.5% of the PEG lipid PEG-DOMG and about 38.5% of the structural lipid cholesterol. As a non-limiting example, the lipid nanoparticle comprise about 50% of the cationic lipid DLin-MC3-DMA, about 10% of the non-cationic lipid DSPC, about 1.5% of the PEG lipid PEG-DMG and about 38.5% of the structural lipid cholesterol. As yet another non-limiting example, the lipid nanoparticle comprise about 55% of the cationic lipid L319, about 10% of the non-cationic lipid DSPC, about 2.5% of the PEG lipid PEG-DMG and about 32.5% of the structural lipid cholesterol.

[0824] In one embodiment, the cationic lipid can be selected from, but not limited to, a cationic lipid described in International Publication Nos. WO2012040184, WO2011153120, WO2011149733, WO2011090965, WO2011043913, WO2011022460, WO2012061259, WO2012054365, WO2012044638, WO2010080724, WO201021865, WO2008103276, WO2013086373 and WO2013086354, US Patent Nos. 7,893,302, 7,404,969, 8,283,333, and 8,466,122 and US Patent Publication No. US20100036115, US20120202871, US20130064894, US20130129785, US20130150625, US20130178541 and US20130225836; the contents of each of which are herein incorporated by reference in their entirety. In another embodiment, the cationic lipid can be selected from, but not limited to, formula A described in International Publication Nos. WO2012040184, WO2011153120, WO2011149733, WO2011090965, WO2011043913, WO2011022460, WO2012061259, WO2012054365, WO2012044638 and WO2013116126 or US Patent Publication No. US20130178541 and US20130225836; the contents of each of which is herein incorporated by reference in their entirety. In yet another

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embodiment, the cationic lipid can be selected from, but not limited to, formula CLI-CLXXIX of International Publication No. WO2008103276, formula CLI-CLXXIX of US Patent No. 7,893,302, formula CLI-CLXXXXII of US Patent No. 7,404,969 and formula I-VI of US Patent Publication No. US20100036115, formula I of US Patent Publication No US20130123338; each of which is herein incorporated by reference in their entirety. As a non-limiting example, the cationic lipid can be selected from (20Z,23Z)-N,N-dimethylnonacosa-20,23-dien-10-amine, (17Z,20Z)-N,N-dimemylhexacosa-17,20-dien-9-amine, (1Z,19Z)-N5N-dimethylpentacosa-l 6, 19-dien-8-amine, (13Z,16Z)-N,N-dimethyldocosa-13,16-dien-5-amine, (12Z,15Z)-N,N-dimethylhenicosa-12,15-dien-4-amine, (14Z,17Z)-N,N-dimethyltricosa-14,17-dien-6-amine, (15Z,18Z)-N,N-dimethyltetracosa-15,18-dien-7-amine, (18Z,21Z)-N,N-dimethylheptacosa-18,21-dien-10-amine, (15Z,18Z)-N,N-dimethyltetracosa-15,18-dien-5-amine, (14Z,17Z)-N,N-dimethyltricosa-14,17-dien-4-amine, (19Z,22Z)-N,N-dimeihyloctacosa-19,22-dien-9-amine, (18Z,21 Z)-N,N-dimethylheptacosa- 18 ,21 -dien-8 –amine, (17Z,20Z)-N,N-dimethylhexacosa-17,20-dien-7-amine, (16Z,19Z)-N,N-dimethylpentacosa-16,19-dien-6-amine, (22Z,25Z)-N,N-dimethylhentriaconta-22,25-dien-10-amine, (21 Z ,24Z)-N,N-dimethyltriaconta-21,24-dien-9-amine, (18Z)-N,N-dimetylheptacos-18-en-10-amine, (17Z)-N,N-dimethylhexacos-17-en-9-amine, (19Z,22Z)-N,N-dimethyloctacosa-19,22-dien-7-amine, N,N-dimethylheptacosan-10-amine, (20Z,23Z)-N-ethyl-N-methylnonacosa-20,23-dien-l0-amine, 1-[(11Z,14Z)-l-nonylicosa-11,14-dien-l-yl] pyrrolidine, (20Z)-N,N-dimethylheptacos-20-en-l 0-amine, (15Z)-N,N-dimethyl eptacos-15-en-l 0-amine, (14Z)-N,N-dimethylnonacos-14-en-l0-amine, (17Z)-N,N-dimethylnonacos-17-en-l0-amine, (24Z)-N,N-dimethyltritriacont-24-en-l0-amine, (20Z)-N,N-dimethylnonacos-20-en-l 0-amine, (22Z)-N,N-dimethylhentriacont-22-en-l0-amine, (16Z)-N,N-dimethylpentacos-16-en-8-amine, (12Z,15Z)-N,N-dimethyl-2-nonylhenicosa-12,15-dien-1–amine, (13Z,16Z)-N,N-dimethyl-3-nonyldocosa-l3,16-dien-l–amine, N,N-dimethyl-l-[(lS,2R)-2-octylcyclopropyl] eptadecan-8-amine, 1-[(1S,2R)-2-hexylcyclopropyl]-N,N-dimethylnonadecan-10-amine, N,N-dimethyl-1-[(1S ,2R)-2-octylcyclopropyl]nonadecan-10-amine, N,N-dimethyl-21-[(lS,2R)-2-octylcyclopropyl]henicosan-l0-amine,N,N-dimethyl-1-[(1S,2S)-2-{[(lR,2R)-2-pentylcycIopropyl]methyl}cyclopropyl]nonadecan-10-amine,N,N-dimethyl-1-[(1S,2R)-2-octylcyclopropyl]hexadecan-8-amine, N,N-dimethyl-[(lR,2S)-2-undecylcyclopropyl]tetradecan-5-amine, N,N-dimethyl-3-{7-[(1S,2R)-2-octylcyclopropyl]heptyl} dodecan-1–amine, 1-[(1R,2S)-2-hepty lcyclopropyl]-N,N-dimethyloctadecan-9–amine, 1-[(1S,2R)-2-decylcyclopropyl]-N,N-dimethylpentadecan-6-amine, N,N-dimethyl-l-[(lS,2R)-2-

octylcyclopropyl]pentadecan-8-amine, R-N,N-dimethyl-1-[(9Z,12Z)-octadeca-9,12-dien-1-yloxy]-3-(octyloxy)propan-2-amine, S-N,N-dimethyl-1-[(9Z,12Z)-octadeca-9,12-dien-1-yloxy]-3-(octyloxy)propan-2-amine, 1-{2-[(9Z,12Z)-octadeca-9,12-dien-1-yloxy]-1-[(octyloxy)methyl]ethyl}pyrrolidine, (2S)-N,N-dimethyl-1-[(9Z,12Z)-octadeca-9,12-dien-1-yloxy]-3-[(5Z)-oct-5-en-1-yloxy]propan-2-amine, 1-{2-[(9Z,12Z)-octadeca-9,12-dien-1-yloxy]-1-[(octyloxy)methyl]ethyl}azetidine, (2S)-1-(hexyloxy)-N,N-dimethyl-3-[(9Z,12Z)-octadeca-9,12-dien-1-yloxy]propan-2-amine, (2S)-1-(heptyloxy)-N,N-dimethyl-3-[(9Z,12Z)-octadeca-9,12-dien-1-yloxy]propan-2-amine, N,N-dimethyl-1-(nonyloxy)-3-[(9Z,12Z)-octadeca-9,12-dien-1-yloxy]propan-2-amine, N,N-dimethyl-1-[(9Z)-octadec-9-en-1-yloxy]-3-(octyloxy)propan-2-amine; (2S)-N,N-dimethyl-1-[(6Z,9Z,12Z)-octadeca-6,9,12-trien-1-yloxy]-3-(octyloxy)propan-2-amine, (2S)-1-[(11Z,14Z)-icosa-11,14-dien-1-yloxy]-N,N-dimethyl-3-(pentyloxy)propan-2-amine, (2S)-1-(hexyloxy)-3-[(11Z,14Z)-icosa-11,14-dien-1-yloxy]-N,N-dimethylpropan-2-amine, 1-[(11Z,14Z)-icosa-11,14-dien-1-yloxy]-N,N-dimethy1-3-(octyloxy)propan-2-amine, 1-[(13Z,16Z)-docosa-l3,16-dien-l-yloxy]-N,N-dimethyl-3-(octyloxy)propan-2-amine, (2S)-1-[(13Z,16Z)-docosa-13,16-dien-1-yloxy]-3-(hexyloxy)-N,N-dimethylpropan-2-amine, (2S)-1-[(13Z)-docos-13-en-1-yloxy]-3-(hexyloxy)-N,N-dimethylpropan-2-amine, 1-[(13Z)-docos-13-en-1-yloxy]-N,N-dimethyl-3-(octyloxy)propan-2-amine, 1-[(9Z)-hexadec-9-en-1-yloxy]-N,N-dimethyl-3-(octyloxy)propan-2-amine, (2R)-N,N-dimethyl-H(1-metoylo ctyl)oxy]-3-[(9Z,12Z)-octadeca-9,12-dien-1-yloxy]propan-2-amine, (2R)-1-[(3,7-dimethyloctyl)oxy]-N,N-dimethyl-3-[(9Z,12Z)-octadeca-9,12-dien-1-yloxy]propan-2-amine, N,N-dimethyl-1-(octyloxy)-3-({8-[(1S,2S)-2-{[(1R,2R)-2-pentylcyclopropyl]methyl}cyclopropyl]octyl}oxy)propan-2-amine, N,N-dimethyl-1-{[8-(2-oc1ylcyclopropyl)octyl]oxy}-3-(octyloxy)propan-2-amine and (11E,20Z,23Z)-N,N-dimethylnonacosa-11,20,2-trien-10-amine or a pharmaceutically acceptable salt or stereoisomer thereof.

[0825] In one embodiment, the lipid can be a cleavable lipid such as those described in International Publication No. WO2012170889, herein incorporated by reference in its entirety.

[0826] In another embodiment, the lipid can be a cationic lipid such as, but not limited to, Formula (I) of U.S. Patent Application No. US20130064894, the contents of which are herein incorporated by reference in its entirety.

[0827] In one embodiment, the cationic lipid can be synthesized by methods known in the art and/or as described in International Publication Nos. WO2012040184, WO2011153120, WO2011149733, WO2011090965, WO2011043913, WO2011022460, WO2012061259,

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WO2012054365, WO2012044638, WO2010080724, WO201021865, WO2013086373 and WO2013086354; the contents of each of which are herein incorporated by reference in their entirety.

[0828] In another embodiment, the cationic lipid can be a trialkyl cationic lipid. Non-limiting examples of trialkyl cationic lipids and methods of making and using the trialkyl cationic lipids are described in International Patent Publication No. WO2013126803, the contents of which are herein incorporated by reference in its entirety.

[0829] In one embodiment, the LNP formulations of the polynucleotides can contain PEG-c-DOMG at 3% lipid molar ratio. In another embodiment, the LNP formulations of polynucleotides can contain PEG-c-DOMG at 1.5% lipid molar ratio.

[0830] In one embodiment, the pharmaceutical compositions of the polynucleotides can include at least one of the PEGylated lipids described in International Publication No. WO2012099755, the contents of which is herein incorporated by reference in its entirety.

[0831] In one embodiment, the LNP formulation can contain PEG-DMG 2000 (1,2-dimyristoyl-sn-glycero-3-phophoethanolamine-N-[methoxy(polyethylene glycol)-2000). In one embodiment, the LNP formulation can contain PEG-DMG 2000, a cationic lipid known in the art and at least one other component. In another embodiment, the LNP formulation can contain PEG-DMG 2000, a cationic lipid known in the art, DSPC and cholesterol. As a non-limiting example, the LNP formulation can contain PEG-DMG 2000, DLin-DMA, DSPC and cholesterol. As another non-limiting example the LNP formulation can contain PEG-DMG 2000, DLin-DMA, DSPC and cholesterol in a molar ratio of 2:40:10:48 (*see, e.g.*, Geall et al., Nonviral delivery of self-amplifying RNA vaccines, PNAS 2012; PMID: 22908294; herein incorporated by reference in its entirety).

[0832] In one embodiment, the LNP formulation can be formulated by the methods described in International Publication Nos. WO2011127255 or WO2008103276, the contents of each of which is herein incorporated by reference in their entirety. As a non-limiting example, the polynucleotides described herein can be encapsulated in LNP formulations as described in WO2011127255 and/or WO2008103276; each of which is herein incorporated by reference in their entirety.

[0833] In one embodiment, the polynucleotides described herein can be formulated in a nanoparticle to be delivered by a parenteral route as described in U.S. Pub. No. US20120207845; the contents of which are herein incorporated by reference in its entirety.

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[0834] In one embodiment, the Polynucleotides can be formulated in a lipid nanoparticle made by the methods described in US Patent Publication No US20130156845 or International Publication No WO2013093648 or WO2012024526, each of which is herein incorporated by reference in its entirety.

[0835] The lipid nanoparticles described herein can be made in a sterile environment by the system and/or methods described in US Patent Publication No. US20130164400, herein incorporated by reference in its entirety.

[0836] In one embodiment, the LNP formulation can be formulated in a nanoparticle such as a nucleic acid-lipid particle described in US Patent No. 8,492,359, the contents of which are herein incorporated by reference in its entirety. As a non-limiting example, the lipid particle can comprise one or more active agents or therapeutic agents; one or more cationic lipids comprising from about 50 mol % to about 85 mol % of the total lipid present in the particle; one or more non-cationic lipids comprising from about 13 mol % to about 49.5 mol % of the total lipid present in the particle; and one or more conjugated lipids that inhibit aggregation of particles comprising from about 0.5 mol % to about 2 mol % of the total lipid present in the particle. The nucleic acid in the nanoparticle can be the polynucleotides described herein and/or are known in the art.

[0837] In one embodiment, the LNP formulation can be formulated by the methods described in International Publication Nos. WO2011127255 or WO2008103276, the contents of each of which are herein incorporated by reference in their entirety. As a non-limiting example, modified RNA described herein can be encapsulated in LNP formulations as described in WO2011127255 and/or WO2008103276; the contents of each of which are herein incorporated by reference in their entirety.

[0838] In one embodiment, LNP formulations described herein can comprise a polycationic composition. As a non-limiting example, the polycationic composition can be selected from formula 1-60 of US Patent Publication No. US20050222064; the content of which is herein incorporated by reference in its entirety. In another embodiment, the LNP formulations comprising a polycationic composition can be used for the delivery of the modified RNA described herein *in vivo* and/or *in vitro*.

[0839] In one embodiment, the LNP formulations described herein can additionally comprise a permeability enhancer molecule. Non-limiting permeability enhancer molecules are described

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in US Patent Publication No. US20050222064; the content of which is herein incorporated by reference in its entirety.

[0840] In one embodiment, the polynucleotide pharmaceutical compositions can be formulated in liposomes such as, but not limited to, DiLa2 liposomes (Marina Biotech, Bothell, WA), SMARTICLES® (Marina Biotech, Bothell, WA), neutral DOPC (1,2-dioleoyl-sn-glycero-3-phosphocholine) based liposomes (*e.g.*, siRNA delivery for ovarian cancer (Landen et al. Cancer Biology & Therapy 2006 5(12)1708-1713); herein incorporated by reference in its entirety) and hyaluronan-coated liposomes (Quiet Therapeutics, Israel).

[0841] In one embodiment, the Polynucleotides can be formulated in a lyophilized gel-phase liposomal composition as described in US Publication No. US2012060293, herein incorporated by reference in its entirety.

[0842] The nanoparticle formulations can comprise a phosphate conjugate. The phosphate conjugate can increase *in vivo* circulation times and/or increase the targeted delivery of the nanoparticle. Phosphate conjugates for use with the present disclosure can be made by the methods described in International Application No. WO2013033438 or US Patent Publication No. US20130196948, the contents of each of which are herein incorporated by reference in its entirety. As a non-limiting example, the phosphate conjugates can include a compound of any one of the formulas described in International Application No. WO2013033438, herein incorporated by reference in its entirety.

[0843] The nanoparticle formulation can comprise a polymer conjugate. The polymer conjugate can be a water soluble conjugate. The polymer conjugate can have a structure as described in U.S. Patent Application No. 20130059360, the contents of which are herein incorporated by reference in its entirety. In one aspect, polymer conjugates with the polynucleotides of the present disclosure can be made using the methods and/or segmented polymeric reagents described in U.S. Patent Application No. 20130072709, herein incorporated by reference in its entirety. In another aspect, the polymer conjugate can have pendant side groups comprising ring moieties such as, but not limited to, the polymer conjugates described in US Patent Publication No. US20130196948, the contents of which is herein incorporated by reference in its entirety.

[0844] The nanoparticle formulations can comprise a conjugate to enhance the delivery of nanoparticles of the present disclosure in a subject. Further, the conjugate can inhibit phagocytic clearance of the nanoparticles in a subject. In one aspect, the conjugate can be a "self" peptide

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designed from the human membrane protein CD47 (*e.g.*, the "self" particles described by Rodriguez et al (Science 2013 339, 971-975), herein incorporated by reference in its entirety). As shown by Rodriguez et al. the self peptides delayed macrophage-mediated clearance of nanoparticles which enhanced delivery of the nanoparticles. In another aspect, the conjugate can be the membrane protein CD47 (*e.g.*, see Rodriguez et al. Science 2013 339, 971-975, herein incorporated by reference in its entirety). Rodriguez et al. showed that, similarly to "self" peptides, CD47 can increase the circulating particle ratio in a subject as compared to scrambled peptides and PEG coated nanoparticles.

[0845] In one embodiment, the Polynucleotides of the present disclosure are formulated in nanoparticles that comprise a conjugate to enhance the delivery of the nanoparticles of the present disclosure in a subject. The conjugate can be the CD47 membrane or the conjugate can be derived from the CD47 membrane protein, such as the "self" peptide described previously. In another aspect the nanoparticle can comprise PEG and a conjugate of CD47 or a derivative thereof. In yet another aspect, the nanoparticle can comprise both the "self" peptide described above and the membrane protein CD47.

[0846] In another aspect, a "self" peptide and/or CD47 protein can be conjugated to a virus-like particle or pseudovirion, as described herein for delivery of the Polynucleotides of the present disclosure.

[0847] In another embodiment, pharmaceutical compositions comprise the polynucleotides of the present disclosure and a conjugate that can have a degradable linkage. Non-limiting examples of conjugates include an aromatic moiety comprising an ionizable hydrogen atom, a spacer moiety, and a water-soluble polymer. As a non-limiting example, pharmaceutical compositions comprising a conjugate with a degradable linkage and methods for delivering such pharmaceutical compositions are described in US Patent Publication No. US20130184443, the contents of which are herein incorporated by reference in its entirety.

[0848] The nanoparticle formulations can be a carbohydrate nanoparticle comprising a carbohydrate carrier and a polynucleotide. As a non-limiting example, the carbohydrate carrier can include, but is not limited to, an anhydride-modified phytoglycogen or glycogen-type material, phytoglycogen octenyl succinate, phytoglycogen beta-dextrin, anhydride-modified phytoglycogen beta-dextrin. (*See, e.g.*, International Publication No. WO2012109121; the contents of which are herein incorporated by reference in its entirety).

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[0849] Nanoparticle formulations of the present disclosure can be coated with a surfactant or polymer in order to improve the delivery of the particle. In one embodiment, the nanoparticle can be coated with a hydrophilic coating such as, but not limited to, PEG coatings and/or coatings that have a neutral surface charge. The hydrophilic coatings can help to deliver nanoparticles with larger payloads such as, but not limited to, Polynucleotides within the central nervous system. As a non-limiting example nanoparticles comprising a hydrophilic coating and methods of making such nanoparticles are described in US Patent Publication No. US20130183244, the contents of which are herein incorporated by reference in its entirety.

[0850] In one embodiment, the lipid nanoparticles of the present disclosure can be hydrophilic polymer particles. Non-limiting examples of hydrophilic polymer particles and methods of making hydrophilic polymer particles are described in US Patent Publication No. US20130210991, the contents of which are herein incorporated by reference in its entirety.

[0851] In another embodiment, the lipid nanoparticles of the present disclosure can be hydrophobic polymer particles.

[0852] Lipid nanoparticle formulations can be improved by replacing the cationic lipid with a biodegradable cationic lipid that is known as a rapidly eliminated lipid nanoparticle (reLNP). Ionizable cationic lipids, such as, but not limited to, DLinDMA, DLin-KC2-DMA, and DLin-MC3-DMA, have been shown to accumulate in plasma and tissues over time and can be a potential source of toxicity. The rapid metabolism of the rapidly eliminated lipids can improve the tolerability and therapeutic index of the lipid nanoparticles by an order of magnitude from a 1 mg/kg dose to a 10 mg/kg dose in rat. Inclusion of an enzymatically degraded ester linkage can improve the degradation and metabolism profile of the cationic component, while still maintaining the activity of the reLNP formulation. The ester linkage can be internally located within the lipid chain or it can be terminally located at the terminal end of the lipid chain. The internal ester linkage can replace any carbon in the lipid chain.

[0853] In one embodiment, the internal ester linkage can be located on either side of the saturated carbon.

[0854] Lipid nanoparticles can be engineered to alter the surface properties of particles so the lipid nanoparticles can penetrate the mucosal barrier. Mucus is located on mucosal tissue such as, but not limited to, oral (*e.g.*, the buccal and esophageal membranes and tonsil tissue), ophthalmic, gastrointestinal (*e.g.*, stomach, small intestine, large intestine, colon, rectum), nasal, respiratory (*e.g.*, nasal, pharyngeal, tracheal and bronchial membranes), genital (*e.g.*, vaginal,

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cervical and urethral membranes). Nanoparticles larger than 10-200 nm can be used for higher drug encapsulation efficiency and the ability to provide the sustained delivery of a wide array of drugs have been thought to be too large to rapidly diffuse through mucosal barriers. Mucus is continuously secreted, shed, discarded or digested and recycled so most of the trapped particles can be removed from the mucosal tissue within seconds or within a few hours. Large polymeric nanoparticles (200nm -500nm in diameter) that have been coated densely with a low molecular weight polyethylene glycol (PEG) diffused through mucus only 4 to 6-fold lower than the same particles diffusing in water (Lai et al. PNAS 2007 104(5):1482-487; Lai et al. Adv Drug Deliv Rev. 2009 61(2): 158-171; each of which is herein incorporated by reference in their entirety). The transport of nanoparticles can be determined using rates of permeation and/or fluorescent microscopy techniques including, but not limited to, fluorescence recovery after photobleaching (FRAP) and high resolution multiple particle tracking (MPT). As a non-limiting example, compositions that can penetrate a mucosal barrier can be made as described in U.S. Pat. No. 8,241,670 or International Patent Publication No. WO2013110028, the contents of each of which are herein incorporated by reference in its entirety.

[0855] The lipid nanoparticle engineered to penetrate mucus can comprise a polymeric material (*i.e.*, a polymeric core) and/or a polymer-vitamin conjugate and/or a tri-block co-polymer. The polymeric material can include, but is not limited to, polyamines, polyethers, polyamides, polyesters, polycarbamates, polyureas, polycarbonates, poly(styrenes), polyimides, polysulfones, polyurethanes, polyacetylenes, polyethylenes, polyethyeneimines, polyisocyanates, polyacrylates, polymethacrylates, polyacrylonitriles, and polyarylates. The polymeric material can be biodegradable and/or biocompatible. Non-limiting examples of biocompatible polymers are described in International Patent Publication No. WO2013116804, the contents of which are herein incorporated by reference in its entirety. The polymeric material can additionally be irradiated. As a non-limiting example, the polymeric material can be gamma irradiated (See *e.g.*, International App. No. WO201282165, herein incorporated by reference in its entirety). Non-limiting examples of specific polymers include poly(caprolactone) (PCL), ethylene vinyl acetate polymer (EVA), poly(lactic acid) (PLA), poly(L-lactic acid) (PLLA), poly(glycolic acid) (PGA), poly(lactic acid-co-glycolic acid) (PLGA), poly(L-lactic acid-co-glycolic acid) (PLLGA), poly(D,L-lactide) (PDLA), poly(L-lactide) (PLLA), poly(D,L-lactide-co-caprolactone), poly(D,L-lactide-co-caprolactone-co-glycolide), poly(D,L-lactide-co-PEO-co-D,L-lactide), poly(D,L-lactide-co-PPO-co-D,L-lactide), polyalkyl cyanoacralate, polyurethane, poly-L-lysine

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(PLL), hydroxypropyl methacrylate (HPMA), polyethyleneglycol, poly-L-glutamic acid, poly(hydroxy acids), polyanhydrides, polyorthoesters, poly(ester amides), polyamides, poly(ester ethers), polycarbonates, polyalkylenes such as polyethylene and polypropylene, polyalkylene glycols such as poly(ethylene glycol) (PEG), polyalkylene oxides (PEO), polyalkylene terephthalates such as poly(ethylene terephthalate), polyvinyl alcohols (PVA), polyvinyl ethers, polyvinyl esters such as poly(vinyl acetate), polyvinyl halides such as poly(vinyl chloride) (PVC), polyvinylpyrrolidone, polysiloxanes, polystyrene (PS), polyurethanes, derivatized celluloses such as alkyl celluloses, hydroxyalkyl celluloses, cellulose ethers, cellulose esters, nitro celluloses, hydroxypropylcellulose, carboxymethylcellulose, polymers of acrylic acids, such as poly(methyl(meth)acrylate) (PMMA), poly(ethyl(meth)acrylate), poly(butyl(meth)acrylate), poly(isobutyl(meth)acrylate), poly(hexyl(meth)acrylate), poly(isodecyl(meth)acrylate), poly(lauryl(meth)acrylate), poly(phenyl(meth)acrylate), poly(methyl acrylate), poly(isopropyl acrylate), poly(isobutyl acrylate), poly(octadecyl acrylate) and copolymers and mixtures thereof, polydioxanone and its copolymers, polyhydroxyalkanoates, polypropylene fumarate, polyoxymethylene, poloxamers, poly(ortho)esters, poly(butyric acid), poly(valeric acid), poly(lactide-co-caprolactone), PEG-PLGA-PEG and trimethylene carbonate, polyvinylpyrrolidone. The lipid nanoparticle can be coated or associated with a co-polymer such as, but not limited to, a block co-polymer (such as a branched polyether-polyamide block copolymer described in International Publication No. WO2013012476, herein incorporated by reference in its entirety), and (poly(ethylene glycol))-(poly(propylene oxide))-(poly(ethylene glycol)) triblock copolymer (*see, e.g.*, US Publication 20120121718 and US Publication 20100003337 and U.S. Pat. No. 8,263,665; each of which is herein incorporated by reference in their entirety). The co-polymer can be a polymer that is generally regarded as safe (GRAS) and the formation of the lipid nanoparticle can be in such a way that no new chemical entities are created. For example, the lipid nanoparticle can comprise poloxamers coating PLGA nanoparticles without forming new chemical entities that are still able to rapidly penetrate human mucus (Yang et al. Angew. Chem. Int. Ed. 2011 50:2597-2600; the contents of which are herein incorporated by reference in its entirety). A non-limiting scalable method to produce nanoparticles that can penetrate human mucus is described by Xu et al. (*See, e.g.*, J Control Release 2013, 170(2):279-86; the contents of which are herein incorporated by reference in its entirety).

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[0856] The vitamin of the polymer-vitamin conjugate can be vitamin E. The vitamin portion of the conjugate can be substituted with other suitable components such as, but not limited to, vitamin A, vitamin E, other vitamins, cholesterol, a hydrophobic moiety, or a hydrophobic component of other surfactants (*e.g.*, sterol chains, fatty acids, hydrocarbon chains and alkylene oxide chains).

[0857] The lipid nanoparticle engineered to penetrate mucus can include surface altering agents such as, but not limited to, polynucleotides, anionic proteins (*e.g.*, bovine serum albumin), surfactants (*e.g.*, cationic surfactants such as for example dimethyldioctadecyl-ammonium bromide), sugars or sugar derivatives (*e.g.*, cyclodextrin), nucleic acids, polymers (*e.g.*, heparin, polyethylene glycol and poloxamer), mucolytic agents (*e.g.*, N-acetylcysteine, mugwort, bromelain, papain, clerodendrum, acetylcysteine, bromhexine, carbocisteine, eprazinone, mesna, ambroxol, sobrerol, domiodol, letosteine, stepronin, tiopronin, gelsolin, thymosin β4 dornase alfa, neltenexine, erdosteine) and various DNases including rhDNase. The surface altering agent can be embedded or enmeshed in the particle's surface or disposed (*e.g.*, by coating, adsorption, covalent linkage, or other process) on the surface of the lipid nanoparticle. (see *e.g.*, US Publication 20100215580 and US Publication 20080166414 and US20130164343; the contents of each of which is herein incorporated by reference in their entirety).

[0858] In one embodiment, the mucus penetrating lipid nanoparticles can comprise at least one polynucleotide described herein. The polynucleotide can be encapsulated in the lipid nanoparticle and/or disposed on the surface of the particle. The polynucleotide can be covalently coupled to the lipid nanoparticle. Formulations of mucus penetrating lipid nanoparticles can comprise a plurality of nanoparticles. Further, the formulations can contain particles that can interact with the mucus and alter the structural and/or adhesive properties of the surrounding mucus to decrease mucoadhesion that can increase the delivery of the mucus penetrating lipid nanoparticles to the mucosal tissue.

[0859] In another embodiment, the mucus penetrating lipid nanoparticles can be a hypotonic formulation comprising a mucosal penetration enhancing coating. The formulation can be hypotonic for the epithelium to which it is being delivered. Non-limiting examples of hypotonic formulations can be found in International Patent Publication No. WO2013110028, the contents of which are herein incorporated by reference in its entirety.

[0860] In one embodiment, in order to enhance the delivery through the mucosal barrier the polynucleotide formulation can comprise or be a hypotonic solution. Hypotonic solutions were

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found to increase the rate at which mucoinert particles such as, but not limited to, mucus-penetrating particles, were able to reach the vaginal epithelial surface (*see, e.g.*, Ensign et al. Biomaterials 2013 34(28):6922-9; the contents of which is herein incorporated by reference in its entirety).

[0861] In one embodiment, the polynucleotide is formulated as a lipoplex, such as, without limitation, the ATUPLEXTM system, the DACC system, the DBTC system and other siRNA-lipoplex technology from Silence Therapeutics (London, United Kingdom), STEMFECTTM from STEMGENT® (Cambridge, MA), and polyethylenimine (PEI) or protamine-based targeted and non-targeted delivery of nucleic acids (Aleku et al. Cancer Res. 2008 68:9788-9798; Strumberg et al. Int J Clin Pharmacol Ther 2012 50:76-78; Santel et al., Gene Ther 2006 13:1222-1234; Santel et al., Gene Ther 2006 13:1360-1370; Gutbier et al., Pulm Pharmacol. Ther. 2010 23:334-344; Kaufmann et al. Microvasc Res 2010 80:286-293Weide et al. J Immunother. 2009 32:498-507; Weide et al. J Immunother. 2008 31:180-188; Pascolo Expert Opin. Biol. Ther. 4:1285-1294; Fotin-Mleczek et al., 2011 J. Immunother. 34:1-15; Song et al., Nature Biotechnol. 2005, 23:709-717; Peer et al., Proc Natl Acad Sci U S A. 2007 6;104:4095-4100; deFougerolles Hum Gene Ther. 2008 19:125-132; all of which are incorporated herein by reference in its entirety).

[0862] In one embodiment such formulations can also be constructed or compositions altered such that they passively or actively are directed to different cell types in vivo, including but not limited to hepatocytes, immune cells, tumor cells, endothelial cells, antigen presenting cells, and leukocytes (Akinc et al. Mol Ther. 2010 18:1357-1364; Song et al., Nat Biotechnol. 2005 23:709-717; Judge et al., J Clin Invest. 2009 119:661-673; Kaufmann et al., Microvasc Res 2010 80:286-293; Santel et al., Gene Ther 2006 13:1222-1234; Santel et al., Gene Ther 2006 13:1360-1370; Gutbier et al., Pulm Pharmacol. Ther. 2010 23:334-344; Basha et al., Mol. Ther. 2011 19:2186-2200; Fenske and Cullis, Expert Opin Drug Deliv. 2008 5:25-44; Peer et al., Science. 2008 319:627-630; Peer and Lieberman, Gene Ther. 2011 18:1127-1133; all of which are incorporated herein by reference in its entirety). One example of passive targeting of formulations to liver cells includes the DLin-DMA, DLin-KC2-DMA and DLin-MC3-DMA-based lipid nanoparticle formulations that have been shown to bind to apolipoprotein E and promote binding and uptake of these formulations into hepatocytes *in vivo* (Akinc et al. Mol Ther. 2010 18:1357-1364; herein incorporated by reference in its entirety). Formulations can also be selectively targeted through expression of different ligands on their surface as exemplified by,

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but not limited by, folate, transferrin, N-acetylgalactosamine (GalNAc), and antibody targeted approaches (Kolhatkar et al., Curr Drug Discov Technol. 2011 8:197-206; Musacchio and Torchilin, Front Biosci. 2011 16:1388-1412; Yu et al., Mol Membr Biol. 2010 27:286-298; Patil et al., Crit Rev Ther Drug Carrier Syst. 2008 25:1-61; Benoit et al., Biomacromolecules. 2011 12:2708-2714; Zhao et al., Expert Opin Drug Deliv. 2008 5:309-319; Akinc et al., Mol Ther. 2010 18:1357-1364; Srinivasan et al., Methods Mol Biol. 2012 820:105-116; Ben-Arie et al., Methods Mol Biol. 2012 757:497-507; Peer 2010 J Control Release. 20:63-68; Peer et al., Proc Natl Acad Sci U S A. 2007 104:4095-4100; Kim et al., Methods Mol Biol. 2011 721:339-353; Subramanya et al., Mol Ther. 2010 18:2028-2037; Song et al., Nat Biotechnol. 2005 23:709-717; Peer et al., Science. 2008 319:627-630; Peer and Lieberman, Gene Ther. 2011 18:1127-1133; all of which are incorporated herein by reference in its entirety).

[0863] In one embodiment, the polynucleotide is formulated as a solid lipid nanoparticle. A solid lipid nanoparticle (SLN) can be spherical with an average diameter between 10 to 1000 nm. SLN possess a solid lipid core matrix that can solubilize lipophilic molecules and can be stabilized with surfactants and/or emulsifiers. In a further embodiment, the lipid nanoparticle can be a self-assembly lipid-polymer nanoparticle (see Zhang et al., ACS Nano, 2008, 2 (8), pp 1696–1702; the contents of which are herein incorporated by reference in its entirety). As a non-limiting example, the SLN can be the SLN described in International Patent Publication No. WO2013105101, the contents of which are herein incorporated by reference in its entirety. As another non-limiting example, the SLN can be made by the methods or processes described in International Patent Publication No. WO2013105101, the contents of which are herein incorporated by reference in its entirety.

[0864] Liposomes, lipoplexes, or lipid nanoparticles can be used to improve the efficacy of polynucleotides directed protein production as these formulations can be able to increase cell transfection by the polynucleotide; and/or increase the translation of encoded protein. One such example involves the use of lipid encapsulation to enable the effective systemic delivery of polyplex plasmid DNA (Heyes et al., Mol Ther. 2007 15:713-720; herein incorporated by reference in its entirety). The liposomes, lipoplexes, or lipid nanoparticles can also be used to increase the stability of the polynucleotide.

[0865] In one embodiment, the Polynucleotides of the present disclosure can be formulated for controlled release and/or targeted delivery. As used herein, "controlled release" refers to a pharmaceutical composition or compound release profile that conforms to a particular pattern of

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release to effect a therapeutic outcome. In one embodiment, the polynucleotides can be encapsulated into a delivery agent described herein and/or known in the art for controlled release and/or targeted delivery. As used herein, the term "encapsulate" means to enclose, surround or encase. As it relates to the formulation of the compounds of the disclosure, encapsulation can be substantial, complete or partial. The term "substantially encapsulated" means that at least greater than 50, 60, 70, 80, 85, 90, 95, 96, 97, 98, 99, 99.9, 99.9 or greater than 99.999% of the pharmaceutical composition or compound of the disclosure can be enclosed, surrounded or encased within the delivery agent. "Partially encapsulation" means that less than 10, 10, 20, 30, 40 50 or less of the pharmaceutical composition or compound of the disclosure can be enclosed, surrounded or encased within the delivery agent. Advantageously, encapsulation can be determined by measuring the escape or the activity of the pharmaceutical composition or compound of the disclosure using fluorescence and/or electron micrograph. For example, at least 1, 5, 10, 20, 30, 40, 50, 60, 70, 80, 85, 90, 95, 96, 97, 98, 99, 99.9, 99.99 or greater than 99.99% of the pharmaceutical composition or compound of the disclosure are encapsulated in the delivery agent.

[0866] In one embodiment, the controlled release formulation can include, but is not limited to, tri-block co-polymers. As a non-limiting example, the formulation can include two different types of tri-block co-polymers (International Pub. No. WO2012131104 and WO2012131106; the contents of each of which is herein incorporated by reference in its entirety).

[0867] In another embodiment, the Polynucleotides can be encapsulated into a lipid nanoparticle or a rapidly eliminated lipid nanoparticle and the lipid nanoparticles or a rapidly eliminated lipid nanoparticle can then be encapsulated into a polymer, hydrogel and/or surgical sealant described herein and/or known in the art. As a non-limiting example, the polymer, hydrogel or surgical sealant can be PLGA, ethylene vinyl acetate (EVAc), poloxamer, GELSITE® (Nanotherapeutics, Inc. Alachua, FL), HYLENEX® (Halozyme Therapeutics, San Diego CA), surgical sealants such as fibrinogen polymers (Ethicon Inc. Cornelia, GA), TISSELL® (Baxter International, Inc. Deerfield, IL), PEG-based sealants, and COSEAL® (Baxter International, Inc. Deerfield, IL).

[0868] In another embodiment, the lipid nanoparticle can be encapsulated into any polymer known in the art that can form a gel when injected into a subject. As another non-limiting example, the lipid nanoparticle can be encapsulated into a polymer matrix that can be biodegradable.

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[0869] In one embodiment, the polynucleotide formulation for controlled release and/or targeted delivery can also include at least one controlled release coating. Controlled release coatings include, but are not limited to, OPADRY®, polyvinylpyrrolidone/vinyl acetate copolymer, polyvinylpyrrolidone, hydroxypropyl methylcellulose, hydroxypropyl cellulose, hydroxyethyl cellulose, EUDRAGIT RL®, EUDRAGIT RS® and cellulose derivatives such as ethylcellulose aqueous dispersions (AQUACOAT® and SURELEASE®).

[0870] In one embodiment, the polynucleotide controlled release and/or targeted delivery formulation can comprise at least one degradable polyester that can contain polycationic side chains. Degradable polyesters include, but are not limited to, poly(serine ester), poly(L-lactide-co-L-lysine), poly(4-hydroxy-L-proline ester), and combinations thereof. In another embodiment, the degradable polyesters can include a PEG conjugation to form a PEGylated polymer.

[0871] In one embodiment, the polynucleotide controlled release and/or targeted delivery formulation comprising at least one polynucleotide can comprise at least one PEG and/or PEG related polymer derivatives as described in US Patent No. 8,404,222, herein incorporated by reference in its entirety.

[0872] In another embodiment, the polynucleotide controlled release delivery formulation comprising at least one polynucleotide can be the controlled release polymer system described in US20130130348, herein incorporated by reference in its entirety.

[0873] In one embodiment, the Polynucleotides of the present disclosure can be encapsulated in a therapeutic nanoparticle, referred to herein as "therapeutic nanoparticle polynucleotides." Therapeutic nanoparticles can be formulated by methods described herein and known in the art such as, but not limited to, International Pub Nos. WO2010005740, WO2010030763, WO2010005721, WO2010005723, WO2012054923, US Pub. Nos. US20110262491, US20100104645, US20100087337, US20100068285, US20110274759, US20100068286, US20120288541, US20130123351 and US20130230567 and US Pat No. 8,206,747, 8,293,276, 8,318,208 and 8,318,211; the contents of each of which are herein incorporated by reference in their entirety. In another embodiment, therapeutic polymer nanoparticles can be identified by the methods described in US Pub No. US20120140790, the contents of which is herein incorporated by reference in its entirety.

[0874] In one embodiment, the therapeutic nanoparticle polynucleotide can be formulated for sustained release. As used herein, "sustained release" refers to a pharmaceutical composition or

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compound that conforms to a release rate over a specific period of time. The period of time can include, but is not limited to, hours, days, weeks, months and years. As a non-limiting example, the sustained release nanoparticle can comprise a polymer and a therapeutic agent such as, but not limited to, the polynucleotides of the present disclosure (see International Pub No. 2010075072 and US Pub No. US20100216804, US20110217377 and US20120201859, each of which is herein incorporated by reference in their entirety). In another non-limiting example, the sustained release formulation can comprise agents that permit persistent bioavailability such as, but not limited to, crystals, macromolecular gels and/or particulate suspensions (see US Patent Publication No US20130150295, the contents of which is herein incorporated by reference in its entirety).

[0875] In one embodiment, the therapeutic nanoparticle Polynucleotides can be formulated to be target specific. As a non-limiting example, the therapeutic nanoparticles can include a corticosteroid (see International Pub. No. WO2011084518; herein incorporated by reference in its entirety). As a non-limiting example, the therapeutic nanoparticles can be formulated in nanoparticles described in International Pub No. WO2008121949, WO2010005726, WO2010005725, WO2011084521 and US Pub No. US20100069426, US20120004293 and US20100104655, each of which is herein incorporated by reference in their entirety.

[0876] In one embodiment, the nanoparticles of the present disclosure can comprise a polymeric matrix. As a non-limiting example, the nanoparticle can comprise two or more polymers such as, but not limited to, polyethylenes, polycarbonates, polyanhydrides, polyhydroxyacids, polypropylfumerates, polycaprolactones, polyamides, polyacetals, polyethers, polyesters, poly(orthoesters), polycyanoacrylates, polyvinyl alcohols, polyurethanes, polyphosphazenes, polyacrylates, polymethacrylates, polycyanoacrylates, polyureas, polystyrenes, polyamines, polylysine, poly(ethylene imine), poly(serine ester), poly(L-lactide-co-L-lysine), poly(4-hydroxy-L-proline ester) or combinations thereof.

[0877] In one embodiment, the therapeutic nanoparticle comprises a diblock copolymer. In one embodiment, the diblock copolymer can include PEG in combination with a polymer such as, but not limited to, polyethylenes, polycarbonates, polyanhydrides, polyhydroxyacids, polypropylfumerates, polycaprolactones, polyamides, polyacetals, polyethers, polyesters, poly(orthoesters), polycyanoacrylates, polyvinyl alcohols, polyurethanes, polyphosphazenes, polyacrylates, polymethacrylates, polycyanoacrylates, polyureas, polystyrenes, polyamines, polylysine, poly(ethylene imine), poly(serine ester), poly(L-lactide-co-L-lysine), poly(4-

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hydroxy-L-proline ester) or combinations thereof. In another embodiment, the diblock copolymer can comprise the diblock copolymers described in European Patent Publication No. the contents of which are herein incorporated by reference in its entirety. In yet another embodiment, the diblock copolymer can be a high-X diblock copolymer such as those described in International Patent Publication No. WO2013120052, the contents of which are herein incorporated by reference in its entirety.

[0878] As a non-limiting example the therapeutic nanoparticle comprises a PLGA-PEG block copolymer (see US Pub. No. US20120004293 and US Pat No. 8,236,330, each of which is herein incorporated by reference in their entirety). In another non-limiting example, the therapeutic nanoparticle is a stealth nanoparticle comprising a diblock copolymer of PEG and PLA or PEG and PLGA (see US Pat No 8,246,968 and International Publication No. WO2012166923, the contents of each of which are herein incorporated by reference in its entirety). In yet another non-limiting example, the therapeutic nanoparticle is a stealth nanoparticle or a target-specific stealth nanoparticle as described in US Patent Publication No. US20130172406, the contents of which are herein incorporated by reference in its entirety.

[0879] In one embodiment, the therapeutic nanoparticle can comprise a multiblock copolymer (*see, e.g.*, U.S. Pat. No. 8,263,665 and 8,287,910 and US Patent Pub. No. US20130195987; the contents of each of which are herein incorporated by reference in its entirety).

[0880] In yet another non-limiting example, the lipid nanoparticle comprises the block copolymer PEG-PLGA-PEG (*see, e.g.*, the thermosensitive hydrogel (PEG-PLGA-PEG) was used as a TGF-beta1 gene delivery vehicle in Lee et al. Thermosensitive Hydrogel as a Tgf-β1 Gene Delivery Vehicle Enhances Diabetic Wound Healing. Pharmaceutical Research, 2003 20(12): 1995-2000; as a controlled gene delivery system in Li et al. Controlled Gene Delivery System Based on Thermosensitive Biodegradable Hydrogel. Pharmaceutical Research 2003 20(6):884-888; and Chang et al., Non-ionic amphiphilic biodegradable PEG-PLGA-PEG copolymer enhances gene delivery efficiency in rat skeletal muscle. J Controlled Release. 2007 118:245-253; each of which is herein incorporated by reference in its entirety). The Polynucleotides of the present disclosure can be formulated in lipid nanoparticles comprising the PEG-PLGA-PEG block copolymer.

[0881] In one embodiment, the therapeutic nanoparticle can comprise a multiblock copolymer (*see, e.g.*, U.S. Pat. No. 8,263,665 and 8,287,910 and US Patent Pub. No.

US20130195987; the contents of each of which are herein incorporated by reference in its entirety).

[0882] In one embodiment, the block copolymers described herein can be included in a polyion complex comprising a non-polymeric micelle and the block copolymer (*see, e.g.*, U.S. Pub. No. 20120076836; herein incorporated by reference in its entirety).

[0883] In one embodiment, the therapeutic nanoparticle can comprise at least one acrylic polymer. Acrylic polymers include but are not limited to, acrylic acid, methacrylic acid, acrylic acid and methacrylic acid copolymers, methyl methacrylate copolymers, ethoxyethyl methacrylates, cyanoethyl methacrylate, amino alkyl methacrylate copolymer, poly(acrylic acid), poly(methacrylic acid), polycyanoacrylates and combinations thereof.

[0884] In one embodiment, the therapeutic nanoparticles can comprise at least one poly(vinyl ester) polymer. The poly(vinyl ester) polymer can be a copolymer such as a random copolymer. As a non-limiting example, the random copolymer can have a structure such as those described in International Application No. WO2013032829 or US Patent Publication No US20130121954, the contents of which are herein incorporated by reference in its entirety. In one aspect, the poly(vinyl ester) polymers can be conjugated to the polynucleotides described herein. In another aspect, the poly(vinyl ester) polymer that can be used in the present disclosure can be those described in, herein incorporated by reference in its entirety.

[0885] In one embodiment, the therapeutic nanoparticle can comprise at least one diblock copolymer. The diblock copolymer can be, but it not limited to, a poly(lactic) acid-poly(ethylene)glycol copolymer (*see, e.g.*, International Patent Publication No. WO2013044219; herein incorporated by reference in its entirety).

[0886] In one embodiment, the therapeutic nanoparticles can comprise at least one cationic polymer described herein and/or known in the art.

[0887] In one embodiment, the therapeutic nanoparticles can comprise at least one amine-containing polymer such as, but not limited to polylysine, polyethylene imine, poly(amidoamine) dendrimers, poly(beta-amino esters) (*see, e.g.*, U.S. Pat. No. 8,287,849; herein incorporated by reference in its entirety) and combinations thereof.

[0888] In another embodiment, the nanoparticles described herein can comprise an amine cationic lipid such as those described in International Patent Application No. WO2013059496, the contents of which are herein incorporated by reference in its entirety. In one aspect the cationic lipids can have an amino-amine or an amino-amide moiety.

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[0889] In one embodiment, the therapeutic nanoparticles can comprise at least one degradable polyester that can contain polycationic side chains. Degradable polyesters include, but are not limited to, poly(serine ester), poly(L-lactide-co-L-lysine), poly(4-hydroxy-L-proline ester), and combinations thereof. In another embodiment, the degradable polyesters can include a PEG conjugation to form a PEGylated polymer.

[0890] In another embodiment, the therapeutic nanoparticle can include a conjugation of at least one targeting ligand. The targeting ligand can be any ligand known in the art such as, but not limited to, a monoclonal antibody. (Kirpotin et al, Cancer Res. 2006 66:6732-6740; herein incorporated by reference in its entirety).

[0891] In one embodiment, the therapeutic nanoparticle Polynucleotides, *e.g.*, therapeutic nanoparticles comprising at least one polynucleotide can be formulated using the methods described by Podobinski et al in US Patent No. 8,404,799, the contents of which are herein incorporated by reference in its entirety.

[0892] In one embodiment, the Polynucleotides can be encapsulated in, linked to and/or associated with synthetic nanocarriers. Synthetic nanocarriers include, but are not limited to, those described in International Pub. Nos. WO2010005740, WO2010030763, WO201213501, WO2012149252, WO2012149255, WO2012149259, WO2012149265, WO2012149268, WO2012149282, WO2012149301, WO2012149393, WO2012149405, WO2012149411, WO2012149454 and WO2013019669, and US Pub. Nos. US20110262491, US20100104645, US20100087337 and US20120244222, each of which is herein incorporated by reference in their entirety. The synthetic nanocarriers can be formulated using methods known in the art and/or described herein. As a non-limiting example, the synthetic nanocarriers can be formulated by the methods described in International Pub Nos. WO2010005740, WO2010030763 and WO201213501and US Pub. Nos. US20110262491, US20100104645, US20100087337 and US2012024422, each of which is herein incorporated by reference in their entirety. In another embodiment, the synthetic nanocarrier formulations can be lyophilized by methods described in International Pub. No. WO2011072218 and US Pat No. 8,211,473; the content of each of which is herein incorporated by reference in their entirety. In yet another embodiment, formulations of the present disclosure, including, but not limited to, synthetic nanocarriers, can be lyophilized or reconstituted by the methods described in US Patent Publication No. US20130230568, the contents of which are herein incorporated by reference in its entirety.

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[0893] In one embodiment, the synthetic nanocarriers can contain reactive groups to release the polynucleotides described herein (see International Pub. No. WO20120952552 and US Pub No. US20120171229, each of which is herein incorporated by reference in their entirety).

[0894] In one embodiment, the synthetic nanocarriers can be formulated for targeted release. In one embodiment, the synthetic nanocarrier is formulated to release the polynucleotides at a specified pH and/or after a desired time interval. As a non-limiting example, the synthetic nanoparticle can be formulated to release the polynucleotides after 24 hours and/or at a pH of 4.5 (see International Pub. Nos. WO2010138193 and WO2010138194 and US Pub Nos. US20110020388 and US20110027217, each of which is herein incorporated by reference in their entireties).

[0895] In one embodiment, the synthetic nanocarriers can be formulated for controlled and/or sustained release of the polynucleotides described herein. As a non-limiting example, the synthetic nanocarriers for sustained release can be formulated by methods known in the art, described herein and/or as described in International Pub No. WO2010138192 and US Pub No. 20100303850, each of which is herein incorporated by reference in their entirety.

[0896] In one embodiment, the polynucleotide can be formulated for controlled and/or sustained release wherein the formulation comprises at least one polymer that is a crystalline side chain (CYSC) polymer. CYSC polymers are described in U.S. Patent No. 8,399,007, herein incorporated by reference in its entirety.

[0897] In one embodiment, the synthetic nanocarrier can comprise at least one polynucleotide that encodes at least one adjuvant. As non-limiting example, the adjuvant can comprise dimethyldioctadecylammonium-bromide, dimethyldioctadecylammonium-chloride, dimethyldioctadecylammonium-phosphate or dimethyldioctadecylammonium-acetate (DDA) and an apolar fraction or part of said apolar fraction of a total lipid extract of a mycobacterium (*See, e.g.*, U.S. Pat. No. 8,241,610; herein incorporated by reference in its entirety). In another embodiment, the synthetic nanocarrier can comprise at least one polynucleotide and an adjuvant. As a non-limiting example, the synthetic nanocarrier comprising and adjuvant can be formulated by the methods described in International Pub No. WO2011150240 and US Pub No. US20110293700, each of which is herein incorporated by reference in its entirety.

[0898] In one embodiment, the synthetic nanocarrier can encapsulate at least one polynucleotide that encodes a peptide, fragment or region from a virus. As a non-limiting example, the synthetic nanocarrier can include, but is not limited to, the nanocarriers described in

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International Pub No. WO2012024621, WO201202629, WO2012024632 and US Pub No. US20120064110, US20120058153 and US20120058154, each of which is herein incorporated by reference in their entirety.

[0899] In one embodiment, the synthetic nanocarrier can be coupled to a polynucleotide that can be able to trigger a humoral and/or cytotoxic T lymphocyte (CTL) response (*see, e.g.*, International Publication No. WO2013019669, herein incorporated by reference in its entirety).

[0900] In one embodiment, the polynucleotide can be encapsulated in, linked to and/or associated with zwitterionic lipids. Non-limiting examples of zwitterionic lipids and methods of using zwitterionic lipids are described in US Patent Publication No. US20130216607, the contents of which are herein incorporated by reference in its entirety. In one aspect, the zwitterionic lipids can be used in the liposomes and lipid nanoparticles described herein.

[0901] In one embodiment, the polynucleotide can be formulated in colloid nanocarriers as described in US Patent Publication No. US20130197100, the contents of which are herein incorporated by reference in its entirety.

[0902] In one embodiment, the nanoparticle can be optimized for oral administration. The nanoparticle can comprise at least one cationic biopolymer such as, but not limited to, chitosan or a derivative thereof. As a non-limiting example, the nanoparticle can be formulated by the methods described in U.S. Pub. No. 20120282343; herein incorporated by reference in its entirety.

[0903] In some embodiments, LNPs comprise the lipid KL52 (an amino-lipid disclosed in U.S. Application Publication No. 2012/0295832 expressly incorporated herein by reference in its entirety). Activity and/or safety (as measured by examining one or more of ALT/AST, white blood cell count and cytokine induction) of LNP administration can be improved by incorporation of such lipids. LNPs comprising KL52 can be administered intravenously and/or in one or more doses. In some embodiments, administration of LNPs comprising KL52 results in equal or improved mRNA and/or protein expression as compared to LNPs comprising MC3.

[0904] In some embodiments, polynucleotide can be delivered using smaller LNPs. Such particles can comprise a diameter from below 0.1 um up to 100 nm such as, but not limited to, less than 0.1 um, less than 1.0 um, less than 5 um, less than 10 um, less than 15 um, less than 20 um, less than 25 um, less than 30 um, less than 35 um, less than 40 um, less than 50 um, less than 55 um, less than 60 um, less than 65 um, less than 70 um, less than 75 um, less than 80 um, less than 85 um, less than 90 um, less than 95 um, less than 100 um, less than 125 um, less than 150

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um, less than 175 um, less than 200 um, less than 225 um, less than 250 um, less than 275 um, less than 300 um, less than 325 um, less than 350 um, less than 375 um, less than 400 um, less than 425 um, less than 450 um, less than 475 um, less than 500 um, less than 525 um, less than 550 um, less than 575 um, less than 600 um, less than 625 um, less than 650 um, less than 675 um, less than 700 um, less than 725 um, less than 750 um, less than 775 um, less than 800 um, less than 825 um, less than 850 um, less than 875 um, less than 900 um, less than 925 um, less than 950 um, or less than 975 um.

[0905] In another embodiment, polynucleotides can be delivered using smaller LNPs that can comprise a diameter from about 1 nm to about 100 nm, from about 1 nm to about 10 nm, about 1 nm to about 20 nm, from about 1 nm to about 30 nm, from about 1 nm to about 40 nm, from about 1 nm to about 50 nm, from about 1 nm to about 60 nm, from about 1 nm to about 70 nm, from about 1 nm to about 80 nm, from about 1 nm to about 90 nm, from about 5 nm to about from 100 nm, from about 5 nm to about 10 nm, about 5 nm to about 20 nm, from about 5 nm to about 30 nm, from about 5 nm to about 40 nm, from about 5 nm to about 50 nm, from about 5 nm to about 60 nm, from about 5 nm to about 70 nm, from about 5 nm to about 80 nm, from about 5 nm to about 90 nm, about 10 to about 50 nM, from about 20 to about 50 nm, from about 30 to about 50 nm, from about 40 to about 50 nm, from about 20 to about 60 nm, from about 30 to about 60 nm, from about 40 to about 60 nm, from about 20 to about 70 nm, from about 30 to about 70 nm, from about 40 to about 70 nm, from about 50 to about 70 nm, from about 60 to about 70 nm, from about 20 to about 80 nm, from about 30 to about 80 nm, from about 40 to about 80 nm, from about 50 to about 80 nm, from about 60 to about 80 nm, from about 20 to about 90 nm, from about 30 to about 90 nm, from about 40 to about 90 nm, from about 50 to about 90 nm, from about 60 to about 90 nm and/or from about 70 to about 90 nm.

[0906] In some embodiments, such LNPs are synthesized using methods comprising microfluidic mixers. Exemplary microfluidic mixers can include, but are not limited to a slit interdigitial micromixer including, but not limited to those manufactured by Microinnova (Allerheiligen bei Wildon, Austria) and/or a staggered herringbone micromixer (SHM) (Zhigaltsev, I.V. et al., Bottom-up design and synthesis of limit size lipid nanoparticle systems with aqueous and triglyceride cores using millisecond microfluidic mixing have been published (Langmuir. 2012. 28:3633-40; Belliveau, N.M. et al., Microfluidic synthesis of highly potent limit-size lipid nanoparticles for *in vivo* delivery of siRNA. Molecular Therapy-Nucleic Acids. 2012. 1:e37; Chen, D. et al., Rapid discovery of potent siRNA-containing lipid nanoparticles

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enabled by controlled microfluidic formulation. J Am Chem Soc. 2012. 134(16):6948-51; each of which is herein incorporated by reference in its entirety). In some embodiments, methods of LNP generation comprising SHM, further comprise the mixing of at least two input streams wherein mixing occurs by microstructure-induced chaotic advection (MICA). According to this method, fluid streams flow through channels present in a herringbone pattern causing rotational flow and folding the fluids around each other. This method can also comprise a surface for fluid mixing wherein the surface changes orientations during fluid cycling. Methods of generating LNPs using SHM include those disclosed in U.S. Application Publication Nos. 2004/0262223 and 2012/0276209, each of which is expressly incorporated herein by reference in their entirety.

[0907] In one embodiment, the polynucleotide of the present disclosure can be formulated in lipid nanoparticles created using a micromixer such as, but not limited to, a Slit Interdigital Microstructured Mixer (SIMM-V2) or a Standard Slit Interdigital Micro Mixer (SSIMM) or Caterpillar (CPMM) or Impinging-jet (IJMM)from the Institut für Mikrotechnik Mainz GmbH, Mainz Germany).

[0908] In one embodiment, the polynucleotides of the present disclosure can be formulated in lipid nanoparticles created using microfluidic technology (see Whitesides, George M. The Origins and the Future of Microfluidics. Nature, 2006 442: 368-373; and Abraham et al. Chaotic Mixer for Microchannels. Science, 2002 295: 647-651; each of which is herein incorporated by reference in its entirety). As a non-limiting example, controlled microfluidic formulation includes a passive method for mixing streams of steady pressure-driven flows in micro channels at a low Reynolds number (*see, e.g.*, Abraham et al. Chaotic Mixer for Microchannels. Science, 2002 295: 647-651; which is herein incorporated by reference in its entirety).

[0909] In one embodiment, the polynucleotides of the present disclosure can be formulated in lipid nanoparticles created using a micromixer chip such as, but not limited to, those from Harvard Apparatus (Holliston, MA) or Dolomite Microfluidics (Royston, UK). A micromixer chip can be used for rapid mixing of two or more fluid streams with a split and recombine mechanism.

[0910] In one embodiment, the polynucleotides of the disclosure can be formulated for delivery using the drug encapsulating microspheres described in International Patent Publication No. WO2013063468 or U.S. Patent No. 8,440,614, each of which is herein incorporated by reference in its entirety. The microspheres can comprise a compound of the formula (I), (II), (III), (IV), (V) or (VI) as described in International Patent Publication No. WO2013063468, the

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contents of which are herein incorporated by reference in its entirety. In another aspect, the amino acid, peptide, polypeptide, lipids (APPL) are useful in delivering the polynucleotides of the disclosure to cells (see International Patent Publication No. WO2013063468, the contents of which is herein incorporated by reference in its entirety).

[0911] In one embodiment, the polynucleotides of the disclosure can be formulated in lipid nanoparticles having a diameter from about 10 to about 100 nm such as, but not limited to, about 10 to about 20 nm, about 10 to about 30 nm, about 10 to about 40 nm, about 10 to about 50 nm, about 10 to about 60 nm, about 10 to about 70 nm, about 10 to about 80 nm, about 10 to about 90 nm, about 20 to about 30 nm, about 20 to about 40 nm, about 20 to about 50 nm, about 20 to about 60 nm, about 20 to about 70 nm, about 20 to about 80 nm, about 20 to about 90 nm, about 20 to about 100 nm, about 30 to about 40 nm, about 30 to about 50 nm, about 30 to about 60 nm, about 30 to about 70 nm, about 30 to about 80 nm, about 30 to about 90 nm, about 30 to about 100 nm, about 40 to about 50 nm, about 40 to about 60 nm, about 40 to about 70 nm, about 40 to about 80 nm, about 40 to about 90 nm, about 40 to about 100 nm, about 50 to about 60 nm, about 50 to about 70 nm about 50 to about 80 nm, about 50 to about 90 nm, about 50 to about 100 nm, about 60 to about 70 nm, about 60 to about 80 nm, about 60 to about 90 nm, about 60 to about 100 nm, about 70 to about 80 nm, about 70 to about 90 nm, about 70 to about 100 nm, about 80 to about 90 nm, about 80 to about 100 nm and/or about 90 to about 100 nm.

[0912] In one embodiment, the lipid nanoparticles can have a diameter from about 10 to 500 nm.

[0913] In one embodiment, the lipid nanoparticle can have a diameter greater than 100 nm, greater than 150 nm, greater than 200 nm, greater than 250 nm, greater than 300 nm, greater than 350 nm, greater than 400 nm, greater than 450 nm, greater than 500 nm, greater than 550 nm, greater than 600 nm, greater than 650 nm, greater than 700 nm, greater than 750 nm, greater than 800 nm, greater than 850 nm, greater than 900 nm, greater than 950 nm or greater than 1000 nm.

[0914] In one aspect, the lipid nanoparticle can be a limit size lipid nanoparticle described in International Patent Publication No. WO2013059922, the contents of which are herein incorporated by reference in its entirety. The limit size lipid nanoparticle can comprise a lipid bilayer surrounding an aqueous core or a hydrophobic core; where the lipid bilayer can comprise a phospholipid such as, but not limited to, diacylphosphatidylcholine, a diacylphosphatidylethanolamine, a ceramide, a sphingomyelin, a dihydrosphingomyelin, a cephalin, a cerebroside, a C8-C20 fatty acid diacylphophatidylcholine, and 1-palmitoyl-2-oleoyl

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phosphatidylcholine (POPC). In another aspect the limit size lipid nanoparticle can comprise a polyethylene glycol-lipid such as, but not limited to, DLPE-PEG, DMPE-PEG, DPPC-PEG and DSPE-PEG.

[0915] In one embodiment, the polynucleotides can be delivered, localized and/or concentrated in a specific location using the delivery methods described in International Patent Publication No. WO2013063530, the contents of which are herein incorporated by reference in its entirety. As a non-limiting example, a subject can be administered an empty polymeric particle prior to, simultaneously with or after delivering the polynucleotides to the subject. The empty polymeric particle undergoes a change in volume once in contact with the subject and becomes lodged, embedded, immobilized or entrapped at a specific location in the subject.

[0916] In one embodiment, the polynucleotides can be formulated in an active substance release system (*see, e.g.*, US Patent Publication No. US20130102545, the contents of which is herein incorporated by reference in its entirety). The active substance release system can comprise 1) at least one nanoparticle bonded to an oligonucleotide inhibitor strand that is hybridized with a catalytically active nucleic acid and 2) a compound bonded to at least one substrate molecule bonded to a therapeutically active substance (*e.g.*, polynucleotides described herein), where the therapeutically active substance is released by the cleavage of the substrate molecule by the catalytically active nucleic acid.

[0917] In one embodiment, the polynucleotides can be formulated in a nanoparticle comprising an inner core comprising a non-cellular material and an outer surface comprising a cellular membrane. The cellular membrane can be derived from a cell or a membrane derived from a virus. As a non-limiting example, the nanoparticle can be made by the methods described in International Patent Publication No. WO2013052167, herein incorporated by reference in its entirety. As another non-limiting example, the nanoparticle described in International Patent Publication No. WO2013052167, herein incorporated by reference in its entirety, can be used to deliver the polynucleotides described herein.

[0918] In one embodiment, the polynucleotides can be formulated in porous nanoparticle-supported lipid bilayers (protocells). Protocells are described in International Patent Publication No. WO2013056132, the contents of which are herein incorporated by reference in its entirety.

[0919] In one embodiment, the polynucleotides described herein can be formulated in polymeric nanoparticles as described in or made by the methods described in US Patent No. 8,420,123 and 8,518,963 and European Patent No. EP2073848B1, the contents of each of which

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are herein incorporated by reference in their entirety. As a non-limiting example, the polymeric nanoparticle can have a high glass transition temperature such as the nanoparticles described in or nanoparticles made by the methods described in US Patent No. 8,518,963, the contents of which are herein incorporated by reference in its entirety. As another non-limiting example, the polymer nanoparticle for oral and parenteral formulations can be made by the methods described in European Patent No. EP2073848B1, the contents of which are herein incorporated by reference in its entirety.

[0920] In another embodiment, the polynucleotides described herein can be formulated in nanoparticles used in imaging. The nanoparticles can be liposome nanoparticles such as those described in US Patent Publication No US20130129636, herein incorporated by reference in its entirety. As a non-limiting example, the liposome can comprise gadolinium(III)2-{4,7-bis-carboxymethyl-10-[(N,N-distearylamidomethyl-N′-amido-methyl]-1,4,7,10-tetra-azacyclododec-1-yl}-acetic acid and a neutral, fully saturated phospholipid component (*see, e.g.*, US Patent Publication No US20130129636, the contents of which is herein incorporated by reference in its entirety).

[0921] In one embodiment, the nanoparticles that can be used in the present disclosure are formed by the methods described in U.S. Patent Application No. US20130130348, the contents of which is herein incorporated by reference in its entirety.

[0922] The nanoparticles of the present disclosure can further include nutrients such as, but not limited to, those which deficiencies can lead to health hazards from anemia to neural tube defects (*see e.g.*, the nanoparticles described in International Patent Publication No WO2013072929, the contents of which is herein incorporated by reference in its entirety). As a non-limiting example, the nutrient can be iron in the form of ferrous, ferric salts or elemental iron, iodine, folic acid, vitamins or micronutrients.

[0923] In one embodiment, the polynucleotides of the present disclosure can be formulated in a swellable nanoparticle. The swellable nanoparticle can be, but is not limited to, those described in U.S. Patent No. 8,440,231, the contents of which is herein incorporated by reference in its entirety. As a non-limiting embodiment, the swellable nanoparticle can be used for delivery of the polynucleotides of the present disclosure to the pulmonary system (*see, e.g.*, U.S. Patent No. 8,440,231, the contents of which is herein incorporated by reference in its entirety).

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[0924] The polynucleotides of the present disclosure can be formulated in polyanhydride nanoparticles such as, but not limited to, those described in U.S. Patent No. 8,449,916, the contents of which is herein incorporated by reference in its entirety.

[0925] The nanoparticles and microparticles of the present disclosure can be geometrically engineered to modulate macrophage and/or the immune response. In one aspect, the geometrically engineered particles can have varied shapes, sizes and/or surface charges in order to incorporated the polynucleotides of the present disclosure for targeted delivery such as, but not limited to, pulmonary delivery (*see, e.g.*, International Publication No WO2013082111, the contents of which is herein incorporated by reference in its entirety). Other physical features the geometrically engineering particles can have include, but are not limited to, fenestrations, angled arms, asymmetry and surface roughness, charge that can alter the interactions with cells and tissues. As a non-limiting example, nanoparticles of the present disclosure can be made by the methods described in International Publication No WO2013082111, the contents of which is herein incorporated by reference in its entirety.

[0926] In one embodiment, the nanoparticles of the present disclosure can be water soluble nanoparticles such as, but not limited to, those described in International Publication No. WO2013090601, the contents of which is herein incorporated by reference in its entirety. The nanoparticles can be inorganic nanoparticles that have a compact and zwitterionic ligand in order to exhibit good water solubility. The nanoparticles can also have small hydrodynamic diameters (HD), stability with respect to time, pH, and salinity and a low level of non-specific protein binding.

[0927] In one embodiment the nanoparticles of the present disclosure can be developed by the methods described in US Patent Publication No. US20130172406, the contents of which are herein incorporated by reference in its entirety.

[0928] In one embodiment, the nanoparticles of the present disclosure are stealth nanoparticles or target-specific stealth nanoparticles such as, but not limited to, those described in US Patent Publication No. US20130172406; the contents of which is herein incorporated by reference in its entirety. The nanoparticles of the present disclosure can be made by the methods described in US Patent Publication No. US20130172406, the contents of which are herein incorporated by reference in its entirety.

[0929] In another embodiment, the stealth or target-specific stealth nanoparticles can comprise a polymeric matrix. The polymeric matrix can comprise two or more polymers such as,

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but not limited to, polyethylenes, polycarbonates, polyanhydrides, polyhydroxyacids, polypropylfumerates, polycaprolactones, polyamides, polyacetals, polyethers, polyesters, poly(orthoesters), polycyanoacrylates, polyvinyl alcohols, polyurethanes, polyphosphazenes, polyacrylates, polymethacrylates, polycyanoacrylates, polyureas, polystyrenes, polyamines, polyesters, polyanhydrides, polyethers, polyurethanes, polymethacrylates, polyacrylates, polycyanoacrylates or combinations thereof.

[0930] In one embodiment, the nanoparticle can be a nanoparticle-nucleic acid hybrid structure having a high density nucleic acid layer. As a non-limiting example, the nanoparticle-nucleic acid hybrid structure can made by the methods described in US Patent Publication No. US20130171646, the contents of which are herein incorporated by reference in its entirety. The nanoparticle can comprise a nucleic acid such as, but not limited to, polynucleotides described herein and/or known in the art.

[0931] At least one of the nanoparticles of the present disclosure can be embedded in in the core a nanostructure or coated with a low density porous 3-D structure or coating that is capable of carrying or associating with at least one payload within or on the surface of the nanostructure. Non-limiting examples of the nanostructures comprising at least one nanoparticle are described in International Patent Publication No. WO2013123523, the contents of which are herein incorporated by reference in its entirety.

Amino Acid Lipids

[0932] The disclosure also includes pharmaceutical compositions that comprise a formulation of the polynucleotide described herein, *i.e.*, a polynucleotide comprising an ORF encoding an MCM polypeptide, with amino acid lipids. Amino acid lipids are lipophilic compounds comprising an amino acid residue and one or more lipophilic tails. Non-limiting examples of amino acid lipids and methods of making amino acid lipids are described in US Patent No. 8,501,824, the contents of which are herein incorporated by reference in its entirety.

[0933] In some embodiments, the amino acid lipids have a hydrophilic portion and a lipophilic portion. The hydrophilic portion can be an amino acid residue and a lipophilic portion can comprise at least one lipophilic tail.

[0934] In some embodiments, the amino acid lipid formulations can be used to deliver the polynucleotides to a subject.

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[0935] In another embodiment, the amino acid lipid formulations can deliver a polynucleotide in releasable form that comprises an amino acid lipid that binds and releases the polynucleotides. As a non-limiting example, the release of the polynucleotides can be provided by an acid-labile linker such as, but not limited to, those described in U.S. Patent Nos. 7,098,032, 6,897,196, 6,426,086, 7,138,382, 5,563,250, and 5,505,931, the contents of each of which are herein incorporated by reference in its entirety.

Polymers, Biodegradable Nanoparticles, and Core-Shell Nanoparticles

[0936] The disclosure also includes pharmaceutical compositions that comprise a formulation of the polynucleotide described herein, *i.e.*, a polynucleotide comprising an ORF encoding an MCM polypeptide, using natural and/or synthetic polymers. Non-limiting examples of polymers that can be used for delivery include, but are not limited to, DYNAMIC POLYCONJUGATE® (Arrowhead Research Corp., Pasadena, CA) formulations from MIRUS® Bio (Madison, WI) and Roche Madison (Madison, WI), PHASERX™ polymer formulations such as, without limitation, SMARTT POLYMER TECHNOLOGY™ (PHASERX®, Seattle, WA), DMRI/DOPE, poloxamer, VAXFECTIN® adjuvant from Vical (San Diego, CA), chitosan, cyclodextrin from Calando Pharmaceuticals (Pasadena, CA), dendrimers and poly(lactic-co-glycolic acid) (PLGA) polymers. RONDEL™ (RNAi/Oligonucleotide Nanoparticle Delivery) polymers (Arrowhead Research Corporation, Pasadena, CA) and pH responsive co-block polymers such as, but not limited to, PHASERX® (Seattle, WA).

[0937] A non-limiting example of chitosan formulation includes a core of positively charged chitosan and an outer portion of negatively charged substrate (U.S. Pub. No. 20120258176; herein incorporated by reference in its entirety). Chitosan includes, but is not limited to N-trimethyl chitosan, mono-N-carboxymethyl chitosan (MCC), N-palmitoyl chitosan (NPCS), EDTA-chitosan, low molecular weight chitosan, chitosan derivatives, or combinations thereof.

[0938] In some embodiments, the polymers used in the present disclosure have undergone processing to reduce and/or inhibit the attachment of unwanted substances such as, but not limited to, bacteria, to the surface of the polymer. The polymer can be processed by methods known and/or described in the art and/or described in International Pub. No. WO2012150467, herein incorporated by reference in its entirety.

[0939] A non-limiting example of PLGA formulations include, but are not limited to, PLGA injectable depots (*e.g.*, ELIGARD® which is formed by dissolving PLGA in 66% N-methyl-2-

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pyrrolidone (NMP) and the remainder being aqueous solvent and leuprolide. Once injected, the PLGA and leuprolide peptide precipitates into the subcutaneous space).

[0940] Many of these polymer approaches have demonstrated efficacy in delivering oligonucleotides *in vivo* into the cell cytoplasm (reviewed in deFougerolles *Hum Gene Ther.* 2008 19:125-132; herein incorporated by reference in its entirety). Two polymer approaches that have yielded robust *in vivo* delivery of nucleic acids, in this case with small interfering RNA (siRNA), are dynamic polyconjugates and cyclodextrin-based nanoparticles (*see, e.g.,* US Patent Publication No. US20130156721, herein incorporated by reference in its entirety). The first of these delivery approaches uses dynamic polyconjugates and has been shown *in vivo* in mice to effectively deliver siRNA and silence endogenous target mRNA in hepatocytes (Rozema et al., Proc Natl Acad Sci U S A. 2007 104:12982-12887; herein incorporated by reference in its entirety). This particular approach is a multicomponent polymer system whose key features include a membrane-active polymer to which nucleic acid, in this case siRNA, is covalently coupled via a disulfide bond and where both PEG (for charge masking) and *N*-acetylgalactosamine (for hepatocyte targeting) groups are linked via pH-sensitive bonds (Rozema et al., Proc Natl Acad Sci U S A. 2007 104:12982-12887; herein incorporated by reference in its entirety). On binding to the hepatocyte and entry into the endosome, the polymer complex disassembles in the low-pH environment, with the polymer exposing its positive charge, leading to endosomal escape and cytoplasmic release of the siRNA from the polymer. Through replacement of the *N*-acetylgalactosamine group with a mannose group, it was shown one could alter targeting from asialoglycoprotein receptor-expressing hepatocytes to sinusoidal endothelium and Kupffer cells. Another polymer approach involves using transferrin-targeted cyclodextrin-containing polycation nanoparticles. These nanoparticles have demonstrated targeted silencing of the *EWS-FLI1* gene product in transferrin receptor-expressing Ewing's sarcoma tumor cells (Hu-Lieskovan *et al.*, Cancer Res.2005 65: 8984-8982; herein incorporated by reference in its entirety) and siRNA formulated in these nanoparticles was well tolerated in non-human primates (Heidel *et al.*, Proc Natl Acad Sci USA 2007 104:5715-21; herein incorporated by reference in its entirety). Both of these delivery strategies incorporate rational approaches using both targeted delivery and endosomal escape mechanisms.

[0941] The polymer formulation can permit the sustained or delayed release of polynucleotides (*e.g.,* following intramuscular or subcutaneous injection). The altered release profile for the polynucleotide can result in, for example, translation of an encoded protein over

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an extended period of time. The polymer formulation can also be used to increase the stability of the polynucleotide. Biodegradable polymers have been previously used to protect nucleic acids other than polynucleotide from degradation and been shown to result in sustained release of payloads *in vivo* (Rozema et al., Proc Natl Acad Sci U S A. 2007 104:12982-12887; Sullivan et al., Expert Opin Drug Deliv. 2010 7:1433-1446; Convertine et al., Biomacromolecules. 2010 Oct 1; Chu et al., Acc Chem Res. 2012 Jan 13; Manganiello et al., Biomaterials. 2012 33:2301-2309; Benoit et al., Biomacromolecules. 2011 12:2708-2714; Singha et al., Nucleic Acid Ther. 2011 2:133-147; deFougerolles Hum Gene Ther. 2008 19:125-132; Schaffert and Wagner, Gene Ther. 2008 16:1131-1138; Chaturvedi et al., Expert Opin Drug Deliv. 2011 8:1455-1468; Davis, Mol Pharm. 2009 6:659-668; Davis, Nature 2010 464:1067-1070; each of which is herein incorporated by reference in its entirety).

[0942] In some embodiments, the pharmaceutical compositions can be sustained release formulations. In a further embodiment, the sustained release formulations can be for subcutaneous delivery. Sustained release formulations can include, but are not limited to, PLGA microspheres, ethylene vinyl acetate (EVAc), poloxamer, GELSITE® (Nanotherapeutics, Inc. Alachua, FL), HYLENEX® (Halozyme Therapeutics, San Diego CA), surgical sealants such as fibrinogen polymers (Ethicon Inc. Cornelia, GA), TISSELL® (Baxter International, Inc. Deerfield, IL), PEG-based sealants, and COSEAL® (Baxter International, Inc. Deerfield, IL).

[0943] As a non-limiting example modified mRNA can be formulated in PLGA microspheres by preparing the PLGA microspheres with tunable release rates (*e.g.,* days and weeks) and encapsulating the modified mRNA in the PLGA microspheres while maintaining the integrity of the modified mRNA during the encapsulation process. EVAc are non-biodegradable, biocompatible polymers that are used extensively in pre-clinical sustained release implant applications (*e.g.,* extended release products Ocusert a pilocarpine ophthalmic insert for glaucoma or progestasert a sustained release progesterone intrauterine device; transdermal delivery systems Testoderm, Duragesic and Selegiline; catheters). Poloxamer F-407 NF is a hydrophilic, non-ionic surfactant triblock copolymer of polyoxyethylene-polyoxypropylene-polyoxyethylene having a low viscosity at temperatures less than 5°C and forms a solid gel at temperatures greater than 15°C. PEG-based surgical sealants comprise two synthetic PEG components mixed in a delivery device that can be prepared in one minute, seals in 3 minutes and is reabsorbed within 30 days. GELSITE® and natural polymers are capable of in-situ

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gelation at the site of administration. They have been shown to interact with protein and peptide therapeutic candidates through ionic interaction to provide a stabilizing effect.

[0944] Polymer formulations can also be selectively targeted through expression of different ligands as exemplified by, but not limited by, folate, transferrin, and N-acetylgalactosamine (GalNAc) (Benoit et al., Biomacromolecules. 2011 12:2708-2714; Rozema et al., Proc Natl Acad Sci U S A. 2007 104:12982-12887; Davis, Mol Pharm. 2009 6:659-668; Davis, Nature 2010 464:1067-1070; each of which is herein incorporated by reference in its entirety).

[0945] The polynucleotides of the disclosure can be formulated with or in a polymeric compound. The polymer can include at least one polymer such as, but not limited to, polyethenes, polyethylene glycol (PEG), poly(l-lysine)(PLL), PEG grafted to PLL, cationic lipopolymer, biodegradable cationic lipopolymer, polyethyleneimine (PEI), cross-linked branched poly(alkylene imines), a polyamine derivative, a modified poloxamer, a biodegradable polymer, elastic biodegradable polymer, biodegradable block copolymer, biodegradable random copolymer, biodegradable polyester copolymer, biodegradable polyester block copolymer, biodegradable polyester block random copolymer, multiblock copolymers, linear biodegradable copolymer, poly[α-(4-aminobutyl)-L-glycolic acid) (PAGA), biodegradable cross-linked cationic multi-block copolymers, polycarbonates, polyanhydrides, polyhydroxyacids, polypropylfumerates, polycaprolactones, polyamides, polyacetals, polyethers, polyesters, poly(orthoesters), polycyanoacrylates, polyvinyl alcohols, polyurethanes, polyphosphazenes, polyacrylates, polymethacrylates, polycyanoacrylates, polyureas, polystyrenes, polyamines, polylysine, poly(ethylene imine), poly(serine ester), poly(L-lactide-co-L-lysine), poly(4-hydroxy-L-proline ester), acrylic polymers, amine-containing polymers, dextran polymers, dextran polymer derivatives or combinations thereof.

[0946] As a non-limiting example, the polynucleotides of the disclosure can be formulated with the polymeric compound of PEG grafted with PLL as described in U.S. Pat. No. 6,177,274; herein incorporated by reference in its entirety. The formulation can be used for transfecting cells *in vitro* or for *in vivo* delivery of polynucleotide. In another example, the polynucleotide can be suspended in a solution or medium with a cationic polymer, in a dry pharmaceutical composition or in a solution that is capable of being dried as described in U.S. Pub. Nos. 20090042829 and 20090042825; each of which are herein incorporated by reference in their entireties.

[0947] As another non-limiting example the polynucleotides of the disclosure can be formulated with a PLGA-PEG block copolymer (see US Pub. No. US20120004293 and US Pat

No. 8,236,330, herein incorporated by reference in their entireties) or PLGA-PEG-PLGA block copolymers (See U.S. Pat. No. 6,004,573, herein incorporated by reference in its entirety). As a non-limiting example, the polynucleotides of the disclosure can be formulated with a diblock copolymer of PEG and PLA or PEG and PLGA (see US Pat No 8,246,968, herein incorporated by reference in its entirety).

[0948] A polyamine derivative can be used to deliver nucleic acids or to treat and/or prevent a disease or to be included in an implantable or injectable device (U.S. Pub. No. 20100260817 (now U.S. Patent No. 8,460,696) the contents of each of which is herein incorporated by reference in its entirety). As a non-limiting example, a pharmaceutical composition can include the polynucleotide and the polyamine derivative described in U.S. Pub. No. 20100260817 (now U.S. Patent No. 8,460,696; the contents of which are incorporated herein by reference in its entirety. As a non-limiting example the polynucleotides of the present disclosure can be delivered using a polyamine polymer such as, but not limited to, a polymer comprising a 1,3-dipolar addition polymer prepared by combining a carbohydrate diazide monomer with a dialkyne unite comprising oligoamines (U.S. Pat. No. 8,236,280; herein incorporated by reference in its entirety).

[0949] The polynucleotides of the disclosure can be formulated with at least one acrylic polymer. Acrylic polymers include but are not limited to, acrylic acid, methacrylic acid, acrylic acid and methacrylic acid copolymers, methyl methacrylate copolymers, ethoxyethyl methacrylates, cyanoethyl methacrylate, amino alkyl methacrylate copolymer, poly(acrylic acid), poly(methacrylic acid), polycyanoacrylates and combinations thereof.

[0950] In some embodiments, the polynucleotides of the present disclosure can be formulated with at least one polymer and/or derivatives thereof described in International Publication Nos. WO2011115862, WO2012082574 and WO2012068187 and U.S. Pub. No. 20120283427, each of which are herein incorporated by reference in their entireties. In another embodiment, the polynucleotides of the present disclosure can be formulated with a polymer of formula Z as described in WO2011115862, herein incorporated by reference in its entirety. In yet another embodiment, the polynucleotides can be formulated with a polymer of formula Z, Z' or Z" as described in International Pub. Nos. WO2012082574 or WO2012068187 and U.S. Pub. No. 2012028342, each of which are herein incorporated by reference in their entireties. The polymers formulated with the modified RNA of the present disclosure can be synthesized by the

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methods described in International Pub. Nos. WO2012082574 or WO2012068187, each of which are herein incorporated by reference in their entireties.

[0951] The polynucleotides of the disclosure can be formulated with at least one acrylic polymer. Acrylic polymers include but are not limited to, acrylic acid, methacrylic acid, acrylic acid and methacrylic acid copolymers, methyl methacrylate copolymers, ethoxyethyl methacrylates, cyanoethyl methacrylate, amino alkyl methacrylate copolymer, poly(acrylic acid), poly(methacrylic acid), polycyanoacrylates and combinations thereof.

[0952] Formulations of polynucleotides of the disclosure can include at least one amine-containing polymer such as, but not limited to polylysine, polyethylene imine, poly(amidoamine) dendrimers, poly(amine-co-esters) or combinations thereof. As a non-limiting example, the poly(amine-co-esters) can be the polymers described in and/or made by the methods described in International Publication No WO2013082529, the contents of which are herein incorporated by reference in its entirety.

[0953] For example, the polynucleotides of the disclosure can be formulated in a pharmaceutical compound including a poly(alkylene imine), a biodegradable cationic lipopolymer, a biodegradable block copolymer, a biodegradable polymer, or a biodegradable random copolymer, a biodegradable polyester block copolymer, a biodegradable polyester polymer, a biodegradable polyester random copolymer, a linear biodegradable copolymer, PAGA, a biodegradable cross-linked cationic multi-block copolymer or combinations thereof. The biodegradable cationic lipopolymer can be made by methods known in the art and/or described in U.S. Pat. No. 6,696,038, U.S. App. Nos. 20030073619 and 20040142474 each of which is herein incorporated by reference in their entireties. The poly(alkylene imine) can be made using methods known in the art and/or as described in U.S. Pub. No. 20100004315, herein incorporated by reference in its entirety. The biodegradable polymer, biodegradable block copolymer, the biodegradable random copolymer, biodegradable polyester block copolymer, biodegradable polyester polymer, or biodegradable polyester random copolymer can be made using methods known in the art and/or as described in U.S. Pat. Nos. 6,517,869 and 6,267,987, the contents of which are each incorporated herein by reference in their entirety. The linear biodegradable copolymer can be made using methods known in the art and/or as described in U.S. Pat. No. 6,652,886. The PAGA polymer can be made using methods known in the art and/or as described in U.S. Pat. No. 6,217,912 herein incorporated by reference in its entirety. The PAGA polymer can be copolymerized to form a copolymer or block copolymer with

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polymers such as but not limited to, poly-L-lysine, polyarginine, polyornithine, histones, avidin, protamines, polylactides and poly(lactide-co-glycolides). The biodegradable cross-linked cationic multi-block copolymers can be made my methods known in the art and/or as described in U.S. Pat. No. 8,057,821, 8,444,992 or U.S. Pub. No. 2012009145 each of which are herein incorporated by reference in their entireties. For example, the multi-block copolymers can be synthesized using linear polyethyleneimine (LPEI) blocks that have distinct patterns as compared to branched polyethyleneimines. Further, the composition or pharmaceutical composition can be made by the methods known in the art, described herein, or as described in U.S. Pub. No. 20100004315 or U.S. Pat. Nos. 6,267,987 and 6,217,912 each of which are herein incorporated by reference in their entireties.

[0954] The polynucleotides of the disclosure can be formulated with at least one degradable polyester that can contain polycationic side chains. Degradable polyesters include, but are not limited to, poly(serine ester), poly(L-lactide-co-L-lysine), poly(4-hydroxy-L-proline ester), and combinations thereof. In another embodiment, the degradable polyesters can include a PEG conjugation to form a PEGylated polymer.

[0955] The polynucleotides of the disclosure can be formulated with at least one crosslinkable polyester. Crosslinkable polyesters include those known in the art and described in US Pub. No. 20120269761, the contents of which is herein incorporated by reference in its entirety.

[0956] The polynucleotides of the disclosure can be formulated in or with at least one cyclodextrin polymer. Cyclodextrin polymers and methods of making cyclodextrin polymers include those known in the art and described in US Pub. No. 20130184453, the contents of which are herein incorporated by reference in its entirety.

[0957] In some embodiments, the polynucleotides of the disclosure can be formulated in or with at least one crosslinked cation-binding polymers. Crosslinked cation-binding polymers and methods of making crosslinked cation-binding polymers include those known in the art and described in International Patent Publication No. WO2013106072, WO2013106073 and WO2013106086, the contents of each of which are herein incorporated by reference in its entirety.

[0958] In some embodiments, the polynucleotides of the disclosure can be formulated in or with at least one branched polymer. Branched polymers and methods of making branched polymers include those known in the art and described in International Patent Publication No.

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WO2013113071, the contents of each of which are herein incorporated by reference in its entirety.

[0959] In some embodiments, the polynucleotides of the disclosure can be formulated in or with at least PEGylated albumin polymer. PEGylated albumin polymer and methods of making PEGylated albumin polymer include those known in the art and described in US Patent Publication No. US20130231287, the contents of each of which are herein incorporated by reference in its entirety.

[0960] In some embodiments, the polymers described herein can be conjugated to a lipid-terminating PEG. As a non-limiting example, PLGA can be conjugated to a lipid-terminating PEG forming PLGA-DSPE-PEG. As another non-limiting example, PEG conjugates for use with the present disclosure are described in International Publication No. WO2008103276, herein incorporated by reference in its entirety. The polymers can be conjugated using a ligand conjugate such as, but not limited to, the conjugates described in U.S. Pat. No. 8,273,363, herein incorporated by reference in its entirety.

[0961] In some embodiments, the polynucleotides disclosed herein can be mixed with the PEGs or the sodium phosphate/sodium carbonate solution prior to administration. In another embodiment, a polynucleotides encoding a protein of interest can be mixed with the PEGs and also mixed with the sodium phosphate/sodium carbonate solution. In yet another embodiment, polynucleotides encoding a protein of interest can be mixed with the PEGs and a polynucleotides encoding a second protein of interest can be mixed with the sodium phosphate/sodium carbonate solution.

[0962] In some embodiments, the polynucleotides described herein can be conjugated with another compound. Non-limiting examples of conjugates are described in US Patent Nos. 7,964,578 and 7,833,992, each of which are herein incorporated by reference in their entireties. In another embodiment, modified RNA of the present disclosure can be conjugated with conjugates of formula 1-122 as described in US Patent Nos. 7,964,578 and 7,833,992, each of which are herein incorporated by reference in their entireties. The polynucleotides described herein can be conjugated with a metal such as, but not limited to, gold. (*See, e.g.,* Giljohann et al. Journ. Amer. Chem. Soc. 2009 131(6): 2072-2073; herein incorporated by reference in its entirety). In another embodiment, the polynucleotides described herein can be conjugated and/or encapsulated in gold-nanoparticles. (International Pub. No. WO201216269 and U.S. Pub. No.

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20120302940 and US20130177523; the contents of each of which is herein incorporated by reference in its entirety).

[0963] As described in U.S. Pub. No. 20100004313, herein incorporated by reference in its entirety, a gene delivery composition can include a nucleotide sequence and a poloxamer. For example, the polynucleotides of the present disclosure can be used in a gene delivery composition with the poloxamer described in U.S. Pub. No. 20100004313.

[0964] In some embodiments, the polymer formulation of the present disclosure can be stabilized by contacting the polymer formulation, which can include a cationic carrier, with a cationic lipopolymer that can be covalently linked to cholesterol and polyethylene glycol groups. The polymer formulation can be contacted with a cationic lipopolymer using the methods described in U.S. Pub. No. 20090042829 herein incorporated by reference in its entirety. The cationic carrier can include, but is not limited to, polyethylenimine, poly(trimethylenimine), poly(tetramethylenimine), polypropylenimine, aminoglycoside-polyamine, dideoxy-diamino-b-cyclodextrin, spermine, spermidine, poly(2-dimethylamino)ethyl methacrylate, poly(lysine), poly(histidine), poly(arginine), cationized gelatin, dendrimers, chitosan, 1,2-Dioleoyl-3-Trimethylammonium-Propane(DOTAP), N-[1-(2,3-dioleoyloxy)propyl]-N,N,N-trimethylammonium chloride (DOTMA), 1-[2-(oleoyloxy)ethyl]-2-oleyl-3-(2-hydroxyethyl)imidazolinium chloride (DOTIM), 2,3-dioleyloxy-N-[2(sperminecarboxamido)ethyl]-N,N-dimethyl-1-propanaminium trifluoroacetate (DOSPA), 3B-[N—(N′,N′-Dimethylaminoethane)-carbamoyl]Cholesterol Hydrochloride (DC-Cholesterol HCl) diheptadecylamidoglycyl spermidine (DOGS), N,N-distearyl-N,N-dimethylammonium bromide (DDAB), N-(1,2-dimyristyloxyprop-3-yl)-N,N-dimethyl-N-hydroxyethyl ammonium bromide (DMRIE), N,N-dioleyl-N,N-dimethylammonium chloride DODAC) and combinations thereof. As a non-limiting example, the polynucleotides can be formulated with a cationic lipopolymer such as those described in U.S. Patent Application No. 20130065942, herein incorporated by reference in its entirety.

[0965] The polynucleotides of the disclosure can be formulated in a polyplex of one or more polymers (*See, e.g.,* U.S. Pat. No. 8,501,478, U.S. Pub. No. 20120237565 and 20120270927 and 20130149783 and International Patent Pub. No. WO2013090861; the contents of each of which is herein incorporated by reference in its entirety). As a non-limiting example, the polyplex can be formed using the novel alpha-aminoamidine polymers described in International Publication No. WO2013090861, the contents of which are herein incorporated by reference in its entirety.

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As another non-limiting example, the polyplex can be formed using the click polymers described in US Patent No. 8,501,478, the contents of which is herein incorporated by reference in its entirety.

[0966] In some embodiments, the polyplex comprises two or more cationic polymers. The cationic polymer can comprise a poly(ethylene imine) (PEI) such as linear PEI. In another embodiment, the polyplex comprises p(TETA/CBA) its PEGylated analog p(TETA/CBA)-g-PEG2k and mixtures thereof (*see, e.g.,* US Patent Publication No. US20130149783, the contents of which are herein incorporated by reference in its entirety.

[0967] The polynucleotides of the disclosure can also be formulated as a nanoparticle using a combination of polymers, lipids, and/or other biodegradable agents, such as, but not limited to, calcium phosphate. Components can be combined in a core-shell, hybrid, and/or layer-by-layer architecture, to allow for fine-tuning of the nanoparticle so to delivery of the polynucleotide, polynucleotides can be enhanced (Wang et al., Nat Mater. 2006 5:791-796; Fuller et al., Biomaterials. 2008 29:1526-1532; DeKoker et al., Adv Drug Deliv Rev. 2011 63:748-761; Endres et al., Biomaterials. 2011 32:7721-7731; Su et al., Mol Pharm. 2011 Jun 6;8(3):774-87; herein incorporated by reference in its entirety). As a non-limiting example, the nanoparticle can comprise a plurality of polymers such as, but not limited to hydrophilic-hydrophobic polymers (*e.g.,* PEG-PLGA), hydrophobic polymers (*e.g.,* PEG) and/or hydrophilic polymers (International Pub. No. WO20120225129; the contents of which is herein incorporated by reference in its entirety).

[0968] As another non-limiting example the nanoparticle comprising hydrophilic polymers for the polynucleotides can be those described in or made by the methods described in International Patent Publication No. WO2013119936, the contents of which are herein incorporated by reference in its entirety.

[0969] In some embodiments, the biodegradable polymers that can be used in the present disclosure are poly(ether-anhydride) block copolymers. As a non-limiting example, the biodegradable polymers used herein can be a block copolymer as described in International Patent Publication No WO2006063249, herein incorporated by reference in its entirety, or made by the methods described in International Patent Publication No WO2006063249, herein incorporated by reference in its entirety.

[0970] In another embodiment, the biodegradable polymers that can be used in the present disclosure are alkyl and cycloalkyl terminated biodegradable lipids. As a non-limiting example,

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the alkyl and cycloalkyl terminated biodegradable lipids can be those described in International Publication No. WO2013086322 and/or made by the methods described in International Publication No. WO2013086322; the contents of which are herein incorporated by reference in its entirety.

[0971] In yet another embodiment, the biodegradable polymers that can be used in the present disclosure are cationic lipids having one or more biodegradable group located in a lipid moiety. As a non-limiting example, the biodegradable lipids can be those described in US Patent Publication No. US20130195920, the contents of which are herein incorporated by reference in its entirety.

[0972] Biodegradable calcium phosphate nanoparticles in combination with lipids and/or polymers have been shown to deliver polynucleotides *in vivo*. In some embodiments, a lipid coated calcium phosphate nanoparticle, which can also contain a targeting ligand such as anisamide, can be used to deliver the polynucleotide, polynucleotides of the present disclosure. For example, to effectively deliver siRNA in a mouse metastatic lung model a lipid coated calcium phosphate nanoparticle was used (Li et al., J Contr Rel. 2010 142: 416-421; Li et al., J Contr Rel. 2012 158:108-114; Yang et al., Mol Ther. 2012 20:609-615; herein incorporated by reference in its entirety). This delivery system combines both a targeted nanoparticle and a component to enhance the endosomal escape, calcium phosphate, in order to improve delivery of the siRNA.

[0973] In some embodiments, calcium phosphate with a PEG-polyanion block copolymer can be used to delivery polynucleotides (Kazikawa et al., J Contr Rel. 2004 97:345-356; Kazikawa et al., J Contr Rel. 2006 111:368-370; the contents of each of which are herein incorporated by reference in its entirety).

[0974] In some embodiments, a PEG-charge-conversional polymer (Pitella et al., Biomaterials. 2011 32:3106-3114; the contents of which are herein incorporated by reference in its entirety) can be used to form a nanoparticle to deliver the polynucleotides of the present disclosure. The PEG-charge-conversional polymer can improve upon the PEG-polyanion block copolymers by being cleaved into a polycation at acidic pH, thus enhancing endosomal escape.

[0975] In some embodiments, a polymer used in the present disclosure can be a pentablock polymer such as, but not limited to, the pentablock polymers described in International Patent Publication No. WO2013055331, herein incorporated by reference in its entirety. As a non-limiting example, the pentablock polymer comprises PGA-PCL-PEG-PCL-PGA, wherein PEG is

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polyethylene glycol, PCL is poly(E-caprolactone), PGA is poly(glycolic acid), and PLA is poly(lactic acid). As another non-limiting example, the pentablock polymer comprises PEG-PCL- PLA-PCL-PEG, wherein PEG is polyethylene glycol, PCL is poly(E-caprolactone), PGA is poly(glycolic acid), and PLA is poly(lactic acid).

[0976] In some embodiments, a polymer that can be used in the present disclosure comprises at least one diepoxide and at least one aminoglycoside (*See, e.g.,* International Patent Publication No. WO2013055971, the contents of which are herein incorporated by reference in its entirety). The diepoxide can be selected from, but is not limited to, 1,4 butanediol diglycidyl ether (1,4 B), 1,4-cyclohexanedimethanol diglycidyl ether (1,4 C), 4-vinylcyclohexene diepoxide (4VCD), ethyleneglycol diglycidyl ether (EDGE), glycerol diglycidyl ether (GDE), neopentylglycol diglycidyl ether (NPDGE), poly(ethyleneglycol) diglycidyl ether (PEGDE), poly(propyleneglycol) diglycidyl ether (PPGDE) and resorcinol diglycidyl ether (RDE). The aminoglycoside can be selected from, but is not limited to, streptomycin, neomycin, framycetin, paromomycin, ribostamycin, kanamycin, amikacin, arbekacin, bekanamycin, dibekacin, tobramycin, spectinomycin, hygromycin, gentamicin, netilmicin, sisomicin, isepamicin, verdamicin, astromicin, and apramycin. As a non-limiting example, the polymers can be made by the methods described in International Patent Publication No. WO2013055971, the contents of which are herein incorporated by reference in its entirety. As another non-limiting example, compositions comprising any of the polymers comprising at least one least one diepoxide and at least one aminoglycoside can be made by the methods described in International Patent Publication No. WO2013055971, the contents of which are herein incorporated by reference in its entirety.

[0977] In some embodiments, a polymer that can be used in the present disclosure can be a cross-linked polymer. As a non-limiting example, the cross-linked polymers can be used to form a particle as described in US Patent No. 8,414,927, the contents of which are herein incorporated by reference in its entirety. As another non-limiting example, the cross-linked polymer can be obtained by the methods described in US Patent Publication No. US20130172600, the contents of which are herein incorporated by reference in its entirety.

[0978] In another embodiment, a polymer that can be used in the present disclosure can be a cross-linked polymer such as those described in US Patent No. 8,461,132, the contents of which are herein incorporated by reference in its entirety. As a non-limiting example, the cross-linked polymer can be used in a therapeutic composition for the treatment of a body tissue. The

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therapeutic composition can be administered to damaged tissue using various methods known in the art and/or described herein such as injection or catheterization.

[0979] In some embodiments, a polymer that can be used in the present disclosure can be a di-alphatic substituted pegylated lipid such as, but not limited to, those described in International Patent Publication No. WO2013049328, the contents of which are herein incorporated by reference in its entirety.

[0980] In some embodiments, a block copolymer is PEG-PLGA-PEG (*see, e.g.,* the thermosensitive hydrogel (PEG-PLGA-PEG) was used as a TGF-beta1 gene delivery vehicle in Lee et al. Thermosensitive Hydrogel as a Tgf-β1 Gene Delivery Vehicle Enhances Diabetic Wound Healing. Pharmaceutical Research, 2003 20(12): 1995-2000; as a controlled gene delivery system in Li et al. Controlled Gene Delivery System Based on Thermosensitive Biodegradable Hydrogel. Pharmaceutical Research 2003 20(6):884-888; and Chang et al., Non-ionic amphiphilic biodegradable PEG-PLGA-PEG copolymer enhances gene delivery efficiency in rat skeletal muscle. J Controlled Release. 2007 118:245-253; each of which is herein incorporated by reference in its entirety) can be used in the present disclosure. The present disclosure can be formulated with PEG-PLGA-PEG for administration such as, but not limited to, intramuscular and subcutaneous administration.

[0981] In another embodiment, the PEG-PLGA-PEG block copolymer is used in the present disclosure to develop a biodegradable sustained release system. In one aspect, the polynucleotides of the present disclosure are mixed with the block copolymer prior to administration. In another aspect, the polynucleotides acids of the present disclosure are co-administered with the block copolymer.

[0982] In some embodiments, the polymer used in the present disclosure can be a multi-functional polymer derivative such as, but not limited to, a multi-functional N-maleimidyl polymer derivatives as described in US Patent No US8454946, the contents of which are herein incorporated by reference in its entirety.

[0983] The use of core-shell nanoparticles has additionally focused on a high-throughput approach to synthesize cationic cross-linked nanogel cores and various shells (Siegwart et al., Proc Natl Acad Sci U S A. 2011 108:12996-13001; the contents of which are herein incorporated by reference in its entirety). The complexation, delivery, and internalization of the polymeric nanoparticles can be precisely controlled by altering the chemical composition in both the core and shell components of the nanoparticle. For example, the core-shell nanoparticles can

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efficiently deliver siRNA to mouse hepatocytes after they covalently attach cholesterol to the nanoparticle.

[0984] In some embodiments, a hollow lipid core comprising a middle PLGA layer and an outer neutral lipid layer containing PEG can be used to delivery of the polynucleotide, polynucleotides of the present disclosure. As a non-limiting example, in mice bearing a luciferease-expressing tumor, it was determined that the lipid-polymer-lipid hybrid nanoparticle significantly suppressed luciferase expression, as compared to a conventional lipoplex (Shi et al, Angew Chem Int Ed. 2011 50:7027-7031; herein incorporated by reference in its entirety).

[0985] In some embodiments, the lipid nanoparticles can comprise a core of the polynucleotides disclosed herein and a polymer shell. The polymer shell can be any of the polymers described herein and are known in the art. In an additional embodiment, the polymer shell can be used to protect the polynucleotides in the core.

[0986] Core–shell nanoparticles for use with the polynucleotides of the present disclosure are described and can be formed by the methods described in U.S. Pat. No. 8,313,777 or International Patent Publication No. WO2013124867, the contents of each of which are herein incorporated by reference in their entirety.

[0987] In some embodiments, the core-shell nanoparticles can comprise a core of the polynucleotides disclosed herein and a polymer shell. The polymer shell can be any of the polymers described herein and are known in the art. In an additional embodiment, the polymer shell can be used to protect the polynucleotides in the core.

[0988] In some embodiments, the polymer used with the formulations described herein can be a modified polymer (such as, but not limited to, a modified polyacetal) as described in International Publication No. WO2011120053, the contents of which are herein incorporated by reference in its entirety.

[0989] In some embodiments, the formulation can be a polymeric carrier cargo complex comprising a polymeric carrier and at least one nucleic acid molecule. Non-limiting examples of polymeric carrier cargo complexes are described in International Patent Publications Nos. WO2013113326, WO2013113501, WO2013113325, WO2013113502 and WO2013113736 and European Patent Publication No. EP2623121, the contents of each of which are herein incorporated by reference in their entireties. In one aspect the polymeric carrier cargo complexes can comprise a negatively charged nucleic acid molecule such as, but not limited to, those

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described in International Patent Publication Nos. WO2013113325 and WO2013113502, the contents of each of which are herein incorporated by reference in its entirety.

[0990] In some embodiments, a pharmaceutical composition can comprise polynucleotides of the disclosure and a polymeric carrier cargo complex (*See, e.g.,* the antigens described in International Patent Publications Nos. WO2013113326, WO2013113501, WO2013113325, WO2013113502 and WO2013113736 and European Patent Publication No. EP2623121, the contents of each of which are herein incorporated by reference in their entireties).

[0991] In some embodiments, the polymer used with the formulations described herein can be a modified polymer (such as, but not limited to, a modified polyacetal) as described in International Publication No. WO2011120053, the contents of which are herein incorporated by reference in its entirety

Peptides and Proteins

[0992] The disclosure also includes pharmaceutical compositions that comprise a formulation of the polynucleotide described herein, *i.e.*, a polynucleotide comprising an ORF encoding an MCM polypeptide, using one or more peptides and/or proteins. The polynucleotides of the disclosure can be formulated with peptides and/or proteins in order to increase transfection of cells by the polynucleotide. In some embodiments, peptides such as, but not limited to, proteins and peptides that enable intracellular or mitochondrial delivery can be used to deliver pharmaceutical formulations.

[0993] Formulations of the disclosure including peptides or proteins can be used to increase cell transfection by the polynucleotide, alter the biodistribution of the polynucleotide (*e.g.,* by targeting specific tissues or cell types), and/or increase the translation of encoded protein. (See *e.g.,* International Pub. No. WO2012110636 and WO2013123298; the contents of which are herein incorporated by reference in its entirety).

[0994] In some embodiments, the cell penetrating peptide can be, but is not limited to, those described in US Patent Publication No US20130129726, US20130137644 and US20130164219, each of which is herein incorporated by reference in its entirety.

Self-Assembled Macromolecules

[0995] The disclosure also includes pharmaceutical compositions that comprise a formulation of the polynucleotide described herein, *i.e.*, a polynucleotide comprising an ORF

encoding an MCM polypeptide, with amphiphilic macromolecules (AMs) for delivery. AMs comprise biocompatible amphiphilic polymers that have an alkylated sugar backbone covalently linked to poly(ethylene glycol). In aqueous solution, the AMs self-assemble to form micelles. Non-limiting examples of methods of forming AMs and AMs are described in US Patent Publication No. US20130217753, the contents of which are herein incorporated by reference in its entirety.

Cations and Anions

[0996] The disclosure also includes pharmaceutical compositions that comprise a formulation of the polynucleotide described herein, *i.e.*, a polynucleotide comprising an ORF encoding an MCM polypeptide, with cations or anions. In some embodiments, the formulations include metal cations such as, but not limited to, Zn2+, Ca2+, Cu2+, Mg+ and combinations thereof. As a non-limiting example, formulations can include polymers and a polynucleotides complexed with a metal cation (*see, e.g.,* U.S. Pat. Nos. 6,265,389 and 6,555,525, each of which is herein incorporated by reference in its entirety).

[0997] In some embodiments, cationic nanoparticles comprising combinations of divalent and monovalent cations can be formulated with polynucleotides. Such nanoparticles can form spontaneously in solution over a given period (*e.g.*, hours, days, etc.). Such nanoparticles do not form in the presence of divalent cations alone or in the presence of monovalent cations alone. The delivery of polynucleotides in cationic nanoparticles or in one or more depot comprising cationic nanoparticles can improve polynucleotide bioavailability by acting as a long-acting depot and/or reducing the rate of degradation by nucleases.

Suspension formulations

[0998] The disclosure also includes pharmaceutical compositions that comprise a formulation of the polynucleotide described herein, *i.e.*, a polynucleotide comprising an ORF encoding an MCM polypeptide, in suspensions. In some embodiments, suspension formulations are provided comprising polynucleotides, water immiscible oil depots, surfactants and/or co-surfactants and/or co-solvents. Combinations of oils and surfactants can enable suspension formulation with polynucleotides. Delivery of polynucleotides in a water immiscible depot can be used to improve bioavailability through sustained release of mRNA from the depot to the surrounding physiologic environment and prevent polynucleotides degradation by nucleases.

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[0999] In some embodiments, suspension formulations of mRNA can be prepared using combinations of polynucleotides, oil-based solutions and surfactants. Such formulations can be prepared as a two-part system comprising an aqueous phase comprising polynucleotides and an oil-based phase comprising oil and surfactants. Exemplary oils for suspension formulations can include, but are not limited to sesame oil and Miglyol (comprising esters of saturated coconut and palmkernel oil-derived caprylic and capric fatty acids and glycerin or propylene glycol), corn oil, soybean oil, peanut oil, beeswax and/or palm seed oil. Exemplary surfactants can include, but are not limited to Cremophor, polysorbate 20, polysorbate 80, polyethylene glycol, transcutol, Capmul®, labrasol, isopropyl myristate, and/or Span 80. In some embodiments, suspensions can comprise co-solvents including, but not limited to ethanol, glycerol and/or propylene glycol.

[01000] Suspensions can be formed by first preparing polynucleotides formulation comprising an aqueous solution of polynucleotide and an oil-based phase comprising one or more surfactants. Suspension formation occurs as a result of mixing the two phases (aqueous and oil-based). In some embodiments, such a suspension can be delivered to an aqueous phase to form an oil-in-water emulsion. In some embodiments, delivery of a suspension to an aqueous phase results in the formation of an oil-in-water emulsion in which the oil-based phase comprising polynucleotides forms droplets that can range in size from nanometer-sized droplets to micrometer-sized droplets. In some embodiments, specific combinations of oils, surfactants, cosurfactants and/or co-solvents can be utilized to suspend polynucleotides in the oil phase and/or to form oil-in-water emulsions upon delivery into an aqueous environment.

[01001] In some embodiments, suspensions can provide modulation of the release of polynucleotides into the surrounding environment. In such embodiments, polynucleotides release can be modulated by diffusion from a water immiscible depot followed by resolubilization into a surrounding environment (*e.g.*, an aqueous environment).

[01002] In some embodiments, polynucleotides within a water immiscible depot (*e.g.*, suspended within an oil phase) can result in altered polynucleotides stability (*e.g.*, altered degradation by nucleases).

[01003] In some embodiments, polynucleotides can be formulated such that upon injection, an emulsion forms spontaneously (*e.g.*, when delivered to an aqueous phase). Such particle formation can provide a high surface area to volume ratio for release of polynucleotides from an oil phase to an aqueous phase.

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[01004] In some embodiments, the polynucleotides can be formulated in a nanoemulsion such as, but not limited to, the nanoemulsions described in US Patent No. 8,496,945, the contents of which are herein incorporated by reference in its entirety. The nanoemulsions can comprise nanoparticles described herein. As a non-limiting example, the nanoparticles can comprise a liquid hydrophobic core that can be surrounded or coated with a lipid or surfactant layer. The lipid or surfactant layer can comprise at least one membrane-integrating peptide and can also comprise a targeting ligand (*see, e.g.,* US Patent No. 8,496,945, the contents of which are herein incorporated by reference in its entirety).

Semi-solid Compositions

[01005] The disclosure also includes pharmaceutical compositions that comprise a formulation of the polynucleotide described herein, *i.e.*, a polynucleotide comprising an ORF encoding an MCM polypeptide, in semi-solid compositions. In some embodiments, the polynucleotides can be formulated with a hydrophobic matrix to form a semi-solid composition. As a non-limiting example, the semi-solid composition or paste-like composition can be made by the methods described in International Patent Publication No WO201307604, herein incorporated by reference in its entirety. The semi-solid composition can be a sustained release formulation as described in International Patent Publication No WO201307604, herein incorporated by reference in its entirety.

[01006] In another embodiment, the semi-solid composition can further have a micro-porous membrane or a biodegradable polymer formed around the composition (*see, e.g.,* International Patent Publication No WO201307604, herein incorporated by reference in its entirety).

[01007] The semi-solid composition using the polynucleotides of the present disclosure can have the characteristics of the semi-solid mixture as described in International Patent Publication No WO201307604, herein incorporated by reference in its entirety (*e.g.,* a modulus of elasticity of at least 10^{-4} N·mm^{-2}, and/or a viscosity of at least 100mPa·s).

Surgical Sealants: Gels and Hydrogels

[01008] The disclosure also includes pharmaceutical compositions that comprise a formulation of the polynucleotide described herein, *i.e.*, a polynucleotide comprising an ORF encoding an MCM polypeptide, with surgical sealants. In some embodiments, the polynucleotides disclosed herein can be encapsulated into any hydrogel known in the art that can

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form a gel when injected into a subject. Surgical sealants such as gels and hydrogels are described in International Patent Application No. PCT/US2014/027077, the contents of which are herein incorporated by reference in its entirety.

Conjugates

[01009] The disclosure includes pharmaceutical compositions that comprise conjugates of the polynucleotide described herein, *i.e.*, a polynucleotide comprising an ORF encoding an MCM polypeptide. The polynucleotides of the disclosure include conjugates, such as a polynucleotide covalently linked to a carrier or targeting group, or including two encoding regions that together produce a fusion protein (*e.g.,* bearing a targeting group and therapeutic protein or peptide).

[01010] The conjugates of the disclosure include a naturally occurring substance, such as a protein (*e.g.,* human serum albumin (HSA), low-density lipoprotein (LDL), high-density lipoprotein (HDL), or globulin); an carbohydrate (*e.g.,* a dextran, pullulan, chitin, chitosan, inulin, cyclodextrin or hyaluronic acid); or a lipid. The ligand can also be a recombinant or synthetic molecule, such as a synthetic polymer, *e.g.,* a synthetic polyamino acid, an oligonucleotide (*e.g.*, an aptamer). Examples of polyamino acids include polyamino acid is a polylysine (PLL), poly L-aspartic acid, poly L-glutamic acid, styrene-maleic acid anhydride copolymer, poly(L-lactide-co-glycolied) copolymer, divinyl ether-maleic anhydride copolymer, N-(2-hydroxypropyl)methacrylamide copolymer (HMPA), polyethylene glycol (PEG), polyvinyl alcohol (PVA), polyurethane, poly(2-ethylacryllic acid), N-isopropylacrylamide polymers, or polyphosphazine. Example of polyamines include: polyethylenimine, polylysine (PLL), spermine, spermidine, polyamine, pseudopeptide-polyamine, peptidomimetic polyamine, dendrimer polyamine, arginine, amidine, protamine, cationic lipid, cationic porphyrin, quaternary salt of a polyamine, or an alpha helical peptide.

[01011] In some embodiments, the conjugate of the present disclosure can function as a carrier for the polynucleotides of the present disclosure. The conjugate can comprise a cationic polymer such as, but not limited to, polyamine, polylysine, polyalkylenimine, and polyethylenimine that can be grafted to with poly(ethylene glycol). As a non-limiting example, the conjugate can be similar to the polymeric conjugate and the method of synthesizing the polymeric conjugate described in U.S. Pat. No. 6,586,524 herein incorporated by reference in its entirety.

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[01012] A non-limiting example of a method for conjugation to a substrate is described in US Patent Publication No. US20130211249, the contents of which are herein incorporated by reference in its entirety. The method can be used to make a conjugated polymeric particle comprising a polynucleotide.

[01013] The conjugates can also include targeting groups, *e.g.,* a cell or tissue targeting agent, *e.g.,* a lectin, glycoprotein, lipid or protein, *e.g.,* an antibody, that binds to a specified cell type such as a kidney cell. A targeting group can be a thyrotropin, melanotropin, lectin, glycoprotein, surfactant protein A, Mucin carbohydrate, multivalent lactose, multivalent galactose, N-acetyl-galactosamine, N-acetyl-glucosamine multivalent mannose, multivalent fucose, glycosylated polyaminoacids, multivalent galactose, transferrin, bisphosphonate, polyglutamate, polyaspartate, a lipid, cholesterol, a steroid, bile acid, folate, vitamin B12, biotin, an RGD peptide, an RGD peptide mimetic or an aptamer.

[01014] Targeting groups can be proteins, *e.g.,* glycoproteins, or peptides, *e.g.,* molecules having a specific affinity for a co-ligand, or antibodies *e.g.,* an antibody, that binds to a specified cell type such as a cancer cell, endothelial cell, or bone cell. Targeting groups can also include hormones and hormone receptors. They can also include non-peptidic species, such as lipids, lectins, carbohydrates, vitamins, cofactors, multivalent lactose, multivalent galactose, N-acetyl-galactosamine, N-acetyl-glucosamine multivalent mannose, multivalent frucose, or aptamers. The ligand can be, for example, a lipopolysaccharide, or an activator of p38 MAP kinase.

[01015] The targeting group can be any ligand that is capable of targeting a specific receptor. Examples include, without limitation, folate, GalNAc, galactose, mannose, mannose-6P, apatamers, integrin receptor ligands, chemokine receptor ligands, transferrin, biotin, serotonin receptor ligands, PSMA, endothelin, GCPII, somatostatin, LDL, and HDL ligands. In particular embodiments, the targeting group is an aptamer. The aptamer can be unmodified or have any combination of modifications disclosed herein.

[01016] As a non-limiting example, the targeting group can be a glutathione receptor (GR)-binding conjugate for targeted delivery across the blood-central nervous system barrier (*See, e.g.,* US Patent Publication No. US20130216610l2, the contents of which are herein incorporated by reference in its entirety.

[01017] In some embodiments, the conjugate of the present disclosure can be a synergistic biomolecule-polymer conjugate. The synergistic biomolecule-polymer conjugate can be long-acting continuous-release system to provide a greater therapeutic efficacy. The synergistic

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biomolecule-polymer conjugate can be those described in US Patent Publication No. US20130195799, the contents of which are herein incorporated by reference in its entirety.

[01018] In another embodiment, the conjugate that can be used in the present disclosure can be an aptamer conjugate. Non-limiting examples of apatamer conjugates are described in International Patent Publication No. WO2012040524, the contents of which are herein incorporated by reference in its entirety. The aptamer conjugates can be used to provide targeted delivery of formulations comprising polynucleotides.

[01019] In some embodiments, the conjugate that can be used in the present disclosure can be an amine containing polymer conjugate. Non-limiting examples of amine containing polymer conjugate are described in US Patent No. US 8,507,653, the contents of which are herein incorporated by reference in its entirety.

[01020] In some embodiments, pharmaceutical compositions of the present disclosure can include chemical modifications such as, but not limited to, modifications similar to locked nucleic acids.

[01021] Representative U.S. Patents that teach the preparation of locked nucleic acid (LNA) such as those from Santaris, include, but are not limited to, the following: U.S. Pat. Nos. 6,268,490; 6,670,461; 6,794,499; 6,998,484; 7,053,207; 7,084,125; and 7,399,845, each of which is herein incorporated by reference in its entirety.

[01022] Representative U.S. patents that teach the preparation of PNA compounds include, but are not limited to, U.S. Pat. Nos. 5,539,082; 5,714,331; and 5,719,262, each of which is herein incorporated by reference. Further teaching of PNA compounds can be found, for example, in Nielsen *et al.*, Science, 1991, 254, 1497-1500.

[01023] Some embodiments featured in the disclosure include polynucleotides with phosphorothioate backbones and oligonucleosides with other modified backbones, and in particular --CH_2--NH--CH_2--, --CH_2--N(CH_3)--O--CH_2--[known as a methylene (methylimino) or MMI backbone], --CH_2--O--N(CH_3)--CH_2--, --CH_2--N(CH_3)--N(CH_3)--CH_2-- and --N(CH_3)--CH_2--CH_2--[wherein the native phosphodiester backbone is represented as --O—P$(O)_2$--O--CH_2--] of the above-referenced U.S. Pat. No. 5,489,677, and the amide backbones of the above-referenced U.S. Pat. No. 5,602,240. In some embodiments, the polynucleotides featured herein have morpholino backbone structures of the above-referenced U.S. Pat. No. 5,034,506.

[01024] Modifications at the 2' position can also aid in delivery. For example, modifications at the 2' position are not located in a polypeptide-coding sequence, *i.e.*, not in a translatable region.

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Modifications at the 2' position can be located in a 5'UTR, a 3'UTR and/or a tailing region. Modifications at the 2' position can include one of the following at the 2' position: H (*i.e.*, 2'-deoxy); F; O-, S-, or N-alkyl; O-, S-, or N-alkenyl; O-, S- or N-alkynyl; or O-alkyl-O-alkyl, wherein the alkyl, alkenyl and alkynyl can be substituted or unsubstituted C_1 to C_{10} alkyl or C_2 to C_{10} alkenyl and alkynyl. Exemplary suitable modifications include $O[(CH_2)_nO]_mCH_3$, $O(CH_2)_nOCH_3$, $O(CH_2)_nNH_2$, $O(CH_2)_nCH_3$, $O(CH_2)_nONH_2$, and $O(CH_2)_nON[(CH_2)_nCH_3)]_2$, where n and m are from 1 to about 10. In other embodiments, the polynucleotides include one of the following at the 2' position: C_1 to C_{10} lower alkyl, substituted lower alkyl, alkaryl, aralkyl, O-alkaryl or O-aralkyl, SH, SCH_3, OCN, Cl, Br, CN, CF_3, OCF_3, $SOCH_3$, SO_2CH_3, ONO_2, NO_2, N_3, NH_2, heterocycloalkyl, heterocycloalkaryl, aminoalkylamino, polyalkylamino, substituted silyl, an RNA cleaving group, a reporter group, an intercalator, a group for improving the pharmacokinetic properties, or a group for improving the pharmacodynamic properties, and other substituents having similar properties. In some embodiments, the modification includes a 2'-methoxyethoxy (2'-O--$CH_2CH_2OCH_3$, also known as 2'-O-(2-methoxyethyl) or 2'-MOE) (Martin *et al.*, *Helv. Chim. Acta*, 1995, 78:486-504) *i.e.*, an alkoxy-alkoxy group. Another exemplary modification is 2'-dimethylaminooxyethoxy, *i.e.*, a $O(CH_2)_2ON(CH_3)_2$ group, also known as 2'-DMAOE, as described in examples herein below, and 2'-dimethylaminoethoxyethoxy (also known in the art as 2'-O-dimethylaminoethoxyethyl or 2'-DMAEOE), *i.e.*, 2'-O--CH_2--O--CH_2--$N(CH_2)_2$, also described in examples herein below. Other modifications include 2'-methoxy (2'-OCH_3), 2'-aminopropoxy (2'-$OCH_2CH_2CH_2NH_2$) and 2'-fluoro (2'-F). Similar modifications can also be made at other positions, particularly the 3' position of the sugar on the 3' terminal nucleotide or in 2'-5' linked dsRNAs and the 5' position of 5' terminal nucleotide. Polynucleotides of the disclosure can also have sugar mimetics such as cyclobutyl moieties in place of the pentofuranosyl sugar. Representative U.S. patents that teach the preparation of such modified sugar structures include, but are not limited to, U.S. Pat. Nos. 4,981,957; 5,118,800; 5,319,080; 5,359,044; 5,393,878; 5,446,137; 5,466,786; 5,514,785; 5,519,134; 5,567,811; 5,576,427; 5,591,722; 5,597,909; 5,610,300; 5,627,053; 5,639,873; 5,646,265; 5,658,873; 5,670,633; and 5,700,920; the contents of each of which is herein incorporated by reference in their entirety.

[01025] In still other embodiments, the polynucleotide is covalently conjugated to a cell penetrating polypeptide. The cell-penetrating peptide can also include a signal sequence or a targeting sequence. The conjugates of the disclosure can be designed to have increased stability;

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increased cell transfection; and/or altered the biodistribution (*e.g.,* targeted to specific tissues or cell types).

[01026] In some embodiments, the polynucleotides can be conjugated to an agent to enhance delivery. As a non-limiting example, the agent can be a monomer or polymer such as a targeting monomer or a polymer having targeting blocks as described in International Publication No. WO2011062965, herein incorporated by reference in its entirety. In another non-limiting example, the agent can be a transport agent covalently coupled to the polynucleotides of the present disclosure (*See, e.g.,* U.S. Pat. Nos. 6,835.393 and 7,374,778, each of which is herein incorporated by reference in its entirety). In yet another non-limiting example, the agent can be a membrane barrier transport enhancing agent such as those described in U.S. Pat. Nos. 7,737,108 and 8,003,129, each of which is herein incorporated by reference in its entirety.

[01027] In another embodiment, polynucleotides can be conjugated to SMARTT POLYMER TECHNOLOGY® (PHASERX®, Inc. Seattle, WA).

[01028] In another aspect, the conjugate can be a peptide that selectively directs the nanoparticle to neurons in a tissue or organism. As a non-limiting example, the peptide used can be, but is not limited to, the peptides described in US Patent Publication No US20130129627, herein incorporated by reference in its entirety.

[01029] In yet another aspect, the conjugate can be a peptide that can assist in crossing the blood-brain barrier.

Nanoparticle Formulations

Self-Assembled Nanoparticles

[01030] The disclosure also includes pharmaceutical compositions that comprise a formulation of the polynucleotide described herein, *i.e.*, a polynucleotide comprising an ORF encoding an MCM polypeptide, with self-assembled nanoparticles. Nucleic acid self-assembled nanoparticles are described in International Patent Application No. PCT/US2014/027077, the contents of which are herein incorporated by reference in its entirety, such as in paragraphs [000740] – [000743]. Polymer-based self-assembled nanoparticles are described in International Patent Application No. PCT/US2014/027077, the contents of which are herein incorporated by reference in its entirety.

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Nanoparticle Mimics

[01031] The disclosure includes pharmaceutical compositions that comprise a nanoparticle mimic formulation of the polynucleotide described herein, *i.e.*, a polynucleotide comprising an ORF encoding an MCM polypeptide. In some embodiments, the polynucleotides of the disclosure is be encapsulated within and/or absorbed to a nanoparticle mimic. A nanoparticle mimic can mimic the delivery function organisms or particles such as, but not limited to, pathogens, viruses, bacteria, fungus, parasites, prions and cells. As a non-limiting example the polynucleotides of the disclosure can be encapsulated in a non-viron particle that can mimic the delivery function of a virus (see International Pub. No. WO2012006376 and US Patent Publication No. US20130171241 and US20130195968, the contents of each of which are herein incorporated by reference in its entirety).

Nanotubes

[01032] The disclosure includes pharmaceutical compositions that comprise a nanotube formulation of the polynucleotide described herein, *i.e.*, a polynucleotide comprising an ORF encoding an MCM polypeptide. The polynucleotides of the disclosure can be attached or otherwise bound to at least one nanotube such as, but not limited to, rosette nanotubes, rosette nanotubes having twin bases with a linker, carbon nanotubes and/or single-walled carbon nanotubes, The polynucleotides can be bound to the nanotubes through forces such as, but not limited to, steric, ionic, covalent and/or other forces. Nanotubes and nanotube formulations comprising polynucleotides are described in International Patent Application No. PCT/US2014/027077, the contents of which are herein incorporated by reference in its entirety.

Inorganic Nanoparticles

[01033] The disclosure also includes pharmaceutical compositions that comprise a formulation of the polynucleotide described herein, *i.e.*, a polynucleotide comprising an ORF encoding an MCM polypeptide, in inorganic nanoparticles. Example methods are provided in U.S. Pat. No. 8,257,745, herein incorporated by reference in its entirety. The inorganic nanoparticles can include, but are not limited to, clay substances that are water swellable. As a non-limiting example, the inorganic nanoparticle can include synthetic smectite clays that are made from simple silicates (*See, e.g.,* U.S. Pat. No. 5,585,108 and 8,257,745 each of which are herein incorporated by reference in their entirety).

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[01034] In some embodiments, the inorganic nanoparticles can comprise a core of the polynucleotides disclosed herein and a polymer shell. The polymer shell can be any of the polymers described herein and are known in the art. In an additional embodiment, the polymer shell can be used to protect the polynucleotides in the core.

Semi-conductive and Metallic Nanoparticles

[01035] The disclosure also includes pharmaceutical compositions that comprise a formulation of the polynucleotide described herein, *i.e.*, a polynucleotide comprising an ORF encoding an MCM polypeptide, with water-dispersible nanoparticles comprising a semiconductive or metallic material (U.S. Pub. No. 20120228565; herein incorporated by reference in its entirety) or formed in a magnetic nanoparticle (U.S. Pub. No. 20120265001 and 20120283503; each of which is herein incorporated by reference in its entirety). The water-dispersible nanoparticles can be hydrophobic nanoparticles or hydrophilic nanoparticles.

[01036] In some embodiments, the semi-conductive and/or metallic nanoparticles can comprise a core of the polynucleotides disclosed herein and a polymer shell. The polymer shell can be any of the polymers described herein and are known in the art. In an additional embodiment, the polymer shell can be used to protect the polynucleotides in the core.

Molded Nanoparticles and Microparticles

[01037] The disclosure also includes pharmaceutical compositions that comprise a formulation of the polynucleotide described herein, *i.e.*, a polynucleotide comprising an ORF encoding an MCM polypeptide, in nanoparticles and/or microparticles. These nanoparticles and/or microparticles can be molded into any size shape and chemistry. As an example, the nanoparticles and/or microparticles can be made using the PRINT® technology by LIQUIDA TECHNOLOGIES® (Morrisville, NC) (*See, e.g.,* International Pub. No. WO2007024323; the contents of which are herein incorporated by reference in its entirety).

[01038] In some embodiments, the molded nanoparticles can comprise a core of the polynucleotides disclosed herein and a polymer shell. The polymer shell can be any of the polymers described herein and are known in the art. In an additional embodiment, the polymer shell can be used to protect the polynucleotides in the core.

[01039] In some embodiments, the polynucleotides of the present disclosure can be formulated in microparticles. The microparticles can contain a core of the polynucleotides and a cortex of a biocompatible and/or biodegradable polymer. As a non-limiting example, the

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microparticles that can be used with the present disclosure can be those described in U.S. Patent No. 8,460,709, U.S. Patent Publication No. US20130129830 and International Patent Publication No WO2013075068, each of which is herein incorporated by reference in its entirety. As another non-limiting example, the microparticles can be designed to extend the release of the polynucleotides of the present disclosure over a desired period of time (*see, e.g.*, extended release of a therapeutic protein in U.S. Patent Publication No. US20130129830, herein incorporated by reference in its entirety).

[01040] The microparticle for use with the present disclosure can have a diameter of at least 1 micron to at least 100 microns (*e.g.,* at least 1 micron, at least 5 micron, at least 10 micron, at least 15 micron, at least 20 micron, at least 25 micron, at least 30 micron, at least 35 micron, at least 40 micron, at least 45 micron, at least 50 micron, at least 55 micron, at least 60 micron, at least 65 micron, at least 70 micron, at least 75 micron, at least 80 micron, at least 85 micron, at least 90 micron, at least 95 micron, at least 97 micron, at least 99 micron, and at least 100 micron).

NanoJackets and NanoLiposomes

[01041] The disclosure also includes pharmaceutical compositions that comprise a formulation of the polynucleotide described herein, *i.e.*, a polynucleotide comprising an ORF encoding an MCM polypeptide, with NanoJackets and NanoLiposomes by Keystone Nano (State College, PA). NanoJackets are made of compounds that are naturally found in the body including calcium, phosphate and can also include a small amount of silicates. Nanojackets can range in size from 5 to 50 nm and can be used to deliver hydrophilic and hydrophobic compounds such as, but not limited to, polynucleotides.

[01042] NanoLiposomes are made of lipids such as, but not limited to, lipids that naturally occur in the body. NanoLiposomes can range in size from 60-80 nm and can be used to deliver hydrophilic and hydrophobic compounds such as, but not limited to, polynucleotides. In one aspect, the polynucleotides disclosed herein are formulated in a NanoLiposome such as, but not limited to, Ceramide NanoLiposomes.Cells

[01043] The disclosure also includes cells that comprise a polynucleotide described herein, *i.e.*, a polynucleotide comprising an ORF encoding an MCM polypeptide. The polynucleotides of the disclosure can be transfected *ex vivo* into cells, which are subsequently transplanted into a subject. As non-limiting examples, the pharmaceutical compositions can include red blood cells

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to deliver modified RNA to liver and myeloid cells, virosomes to deliver modified RNA in virus-like particles (VLPs), and electroporated cells such as, but not limited to, from MAXCYTE® (Gaithersburg, MD) and from ERYTECH® (Lyon, France) to deliver modified RNA. Examples of use of red blood cells, viral particles and electroporated cells to deliver payloads other than polynucleotides have been documented (Godfrin et al., Expert Opin Biol Ther. 2012 12:127-133; Fang et al., Expert Opin Biol Ther. 2012 12:385-389; Hu et al., Proc Natl Acad Sci U S A. 2011 108:10980-10985; Lund et al., Pharm Res. 2010 27:400-420; Huckriede et al., J Liposome Res. 2007;17:39-47; Cusi, Hum Vaccin. 2006 2:1-7; de Jonge et al., Gene Ther. 2006 13:400-411; all of which are herein incorporated by reference in its entirety).

[01044] The polynucleotides can be delivered in synthetic VLPs synthesized by the methods described in International Pub No. WO2011085231 and WO2013116656 and US Pub No. 20110171248, the contents of each of which are herein incorporated by reference in their entireties.

[01045] Cell-based formulations of the polynucleotides of the disclosure can be used to ensure cell transfection (*e.g.,* in the cellular carrier), alter the biodistribution of the polynucleotide (*e.g.,* by targeting the cell carrier to specific tissues or cell types), and/or increase the translation of encoded protein.

[01046] A variety of methods are known in the art and suitable for introduction of nucleic acid into a cell, including viral and non-viral mediated techniques. Examples of typical non-viral mediated techniques include, but are not limited to, electroporation, calcium phosphate mediated transfer, nucleofection, sonoporation, heat shock, magnetofection, liposome mediated transfer, microinjection, microprojectile mediated transfer (nanoparticles), cationic polymer mediated transfer (DEAE-dextran, polyethylenimine, polyethylene glycol (PEG) and the like) or cell fusion.

[01047] The technique of sonoporation, or cellular sonication, is the use of sound (*e.g.,* ultrasonic frequencies) for modifying the permeability of the cell plasma membrane. Sonoporation methods are known to those in the art and are used to deliver nucleic acids *in vivo* (Yoon and Park, Expert Opin Drug Deliv. 2010 7:321-330; Postema and Gilja, Curr Pharm Biotechnol. 2007 8:355-361; Newman and Bettinger, Gene Ther. 2007 14:465-475; all herein incorporated by reference in their entirety). Sonoporation methods are known in the art and are also taught for example as it relates to bacteria in US Patent Publication 20100196983 and as it

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relates to other cell types in, for example, US Patent Publication 20100009424, each of which are incorporated herein by reference in their entirety.

[01048] Electroporation techniques are also well known in the art and are used to deliver nucleic acids *in vivo* and clinically (Andre et al., Curr Gene Ther. 2010 10:267-280; Chiarella et al., Curr Gene Ther. 2010 10:281-286; Hojman, Curr Gene Ther. 2010 10:128-138; all herein incorporated by reference in their entirety). Electroporation devices are sold by many companies worldwide including, but not limited to BTX® Instruments (Holliston, MA) (*e.g.,* the AgilePulse *In Vivo* System) and Inovio (Blue Bell, PA) (*e.g.,* Inovio SP-5P intramuscular delivery device or the CELLECTRA® 3000 intradermal delivery device). In some embodiments, polynucleotides can be delivered by electroporation.

[01049] In some embodiments, the cells are selected from the group consisting of mammalian cells, bacterial cells, plant, microbial, algal and fungal cells. In some embodiments, the cells are mammalian cells, such as, but not limited to, human, mouse, rat, goat, horse, rabbit, hamster or cow cells. In a further embodiment, the cells can be from an established cell line, including, but not limited to, HeLa, NS0, SP2/0, KEK 293T, Vero, Caco, Caco-2, MDCK, COS-1, COS-7, K562, Jurkat, CHO-K1, DG44, CHOK1SV, CHO-S, Huvec, CV-1, Huh-7, NIH3T3, HEK293, 293, A549, HepG2, IMR-90, MCF-7, U-20S, Per.C6, SF9, SF21 or Chinese Hamster Ovary (CHO) cells.

[01050] In certain embodiments, the cells are fungal cells, such as, but not limited to, Chrysosporium cells, Aspergillus cells, Trichoderma cells, Dictyostelium cells, Candida cells, Saccharomyces cells, Schizosaccharomyces cells, and Penicillium cells.

[01051] In certain embodiments, the cells are bacterial cells such as, but not limited to, E. coli, B. subtilis, or BL21 cells. Primary and secondary cells to be transfected by the methods of the disclosure can be obtained from a variety of tissues and include, but are not limited to, all cell types that can be maintained in culture. For examples, primary and secondary cells that can be transfected by the methods of the disclosure include, but are not limited to, fibroblasts, keratinocytes, epithelial cells (*e.g.,* mammary epithelial cells, intestinal epithelial cells), endothelial cells, glial cells, neural cells, formed elements of the blood (*e.g.,* lymphocytes, bone marrow cells), muscle cells and precursors of these somatic cell types. Primary cells can also be obtained from a donor of the same species or from another species (*e.g.,* mouse, rat, rabbit, cat, dog, pig, cow, bird, sheep, goat, horse).

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Minicells

[01052] The disclosure also includes minicells that comprise a polynucleotide described herein, *i.e.*, a polynucleotide comprising an ORF encoding an MCM polypeptide. In one aspect, the polynucleotides can be formulated in bacterial minicells. As a non-limiting example, bacterial minicells can be those described in International Publication No. WO2013088250 or US Patent Publication No. US20130177499, the contents of each of which are herein incorporated by reference in its entirety.

Micro-Organs

[01053] The disclosure also includes micro-organs containing a polynucleotide described herein, *i.e.*, a polynucleotide comprising an ORF encoding an MCM polypeptide. The polynucleotides can be contained in a micro-organ that can then express an encoded polypeptide of interest in a long-lasting therapeutic formulation. Micro-organs and formulations thereof are described in International Patent Application No. PCT/US2014/027077, the contents of which are herein incorporated by reference in its entirety.

Exosomes

[01054] The disclosure also includes pharmaceutical compositions that comprise a formulation of the polynucleotide described herein, *i.e.*, a polynucleotide comprising an ORF encoding an MCM polypeptide, in exosomes. The exosomes can be loaded with at least one polynucleotide and delivered to cells, tissues and/or organisms. As a non-limiting example, the polynucleotides can be loaded in the exosomes described in International Publication No. WO2013084000, herein incorporated by reference in its entirety.

Pseudovirions

[01055] The disclosure also includes pharmaceutical compositions that comprise a formulation of the polynucleotide described herein, *i.e.*, a polynucleotide comprising an ORF encoding an MCM polypeptide, in in Pseudovirions (*e.g.*, pseudo-virions). As a non-limiting example, the pseudovirions can be those developed and/or are described by Aura Biosciences (Cambridge, MA). In one aspect, the pseudovirion can be developed to deliver drugs to keratinocytes and basal membranes (See *e.g.*, US Patent Publication Nos. US20130012450,

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US20130012566, US21030012426 and US20120207840 and International Publication No. WO2013009717, each of which is herein incorporated by reference in its entirety).

[01056] In some embodiments, the pseudovirion used for delivering the polynucleotides of the present disclosure can be derived from viruses such as, but not limited to, herpes and papillomaviruses (*See, e.g.,* US Patent Publication Nos. US Patent Publication Nos. US20130012450, US20130012566, US21030012426 and US20120207840 and International Publication No. WO2013009717, each of which is herein incorporated by reference in its entirety; and Ma et al. HPV pseudovirions as DNA delivery vehicles. Ther Deliv. 2011: 2(4): 427-430; Kines et al. The initial steps leading to papillomavirus infection occur on the basement membrane prior to cell surface binding. PNAS 2009:106(48), 20458-20463; Roberts et al. Genital transmission of HPV in a mouse model is potentiated by nonoxynol-9 and inhibited by carrageenan. Nature Medicine. 2007:13(7) 857-861; Gordon et al., Targeting the Vaginal Mucosa with Human Papillomavirus Pseudovirion Vaccines delivering SIV DNA. J Immunol. 2012 188(2) 714-723; Cuburu et al., Intravaginal immunization with HPV vectors induces tissue-resident CD8+ T cell responses. The Journal of Clinical Investigation. 2012: 122(12) 4606-4620; Hung et al., Ovarian Cancer Gene Therapy Using HPV-16 Pseudovirion Carrying the HSV-tk Gene. PLoS ONE. 2012: 7(7) e40983; Johnson et al., Role of Heparan Sulfate in Attachment to and Infection of the Murine Female Genital Tract by Human Papillomavirus. J Virology. 2009: 83(5) 2067-2074; each of which is herein incorporated by reference in its entirety).

[01057] The pseudovirion can be a virus-like particle (VLP) prepared by the methods described in US Patent Publication No. US20120015899 and US20130177587 and International Patent Publication No. WO2010047839 WO2013116656, WO2013106525 and WO2013122262, the contents of each of which is herein incorporated by reference in its entirety. In one aspect, the VLP can be, but is not limited to, bacteriophages MS, Qβ, R17, fr, GA, Sp, MI, I, MXI, NL95, AP205, f2, PP7, and the plant viruses Turnip crinkle virus (TCV), Tomato bushy stunt virus (TBSV), Southern bean mosaic virus (SBMV) and members of the genus Bromovirus including Broad bean mottle virus, Brome mosaic virus, Cassia yellow blotch virus, Cowpea chlorotic mottle virus (CCMV), Melandrium yellow fleck virus, and Spring beauty latent virus. In another aspect, the VLP can be derived from the influenza virus as described in US Patent Publication No. US20130177587 or US Patent No. 8,506,967, the contents of each of which are herein incorporated by reference in its entirety. In yet another aspect, the VLP can comprise a B7-1 and/or B7-2 molecule anchored to a lipid membrane or the exterior of the particle such as

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described in International Patent Publication No. WO2013116656, the contents of which are herein incorporated by reference in its entirety. In one aspect, the VLP can be derived from norovirus, rotavirus recombinant VP6 protein or double layered VP2/VP6 such as the VLP described in International Patent Publication No. WO2012049366, the contents of which are herein incorporated by reference in its entirety.

[01058] The pseudovirion can be a human papilloma virus-like particle such as, but not limited to, those described in International Publication No. WO2010120266 and US Patent Publication No. US20120171290, each of which is herein incorporated by reference in its entirety and Ma et al. HPV pseudovirions as DNA delivery vehicles. Ther Deliv. 2011: 2(4): 427-430; Kines et al. The initial steps leading to papillomavirus infection occur on the basement membrane prior to cell surface binding. PNAS 2009:106(48), 20458-20463; Roberts et al. Genital transmission of HPV in a mouse model is potentiated by nonoxynol-9 and inhibited by carrageenan. Nature Medicine. 2007:13(7) 857-861; Gordon et al., Targeting the Vaginal Mucosa with Human Papillomavirus Pseudovirion Vaccines delivering SIV DNA. J Immunol. 2012 188(2) 714-723; Cuburu et al., Intravaginal immunization with HPV vectors induces tissue-resident CD8+ T cell responses. The Journal of Clinical Investigation. 2012: 122(12) 4606-4620; Hung et al., Ovarian Cancer Gene Therapy Using HPV-16 Pseudovirion Carrying the HSV-tk Gene. PLoS ONE. 2012: 7(7) e40983; Johnson et al., Role of Heparan Sulfate in Attachment to and Infection of the Murine Female Genital Tract by Human Papillomavirus. J Virology. 2009: 83(5) 2067-2074; each of which is herein incorporated by reference in its entirety.

[01059] In one aspect, the pseudovirions can be virion derived nanoparticles such as, but not limited to, those described in US Patent Publication No. US20130116408 and US20130115247, each of which is herein incorporated by reference in their entirety. The virion derived nanoparticles can be made by the methods described in US Patent Publication No. US20130116408 and US20130115247 or International Patent Publication No. WO2013119877, each of which is herein incorporated by reference in their entirety.

[01060] In some embodiments, the virus-like particle (VLP) can be a self-assembled particle. Non-limiting examples of self-assembled VLPs and methods of making the self-assembled VLPs are described in International Patent Publication No. WO2013122262, the contents of which are herein incorporated by reference in its entirety.

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Silk-Based Delivery

[01061] The disclosure also includes pharmaceutical compositions that are formulated for silk-based delivery of the polynucleotides described herein, *i.e.*, a polynucleotide comprising an ORF encoding an MCM polypeptide. In some embodiments, the polynucleotides can be formulated in a sustained release silk-based delivery system. The silk-based delivery system can be formed by contacting a silk fibroin solution with a therapeutic agent such as, but not limited to, the polynucleotides described herein and/or known in the art. As a non-limiting example, the sustained release silk-based delivery system that can be used in the present disclosure and methods of making such system are described in US Patent Publication No. US20130177611, the contents of which are herein incorporated by reference in its entirety.

Microparticles

[01062] The disclosure includes pharmaceutical compositions that comprise a microparticle formulation of the polynucleotide described herein, *i.e.*, a polynucleotide comprising an ORF encoding an MCM polypeptide. In some embodiments, formulations comprising polynucleotides can comprise microparticles. The microparticles can comprise a polymer described herein and/or known in the art such as, but not limited to, poly(α-hydroxy acid), a polyhydroxy butyric acid, a polycaprolactone, a polyorthoester and a polyanhydride. The microparticle can have adsorbent surfaces to adsorb biologically active molecules such as polynucleotides. As a non-limiting example microparticles for use with the present disclosure and methods of making microparticles are described in US Patent Publication No. US2013195923 and US20130195898 and US Patent No. 8,309,139 and 8,206,749, the contents of each of which are herein incorporated by reference in its entirety.

[01063] In another embodiment, the formulation can be a microemulsion comprising microparticles and polynucleotides. As a non-limiting example, microemulsions comprising microparticles are described in US Patent Publication No. US2013195923 and US20130195898 and US Patent No. 8,309,139 and 8,206,749, the contents of each of which are herein incorporated by reference in its entirety.

Microvesicles

[01064] The disclosure includes pharmaceutical compositions that comprise a microvesicle-based formulation of the polynucleotide described herein, *i.e.*, a polynucleotide comprising an

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ORF encoding an MCM polypeptide. In some embodiments, polynucleotides can be formulated in microvesicles. Non-limiting examples of microvesicles include those described in US Patent Publication No. US20130209544, the contents of which are herein incorporated by reference in its entirety.

[01065] In some embodiments, the microvesicle is an ARRDC1-mediated microvesicles (ARMMs). Non-limiting examples of ARMMs and methods of making ARMMs are described in International Patent Publication No. WO2013119602, the contents of which are herein incorporated by reference in its entirety.

Interpolyelectrolyte Complexes

[01066] The disclosure also includes pharmaceutical compositions that comprise a formulation of the polynucleotide described herein, *i.e.*, a polynucleotide comprising an ORF encoding an MCM polypeptide, in an interpolyelectrolyte complex. Interpolyelectrolyte complexes are formed when charge-dynamic polymers are complexed with one or more anionic molecules. Non-limiting examples of charge-dynamic polymers and interpolyelectrolyte complexes and methods of making interpolyelectrolyte complexes are described in US Patent No. 8,524,368, the contents of which is herein incorporated by reference in its entirety.

Crystalline Polymeric Systems

[01067] The disclosure also includes pharmaceutical compositions that comprise a formulation of the polynucleotide described herein, *i.e.*, a polynucleotide comprising an ORF encoding an MCM polypeptide, in crystalline polymeric systems. Crystalline polymeric systems are polymers with crystalline moieties and/or terminal units comprising crystalline moieties. Non-limiting examples of polymers with crystalline moieties and/or terminal units comprising crystalline moieties termed "CYC polymers," crystalline polymer systems and methods of making such polymers and systems are described in US Patent No. US 8,524,259, the contents of which are herein incorporated by reference in its entirety.

Cryoprotectants for mRNA

[01068] The disclosure also includes pharmaceutical compositions that comprise a formulation of the polynucleotide described herein, *i.e.*, a polynucleotide comprising an ORF encoding an MCM polypeptide, with cyroprotectants. As used herein, there term "cryoprotectant" refers to one or more agent that when combined with a given substance, helps to

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reduce or eliminate damage to that substance that occurs upon freezing. In some embodiments, cryoprotectants are combined with polynucleotides in order to stabilize them during freezing. Frozen storage of mRNA between -20°C and -80°C can be advantageous for long term (*e.g.*, 36 months) stability of polynucleotide. In some embodiments, cryoprotectants are included in polynucleotide formulations to stabilize polynucleotide through freeze/thaw cycles and under frozen storage conditions. Cryoprotectants of the present disclosure can include, but are not limited to sucrose, trehalose, lactose, glycerol, dextrose, raffinose and/or mannitol. Trehalose is listed by the Food and Drug Administration as being generally regarded as safe (GRAS) and is commonly used in commercial pharmaceutical formulations.

Bulking agents

[01069] The disclosure also includes pharmaceutical compositions that comprise a formulation of the polynucleotide described herein, *i.e.*, a polynucleotide comprising an ORF encoding an MCM polypeptide, with bulking agents. As used herein, the term "bulking agent" refers to one or more agents included in formulations to impart a desired consistency to the formulation and/or stabilization of formulation components. In some embodiments, bulking agents are included in lyophilized polynucleotide formulations to yield a "pharmaceutically elegant" cake, stabilizing the lyophilized polynucleotides during long term (*e.g.*, 36 month) storage. Bulking agents of the present disclosure can include, but are not limited to sucrose, trehalose, mannitol, glycine, lactose and/or raffinose. In some embodiments, combinations of cryoprotectants and bulking agents (for example, sucrose/glycine or trehalose/mannitol) can be included to both stabilize polynucleotides during freezing and provide a bulking agent for lyophilization.

[01070] Non-limiting examples of formulations and methods for formulating the polynucleotides of the present disclosure are also provided in International Publication No WO2013090648 filed December 14, 2012, the contents of which are incorporated herein by reference in their entirety.

Inactive Ingredients

[01071] The disclosure also includes pharmaceutical compositions that comprise a formulation of the polynucleotide described herein, *i.e.*, a polynucleotide comprising an ORF encoding an MCM polypeptide, with at least one excipient that is an inactive ingredient. As used

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herein, the term "inactive ingredient" refers to one or more inactive agents included in formulations. In some embodiments, all, none or some of the inactive ingredients that can be used in the formulations of the present disclosure can be approved by the US Food and Drug Administration (FDA). A non-exhaustive list of inactive ingredients and the routes of administration the inactive ingredients can be formulated in are described in International Application No. PCT/US2014/027077.

VII. Method of Use of Polynucleotides

[01072] The polynucleotides of the present disclosure (*i.e.*, a polynucleotide comprising an ORF encoding an MCM polypeptide) can be administered by any route that results in a therapeutically effective outcome. These include, but are not limited to enteral (into the intestine), gastroenteral, epidural (into the dura matter), oral (by way of the mouth), transdermal, peridural, intracerebral (into the cerebrum), intracerebroventricular (into the cerebral ventricles), epicutaneous (application onto the skin), intradermal, (into the skin itself), subcutaneous (under the skin), nasal administration (through the nose), intravenous (into a vein), intravenous bolus, intravenous drip, intraarterial (into an artery), intramuscular (into a muscle), intracardiac (into the heart), intraosseous infusion (into the bone marrow), intrathecal (into the spinal canal), intraperitoneal, (infusion or injection into the peritoneum), intravesical infusion, intravitreal, (through the eye), intracavernous injection (into a pathologic cavity) intracavitary (into the base of the penis), intravaginal administration, intrauterine, extra-amniotic administration, transdermal (diffusion through the intact skin for systemic distribution), transmucosal (diffusion through a mucous membrane), transvaginal, insufflation (snorting), sublingual, sublabial, enema, eye drops (onto the conjunctiva), in ear drops, auricular (in or by way of the ear), buccal (directed toward the cheek), conjunctival, cutaneous, dental (to a tooth or teeth), electro-osmosis, endocervical, endosinusial, endotracheal, extracorporeal, hemodialysis, infiltration, interstitial, intra-abdominal, intra-amniotic, intra-articular, intrabiliary, intrabronchial, intrabursal, intracartilaginous (within a cartilage), intracaudal (within the cauda equine), intracisternal (within the cisterna magna cerebellomedularis), intracorneal (within the cornea), dental intracornal, intracoronary (within the coronary arteries), intracorporus cavernosum (within the dilatable spaces of the corporus cavernosa of the penis), intradiscal (within a disc), intraductal (within a duct of a gland), intraduodenal (within the duodenum), intradural (within or beneath the dura), intraepidermal (to the epidermis), intraesophageal (to the esophagus), intragastric (within

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the stomach), intragingival (within the gingivae), intraileal (within the distal portion of the small intestine), intralesional (within or introduced directly to a localized lesion), intraluminal (within a lumen of a tube), intralymphatic (within the lymph), intramedullary (within the marrow cavity of a bone), intrameningeal (within the meninges), intraocular (within the eye), intraovarian (within the ovary), intrapericardial (within the pericardium), intrapleural (within the pleura), intraprostatic (within the prostate gland), intrapulmonary (within the lungs or its bronchi), intrasinal (within the nasal or periorbital sinuses), intraspinal (within the vertebral column), intrasynovial (within the synovial cavity of a joint), intratendinous (within a tendon), intratesticular (within the testicle), intrathecal (within the cerebrospinal fluid at any level of the cerebrospinal axis), intrathoracic (within the thorax), intratubular (within the tubules of an organ), intratumor (within a tumor), intratympanic (within the aurus media), intravascular (within a vessel or vessels), intraventricular (within a ventricle), iontophoresis (by means of electric current where ions of soluble salts migrate into the tissues of the body), irrigation (to bathe or flush open wounds or body cavities), laryngeal (directly upon the larynx), nasogastric (through the nose and into the stomach), occlusive dressing technique (topical route administration that is then covered by a dressing that occludes the area), ophthalmic (to the external eye), oropharyngeal (directly to the mouth and pharynx), parenteral, percutaneous, periarticular, peridural, perineural, periodontal, rectal, respiratory (within the respiratory tract by inhaling orally or nasally for local or systemic effect), retrobulbar (behind the pons or behind the eyeball), intramyocardial (entering the myocardium), soft tissue, subarachnoid, subconjunctival, submucosal, topical, transplacental (through or across the placenta), transtracheal (through the wall of the trachea), transtympanic (across or through the tympanic cavity), ureteral (to the ureter), urethral (to the urethra), vaginal, caudal block, diagnostic, nerve block, biliary perfusion, cardiac perfusion, photopheresis or spinal. In specific embodiments, compositions can be administered in a way that allows them cross the blood-brain barrier, vascular barrier, or other epithelial barrier. In some embodiments, a formulation for a route of administration can include at least one inactive ingredient.

[01073] The polynucleotides of the present disclosure can be delivered to a cell naked. As used herein in, "naked" refers to delivering polynucleotides free from agents that promote transfection. For example, the polynucleotides delivered to the cell can contain no modifications. The naked polynucleotides can be delivered to the cell using routes of administration known in the art and described herein.

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[01074] The polynucleotides of the present disclosure can be formulated, using the methods described herein. The formulations can contain polynucleotides that can be modified and/or unmodified. The formulations can further include, but are not limited to, cell penetration agents, a pharmaceutically acceptable carrier, a delivery agent, a bioerodible or biocompatible polymer, a solvent, and a sustained-release delivery depot. The formulated polynucleotides can be delivered to the cell using routes of administration known in the art and described herein.

[01075] The compositions can also be formulated for direct delivery to an organ or tissue in any of several ways in the art including, but not limited to, direct soaking or bathing, via a catheter, by gels, powder, ointments, creams, gels, lotions, and/or drops, by using substrates such as fabric or biodegradable materials coated or impregnated with the compositions, and the like.

Parenteral and Injectable Administration

[01076] The present disclosure encompasses the delivery of polynucleotides of the disclosure (*i.e.*, a polynucleotide comprising an ORF encoding an MCM polypeptide) in forms suitable for parenteral and injectable administration. Liquid dosage forms for parenteral administration include, but are not limited to, pharmaceutically acceptable emulsions, microemulsions, solutions, suspensions, syrups, and/or elixirs. In addition to active ingredients, liquid dosage forms can comprise inert diluents commonly used in the art such as, for example, water or other solvents, solubilizing agents and emulsifiers such as ethyl alcohol, isopropyl alcohol, ethyl carbonate, ethyl acetate, benzyl alcohol, benzyl benzoate, propylene glycol, 1,3-butylene glycol, dimethylformamide, oils (in particular, cottonseed, groundnut, corn, germ, olive, castor, and sesame oils), glycerol, tetrahydrofurfuryl alcohol, polyethylene glycols and fatty acid esters of sorbitan, and mixtures thereof. Besides inert diluents, oral compositions can include adjuvants such as wetting agents, emulsifying and suspending agents, sweetening, flavoring, and/or perfuming agents. In certain embodiments for parenteral administration, compositions are mixed with solubilizing agents such as CREMOPHOR®, alcohols, oils, modified oils, glycols, polysorbates, cyclodextrins, polymers, and/or combinations thereof.

[01077] A pharmaceutical composition for parenteral administration can comprise at least one inactive ingredient. Any or none of the inactive ingredients used can have been approved by the US Food and Drug Administration (FDA). A non-exhaustive list of inactive ingredients for use in pharmaceutical compositions for parenteral administration includes hydrochloric acid, mannitol, nitrogen, sodium acetate, sodium chloride and sodium hydroxide.

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[01078] Injectable preparations, for example, sterile injectable aqueous or oleaginous suspensions can be formulated according to the known art using suitable dispersing agents, wetting agents, and/or suspending agents. Sterile injectable preparations can be sterile injectable solutions, suspensions, and/or emulsions in nontoxic parenterally acceptable diluents and/or solvents, for example, as a solution in 1,3-butanediol. Among the acceptable vehicles and solvents that can be employed are water, Ringer's solution, U.S.P., and isotonic sodium chloride solution. Sterile, fixed oils are conventionally employed as a solvent or suspending medium. For this purpose any bland fixed oil can be employed including synthetic mono- or diglycerides. Fatty acids such as oleic acid can be used in the preparation of injectables. The sterile formulation can also comprise adjuvants such as local anesthetics, preservatives and buffering agents.

[01079] Injectable formulations can be sterilized, for example, by filtration through a bacterial-retaining filter, and/or by incorporating sterilizing agents in the form of sterile solid compositions that can be dissolved or dispersed in sterile water or other sterile injectable medium prior to use.

[01080] Injectable formulations can be for direct injection into a region of a tissue, organ and/or subject. As a non-limiting example, a tissue, organ and/or subject can be directly injected a formulation by intramyocardial injection into the ischemic region. (*See, e.g.,* Zangi et al. Nature Biotechnology 2013; the contents of which are herein incorporated by reference in its entirety).

[01081] In order to prolong the effect of an active ingredient, it is often desirable to slow the absorption of the active ingredient from subcutaneous or intramuscular injection. This can be accomplished by the use of a liquid suspension of crystalline or amorphous material with poor water solubility. The rate of absorption of the drug then depends upon its rate of dissolution which, in turn, can depend upon crystal size and crystalline form. Alternatively, delayed absorption of a parenterally administered drug form is accomplished by dissolving or suspending the drug in an oil vehicle. Injectable depot forms are made by forming microencapsule matrices of the drug in biodegradable polymers such as polylactide-polyglycolide. Depending upon the ratio of drug to polymer and the nature of the particular polymer employed, the rate of drug release can be controlled. Examples of other biodegradable polymers include poly(orthoesters) and poly(anhydrides). Depot injectable formulations are prepared by entrapping the drug in liposomes or microemulsions that are compatible with body tissues.

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Therapeutic Use

[01082] The polynucleotides of the present disclosure are used in the preparation, manufacture and therapeutic use of polynucleotide molecules comprising an mRNA encoding a methylmalonyl-CoA mutase (MCM) polypeptide. In some embodiments, the polynucleotides of the present disclosure can be used to treat and/or prevent MCM-related diseases, disorders or conditions. Typically, but not exclusively, the polynucleotides of the present disclosure can be used to treat and/or prevent methylmalonic acidemia. In some embodiments, the nucleotides are used in methods for reducing the levels of methylmalonic acid in a subject in need thereof. For instance, one aspect of the disclosure provides a method of alleviating the symptoms of methylmalonic acidemia in a subject via the administration of a composition comprising a polynucleotide encoding MCM to that subject.

[01083] In some embodiments, the polynucleotides of the present disclosure are used to reduce the level of a metabolite associated with methylmalonic acidemia, the method comprising administering to the subject an effective amount of a polynucleotide encoding an MCM polypeptide. In some embodiments, the administration of an effective amount of a polynucleotide reduces the levels of a biomarker of methylmalonic acidemia such as methylmalonic acid, propionyl-carnitine, acetyl-carnitine, propionyl-CoA, D-methylmalonyl-CoA, L-methylmalonyl-CoA, or a combination thereof in a subject. In some embodiments, the administration of the polynucleotide results in reduction in the level of one or more biomarkers of methylmalonic acidemia within a short period of time after administration of the polynucleotide.

[01084] In some embodiments, the administration of the polynucleotide results in expression of methylmalonyl-CoA mutase in cells of the subject. In some embodiments, administering the polynucleotide results in an increase of MCM enzymatic activity in the subject. For example, in some embodiments, the polynucleotides of the present disclosure are used in methods of administering a composition comprising an mRNA encoding MCM to a subject, wherein the method results in an increase of MCM enzymatic activity in at least some cells of a subject. In some embodiments, the administration of a composition comprising an mRNA encoding MCM to a subject results in an increase of MCM enzymatic activity in cells of subject by at least 10%, at least 25%, at least 50%, at least 75%, at least 100%, or by more than 100%. In some embodiments, the administration of a composition comprising an mRNA encoding MCM to a subject results in an increase of MCM enzymatic activity in cells subject to a level at least 10%,

at least 20%, at least 30%, at least 40%, at least 50%, at least 60%, at least 70%, at least 80%, at least 90%, or to 100% or more of the activity level expected in a normal subject, *e.g.*, a normal human not suffering from MMA. In some embodiments, the administration of the polynucleotide results in expression of methylmalonyl-CoA mutase in at least some of the cells of a subject that persists for a period of time sufficient to allow significant methylmalonyl-CoA metabolism to occur.

[01085] In some embodiments, the expression of the encoded polypeptide is increased. In some embodiments, the IVT polynucleotide increases MCM expression levels in cells when introduced into those cells, *e.g.,* by 20-50%, at least 20%, at least 25%, at least 30%, at least 35%, at least 40%, at least 45%, or at least 50%.

[01086] In some embodiments, the method or use comprises administering a polynucleotide, *e.g.,* mRNA, comprising an ORF having significant sequence similarity to a polynucleotide selected from the group of SEQ ID NOs: 1-207, 732-765, and 772, wherein the ORF encodes an MCM polypeptide. Other aspects of the present disclosure relate to transplantation of cells containing polynucleotides to a mammalian subject. Administration of cells to mammalian subjects is known to those of ordinary skill in the art, and includes, but is not limited to, local implantation (*e.g.,* topical or subcutaneous administration), organ delivery or systemic injection (*e.g.,* intravenous injection or inhalation), and the formulation of cells in pharmaceutically acceptable carriers. Such compositions containing polynucleotides can be formulated for administration intramuscularly, transarterially, intraperitoneally, intravenously, intranasally, subcutaneously, endoscopically, transdermally, or intrathecally.

[01087] In some embodiments, the composition can be formulated for extended release.

[01088] In some embodiments, the present methods are able to catalyze the conversion of at least 0.1%, 0.5%, 1%, 2%, 2.5%, 5%, 10%, 20%, 25%, 30%, 35% 40%, 45%, 50%, 55%, 60%, 65%, 70%, 75%, 80%, 85% or more of L-methylmalonyl-CoA to succinyl-CoA. In some embodiments, a the methods are able to catalyze the conversion of a range of from 0.1% to 5%, 5% to 25%, 10% to 25%, 10% to 30%, 20% to 40%, 10% to 50%, 20% to 50%, 10% to 75%, 20% to 75%, 30% to 75%, 30% to 85%, or 25% to 100% of L-methylmalonyl-CoA to succinyl-CoA.

[01089] In some embodiments, the methods achieve at least 0.1%, 0.5%, 1%, 2%, 2.5%, 5%, 10%, 20%, 25%, 30%, 35% 40%, 45%, 50%, 55%, 60%, 65%, 70%, 75%, 80%, 85% or more of the enzymatic activity sufficient for the synthesis of AdoCbl. In some embodiments, the methods

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achieve a range of from 0.1% to 5%, 5% to 25%, 10% to 25%, 10% to 30%, 20% to 40%, 10% to 50%, 20% to 50%, 10% to 75%, 20% to 75%, 30% to 75%, 30% to 85%, or 25% to 100% of the enzymatic activity sufficient for the synthesis of Adenosylcobalamin (AdoCbl).

[01090] In some embodiments, the methods achieve sufficient enzymatic activity to synthesize at least 0.1%, 0.5%, 1%, 2%, 2.5%, 5%, 10%, 20%, 25%, 30%, 35% 40%, 45%, 50%, 55%, 60%, 65%, 70%, 75%, 80%, 85% or more of the active form of Adenosylcobalamin (AdoCbl), found in healthy individuals. In some embodiments, the methods achieve sufficient enzymatic activity to synthesize a range of from 0.1% to 5%, 5% to 25%, 10% to 25%, 10% to 30%, 20% to 40%, 10% to 50%, 20% to 50%, 10% to 75%, 20% to 75%, 30% to 75%, 30% to 85%, or 25% to 100% of the active form of AdoCbl found in healthy individuals.

[01091] In some embodiments, the methods involve the administration of a polynucleotide in combination with another therapy to a patient in need thereof. Such methods can involve administering a polynucleotide prior to, concurrent with, or subsequent to administration of the additional therapy. In some embodiments, such methods have an additive or synergistic effect. In some embodiments, presented herein is a method for treating MMA, comprising administering to a patient in need thereof an effective amount of a polynucleotide (e.g., mRNA) encoding an MCM polypeptide and an effective amount of another therapy. Examples of such other therapies include, but are not limited to, cobalamin supplements, camitine supplements and antibiotics. In another specific embodiment, presented herein is a method for treating MMA, comprising administering to a patient in need thereof an effective amount of a polynucleotide (e.g., mRNA) encoding an MCM polypeptide and maintaining a low-protein diet.

[01092] In some embodiments, the concentration of methylmalonic acid in biological specimens (*e.g.*, blood, plasma, serum, cerebral spinal fluid, urine, or any other biofluids) of a patient is monitored before, during and/or after a course of treatment involving the administration of a polynucleotide (e.g., mRNA) encoding an MCM polypeptide or a pharmaceutical composition thereof to the patient. In some embodiments, the concentration of methylcitrate in biological specimens (e.g., urine, blood, plasma, serum, cerebral spinal fluid, or any other biofluids) of a patient is monitored before, during and/or after a course of treatment involving the administration of a polynucleotide (e.g., mRNA) encoding an MCM polypeptide or a pharmaceutical composition thereof to the patient. In some embodiments, the concentration of propionylcarnitine in biological specimens (e.g., blood, plasma, serum, cerebral spinal fluid, urine, or any other biofluids) of a patient is monitored before, during and/or after a course of

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treatment involving the administration of a polynucleotide (e.g., mRNA) encoding an MCM polypeptide or a pharmaceutical composition thereof to the patient. In some embodiments, erythrocyte odd long-chain fatty acids (OLCFAs) levels are monitored before, during and/or after a course of treatment involving the administration of a polynucleotide (e.g., mRNA) encoding an MCM polypeptide or a pharmaceutical composition thereof to a patient. In some embodiments, the urinary urea:methylmalonic acid ratio is monitored before, during and/or after a course of treatment involving the administration of a polynucleotide (e.g., mRNA) encoding an MCM polypeptide or a pharmaceutical composition thereof to a patient. The dosage, frequency and/or length of administration of a polynucleotide (e.g., mRNA) encoding an MCM polypeptide or a pharmaceutical composition thereof to a patient may be modified as a result of the concentration of methylmalonic acid, methylcitrate, or propionylcarnitine, erythrocyte odd long-chain fatty acids (OLCFAs) levels, or the urinary urea:methylmalonic acid ratio. Alternatively, changes in one or more of these monitoring parameters (e.g., concentration of methylmalonic acid, methylcitrate, or propionylcarnitine, erythrocyte odd long-chain fatty acids (OLCFAs) levels, or the urinary urea:methylmalonic acid ratio) might indicate that the course of treatment involving the administration of the polynucleotide (e.g., mRNA) encoding an MCM polypeptide or pharmaceutical composition thereof is effective in treating MMA.

[01093] In a specific embodiment, presented herein is a method for treating MMA, comprising: (a) administering to a patient in need thereof one or more doses of a polynucleotide (e.g., mRNA) encoding an MCM polypeptide or a pharmaceutical composition thereof; and (b) monitoring the concentration of methylmalonic acid, methylcitrate, or propionylcarnitine (e.g., detected in biological specimens such as plasma, serum, cerebral spinal fluid, urine, or other biofluids), erythrocyte odd long-chain fatty acids (OLCFAs) levels, or the urinary urea:methylmalonic acid ratio before and/or after step (a). In some embodiments, step (b) comprises monitoring the concentration of methylmalonic acid. In some embodiments, step (b) comprises monitoring the concentration of methylmalonic acid, methylcitrate and/or propionylcarnitine. In some embodiments, the monitoring step (b) is carried out before and/or after a certain number of doses (e.g., 1, 2, 4, 6, 8, 10, 12, 14, 15, or 20 doses, or more doses; or 2 to 4, 2 to 8, 2 to 20 or 2 to 30 doses) or after a certain time period (e.g., 1, 2, 3, 4, 5, 6, or 7 days; or 1, 2, 3, 4, 5, 10, 15, 20, 30, 40, 45, 48, or 50 weeks) of administering the polynucleotide (e.g., mRNA) encoding an MCM polypeptide. In some embodiments, one or more of these monitoring parameters are detected prior to administration of the polynucleotide (e.g., mRNA) encoding an

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MCM polypeptide or pharmaceutical composition thereof. In some embodiments, a decrease in the concentration of methylmalonic acid, methylcitrate, or propionylcamitine, or a decrease in erythrocyte odd long-chain fatty acids (OLCFAs) levels following administration of the polynucleotide or pharmaceutical composition thereof indicates that the course of treatment is effective for treating MMA. In some embodiments, an increase in the urinary urea:methylmalonic acid ratio following administration of the polynucleotide (e.g., mRNA) encoding an MCM polypeptide or pharmaceutical composition thereof indicates that the course of treatment is effective for treating MMA.

[01094] The concentration of methylmalonic acid, methylcitrate, or propionylcamitine, erythrocyte odd long-chain fatty acids (OLCFAs) levels, or the urinary urea:methylmalonic acid ratio of a patient may be detected by any technique known to one of skill in the art. In some embodiments, the method for detecting the concentration of methylmalonic acid, methylcitrate, or propionylcarnitine in a patient involves obtaining a tissue or fluid sample from the patient and detecting the concentration of methylmalonic acid, methylcitrate, propionylcarnitine or urea in the biological sample (e.g., from plasma serum sample, cerebral spinal fluid, urine, or other biofluids) that has been subjected to certain types of treatment (e.g., centrifugation) and detection by use of, e.g., standard gas chromatography/mass spectroscopy (GC/MS) stable-isotope dilution methods, positive chemical ionization gas chromatography mass spectrometry (CI GC-MS) spectroscopic techniques (e.g., UV spectroscopy) or high pressure liquid chromatography (HPLC).

[01095] In some embodiments, the methods for treating MMA provided herein alleviate or manage one, two or more symptoms associated with MMA. Alleviating or managing one, two or more symptoms of MMA may be used as a clinical endpoint for efficacy of a polynucleotide for treating MMA. In some embodiments, the methods for treating MMA provided herein reduce the duration and/or severity of one or more symptoms associated with MMA. In some embodiments, the methods for treating MMA provided herein inhibit the onset, progression and/or recurrence of one or more symptoms associated with MMA. In some embodiments, the methods for treating MMA provided herein reduce the number of symptoms associated with MMA. In some embodiments, the methods for treating MMA provided herein inhibit or reduce the progression of one or more symptoms associated therewith.

[01096] Symptoms associated with MMA include, but are not limited to: apnea, hyperammonemia, metabolic acidosis, lethargy, vomiting, dehydration, hypotonia,

hypoglycemia, repeated yeast infections, renal impairment, mental retardation, developmental delays, seizures, movement disorders, progressive encephalopathy, facial dysmorphism (e.g., high forehead, broad nasal bridge, epicanthal folds, long smooth philtrum, or triangular mouth), stroke, skin lesions (e.g., moniliasis), occasional hepatomegaly, acute onset of choreoathetosis, dystonia, dysphagia, dysarthria, growth problems (e.g., growth failure), kidney disease or failure, tissue damage, feeding problems, cognitive disabilities, metabolic attacks triggered by common infections and reduced glomerular filtration rate (GFR).

[01097] In some embodiments, the methods for treating MMA provided herein reduce or eliminate one, two, or more of the following: metabolic acidosis, developmental delays, movement disorders, metabolic decompensation episodes (e.g., frequency and/or numbers of episodes), skin lesions, hypotonia, seizures, and renal impairment, associated with MMA. In some embodiments, the methods for treating MMA provided herein improve renal function, development, cognitive ability and movement in a patient diagnosed with MMA.

[01098] In some embodiments, the methods for treating MMA provided herein reduce hospitalization (e.g., the frequency or duration of hospitalization) of a patient diagnosed with MMA. In some embodiments, the methods for treating MMA provided herein reduce hospitalization length of a patient diagnosed with MMA. In some embodiments, the methods for treating MMA provided herein decrease the hospitalization rate.

[01099] In some embodiments, the methods provided herein increase the survival of a patient diagnosed with MMA. In some embodiments, the methods for treating MMA provided herein reduce the mortality of subjects diagnosed with MMA. In some embodiments, the methods for treating MMA provided herein increase symptom-free survival of MMA patients. In some embodiments, the methods for treating MMA provided herein do not cure MMA in patients, but prevent the progression or worsening of the disease. In some embodiments, the methods for treating MMA provided herein enhance or improve the therapeutic effect of another therapy.

[01100] In some embodiments, the methods for treating MMA provided herein reduce the concentration of plasma methylmalonic acid in a subject by at least about 5%, 10%, 15%, 20%, 25%, 30%, 35%, 40%, 45%, 50%, 55%, 60%, 65%, 80%, 85%, 90%, 95%, or 100%, or in a range of from 5% to 50%, 10% to 50%, 20% to 50%, 20% to 75%, 25% to 75%, 25% to 90% or 10% to 99% relative to the respective concentration prior to administration of a polynucleotide (e.g., mRNA) encoding an MCM polypeptide, as assessed by methods well known in the art or described herein. In some embodiments, the methods for treating MMA provided herein reduce

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the concentration of urinary methylmalonic acid in a subject by at least about 5%, 10%, 15%, 20%, 25%, 30%, 35%, 40%, 45%, 50%, 55%, 60%, 65%, 80%, 85%, 90%, 95%, or 100%, or in a range of from 5% to 50%, 10% to 50%, 20% to 50%, 20% to 75%, 25% to 75%, 25% to 90% or 10% to 99% relative to the respective concentration prior to administration of a polynucleotide (e.g., mRNA) encoding an MCM polypeptide, as assessed by methods well known in the art or described herein.

[01101] In some embodiments, the methods for treating MMA provided herein reduce the concentration of a metabolite of methylmalonic acid in a subject by at least about 5%, 10%, 15%, 20%, 25%, 30%, 35%, 40%, 45%, 50%, 55%, 60%, 65%, 80%, 85%, 90%, 95%, or 100%, or in a range of from 5% to 50%, 10% to 50%, 20% to 50%, 20% to 75%, 25% to 75%, 25% to 90% or 10% to 99% relative to the respective concentration prior to administration of a polynucleotide (e.g., mRNA) encoding an MCM polypeptide, as assessed by methods well known in the art or described herein. In some embodiments, the methods for treating MMA provided herein reduce the concentration of plasma propionylcamitine in a subject by at least about 5%, 10%, 15%, 20%, 25%, 30%, 35%, 40%, 45%, 50%, 55%, 60%, 65%, 80%, 85%, 90%, 95%, or 100%, or in a range of from 5% to 50%, 10% to 50%, 20% to 50%, 20% to 75%, 25% to 75%, 25% to 90% or 10% to 99% relative to the respective concentration prior to administration of a polynucleotide (e.g., mRNA) encoding an MCM polypeptide, as assessed by methods well known in the art or described herein. In some embodiments, the methods for treating MMA provided herein reduce the concentration of urinary methylcitrate in a subject by at least about 5%, 10%, 15%, 20%, 25%, 30%, 35%, 40%, 45%, 50%, 55%, 60%, 65%, 80%, 85%, 90%, 95%, or 100%, or in a range of from 10% to 50%, 20% to 50%, 20% to 75%, 25% to 75%, 25% to 90% or 10% to 99% relative to the respective concentration prior to administration of a polynucleotide (e.g., mRNA) encoding an MCM polypeptide, as assessed by methods well known in the art or described herein.

[01102] In some embodiments, the methods for treating MMA provided herein reduce the erythrocyte odd-numbered long-chain fatty acids levels in a subject by at least about 5%, 10%, 15%, 20%, 25%, 30%, 35%, 40%, 45%, 50%, 55%, 60%, 65%, 80%, 85%, 90%, 95%, or 100%, or in a range of from 10% to 50%, 20% to 50%, 20% to 75%, 25% to 75%, 25% to 90% or 10% to 99% relative to the respective concentration prior to administration of a polynucleotide (e.g., mRNA) encoding an MCM polypeptide, as assessed by methods well known in the art or described herein. In some embodiments, the methods for treating MMA provided herein increase

the urinary urea:methylmalonic acid ratio in a subject by at least about 5%, 10%, 15%, 20%, 25%, 30%, 35%, 40%, 45%, 50%, 55%, 60%, 65%, 80%, 85%, 90%, 95%, or 100%, or in a range of from 10% to 50%, 20% to 50%, 20% to 75%, 25% to 75%, 25% to 90% or 10% to 99% relative to the respective concentration prior to administration of a polynucleotide (e.g., mRNA) encoding an MCM polypeptide, as assessed by methods well known in the art or described herein.

[01103] In some embodiments, the methods for treating MMA provided herein increase the cellular enzyme activity in a subject by at least about 5%, 10%, 15%, 20%, 25%, 30%, 35%, 40%, 45%, 50%, 55%, 60%, 65%, 80%, 85%, 90%, 95%, or 100%, or in a range of from 10% to 50%, 20% to 50%, 20% to 75%, 25% to 75%, 25% to 90% or 10% to 99% relative to the respective concentration prior to administration of a polynucleotide (e.g., mRNA) encoding an MCM polypeptide, as assessed by methods well known in the art or described herein. In certain embodiment, the increase in cellular enzyme activity is determined by obtaining cells (e.g., fibroblasts or lymphocytes) from the subject, culturing the cells in the presence or absence of a polynucleotide, and comparing the cellular enzyme activity in the presence of the polynucleotide (e.g., mRNA) encoding an MCM polypeptide to the cellular enzyme activity in the absence of the polynucleotide. Techniques for measuring cellular enzyme activity are known in the art and described herein (see, e.g., Section 6, infra).

[01104] In some aspects, the methods for treating MMA provided herein improve or developmental or cognitive function in a subject. In some aspects, the methods for treating MMA provided herein improve control of muscle contractions by a subject as assessed by methods well known in the art. In some embodiments, the methods for treating MMA provided herein improve renal function In some embodiments, the methods for treating MMA provided herein decrease the need for kidney transplant, liver transplant or both. In some embodiments, the methods for treating MMA provided herein decrease the requirement for hospitalization. In some embodiments, the methods for treating MMA provided herein decrease the length and/or frequency of hospitalization.

[01105] In some embodiments, the subject is a male human. In some embodiments, the subject is a female human. In some embodiments, a subject treated for MMA in accordance with the methods provided herein is a fetus. In accordance with this embodiment, a pregnant female may be administered a polynucleotide in a manner that permits the polynucleotide to pass through the placenta to the fetus. Alternatively, the polynucleotide may be administered directly

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to the fetus by, e.g., injection. In some embodiments, a subject treated for MMA in accordance with the methods provided herein is a human infant. In one embodiment, a subject treated for MMA in accordance with the methods provided herein is an elderly human. In another embodiment, a subject treated for MMA in accordance with the methods provided herein is a human adult. In another embodiment, a subject treated for MMA in accordance with the methods provided herein is a human child. In another embodiment, a subject treated for MMA in accordance with the methods provided herein is a human toddler.

[01106] In a specific embodiment, a subject treated for MMA in accordance with the methods provided herein is a human that is less than 5 years old. In another specific embodiment, a subject treated for MMA in accordance with the methods provided herein is a human that is older than 5 years old. In a specific embodiment, a subject treated for MMA in accordance with the methods provided herein is a human that is less than 5 years old, is older than 5 years old, is 18 years old or is older than 18 years old.

[01107] In some embodiments, a subject treated for MMA in accordance with the methods provided herein is administered a polynucleotide (e.g., mRNA) encoding an MCM polypeptide or a pharmaceutical composition thereof, or a combination therapy before any adverse effects or intolerance to therapies other than the polynucleotide develops. In some embodiments, a subject treated for MMA in accordance with the methods provided herein is a refractory patient. In a certain embodiment, a refractory patient is an MMA patient that is refractory to a standard therapy (e.g., carnitine or cobalamin supplements).

[01108] In some embodiments, a subject treated for MMA in accordance with the methods provided herein is a human that has proven refractory to therapies other than treatment with a polynucleotide, but is no longer on these therapies. In some embodiments, a subject treated for MMA in accordance with the methods provided herein is a human already receiving one or more conventional MMA therapies, such as camitine supplements, cobalamin supplements, antibiotics, kidney transplant, and/or liver transplant. In some embodiments, a subject treated for MMA in accordance with the methods provided herein is a human on a low-protein diet. In some embodiments, a subject treated for MMA in accordance with the methods provided herein is a human on a diet that avoids substances containing isoleucine, threonine, methionine, and valine.

[01109] In some embodiments, a subject treated for MMA in accordance with the methods provided herein is a human susceptible to adverse reactions to conventional therapies. In some embodiments, a subject treated for MMA in accordance with the methods provided herein is a

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human that has not received a therapy, e.g., a carnitine supplement, a cobalamin supplement, an antibiotic, a kidney transplant, and/or a liver transplant, prior to the administration of a polynucleotide or a pharmaceutical composition thereof. In some embodiments, a subject treated for MMA in accordance with the methods provided herein is a human that has received a therapy prior to administration of a polynucleotide or a pharmaceutical composition thereof. In some embodiments, a subject treated for MMA in accordance with the methods provided herein is a human that has experienced adverse side effects to the prior therapy or the prior therapy was discontinued due to unacceptable levels of toxicity to the human.

[01110] In some embodiments, a subject treated for MMA in accordance with the methods provided herein is a human diagnosed with a complete (mut^0) or partial (mut^-) defect in methylmalonyl-CoA mutase (MCM). The gene encoding MCM is referred to as the MUT gene and is located on chromosome 6p21.1.

Dosage and Administration

[01111] In accordance with the methods for treating MMA provided herein, a polynucleotide (e.g., mRNA) encoding an MCM polypeptide or a pharmaceutical composition thereof can be administered to a subject in need thereof by a variety of routes in amounts which result in a beneficial or therapeutic effect. A polynucleotide (e.g., mRNA) encoding an MCM polypeptide or pharmaceutical composition thereof may be intravenously administered to a subject in need thereof in accordance with the methods for treating MMA provided herein.

[01112] In accordance with the methods for treating MMA provided herein that involve administration of a polynucleotide (e.g., mRNA) encoding an MCM polypeptide in combination with one or more additional therapies, the polynucleotide (e.g., mRNA) encoding an MCM polypeptide and one or more additional therapies may be administered by the same route or a different route of administration.

[01113] The dosage and frequency of administration of a polynucleotide (e.g., mRNA) encoding an MCM polypeptide or a pharmaceutical composition thereof is administered to a subject in need thereof in accordance with the methods for treating MMA provided herein will be efficacious while minimizing any side effects. The exact dosage and frequency of administration of a polynucleotide (e.g., mRNA) encoding an MCM polypeptide or a pharmaceutical composition thereof can be determined by a practitioner, in light of factors related to the subject that requires treatment. Factors which may be taken into account include

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the severity of the disease state, general health of the subject, age, weight, and gender of the subject, diet, time and frequency of administration, drug combination(s), reaction sensitivities, and tolerance/response to therapy. The dosage and frequency of administration of a polynucleotide (e.g., mRNA) encoding an MCM polypeptide or a pharmaceutical composition thereof may be adjusted over time to provide sufficient levels of the polynucleotide or to maintain the desired effect.

[01114] In some embodiments, a polynucleotide (e.g., mRNA) encoding an MCM polypeptide or a pharmaceutical composition thereof is administered to a subject in need thereof in accordance with the methods for treating MMA provided herein at a dosage and a frequency of administration that achieves one or more of the following: (i) the reduction or amelioration of the severity of one or more MMA symptoms; (ii) the reduction in the duration of one or more symptoms associated with MMA; (iii) the prevention in the recurrence of a symptom associated with MMA; (iv) the reduction in hospitalization of a subject; (v) a reduction in hospitalization length; (vi) the increase in the survival of a subject; (vii) the enhancement or improvement of the therapeutic effect of another therapy; (viii) an improvement in developmental or cognitive ability; (ix) a decrease in the frequency and/or number of metabolic decompensation episodes; (x) an improvement in control of muscle contraction; (xi) a reduction in mortality; (xii) an increase in the survival rate of patients; (xiii) a decrease in hospitalization rate; (xiv) the prevention of the development or onset of one or more symptoms associated with MMA; (xv) the reduction in the number of symptoms associated with MMA; (xvi) an decrease in the concentration of methylmalonic acid in biological fluids (e.g., plasma or urine); (xvii) a decrease in the concentration of metabolites of methylmalonic acid , such as propionylcarnitine or methylcitrate, in biological fluids (e.g., plasma or urine); (xviii) a decrease in erythrocyte odd-numbered long-chain fatty acid levels; (xix) an increase in the urinary urea:methylmalonic acid ratio; (xx) an increase in symptom-free survival of MMA patients; (xxi) an improvement in renal function; and (xxii) improvement in quality of life as assessed by methods well known in the art.

[01115] In some embodiments, a polynucleotide (e.g., mRNA) encoding an MCM polypeptide or a pharmaceutical composition thereof is administered to a subject in need thereof in accordance with the methods for treating MMA provided herein once in a day. In some embodiments, a polynucleotide (e.g., mRNA) encoding an MCM polypeptide or a pharmaceutical composition thereof is administered to a subject in need thereof in accordance with the methods for treating MMA provided herein once every two days. In some embodiments,

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a polynucleotide (e.g., mRNA) encoding an MCM polypeptide or a pharmaceutical composition thereof is administered to a subject in need thereof in accordance with the methods for treating MMA provided herein once every three days. In some embodiments, a polynucleotide (e.g., mRNA) encoding an MCM polypeptide or a pharmaceutical composition thereof is administered to a subject in need thereof in accordance with the methods for treating MMA provided herein once every four days. In some embodiments, a polynucleotide (e.g., mRNA) encoding an MCM polypeptide or a pharmaceutical composition thereof is administered to a subject in need thereof in accordance with the methods for treating MMA provided herein once every five days. In some embodiments, a polynucleotide (e.g., mRNA) encoding an MCM polypeptide or a pharmaceutical composition thereof is administered to a subject in need thereof in accordance with the methods for treating MMA provided herein once every six days. In some embodiments, a polynucleotide (e.g., mRNA) encoding an MCM polypeptide or a pharmaceutical composition thereof is administered to a subject in need thereof in accordance with the methods for treating MMA provided herein once every week. In some embodiments, a polynucleotide (e.g., mRNA) encoding an MCM polypeptide or a pharmaceutical composition thereof is administered to a subject in need thereof in accordance with the methods for treating MMA provided herein once every two weeks. In some embodiments, a polynucleotide (e.g., mRNA) encoding an MCM polypeptide or a pharmaceutical composition thereof is administered to a subject in need thereof in accordance with the methods for treating MMA provided herein once every three weeks. In some embodiments, a polynucleotide (e.g., mRNA) encoding an MCM polypeptide or a pharmaceutical composition thereof is administered to a subject in need thereof in accordance with the methods for treating MMA provided herein once every month. In some embodiments, a polynucleotide (e.g., mRNA) encoding an MCM polypeptide or a pharmaceutical composition thereof is administered to a subject in need thereof in accordance with the methods for treating MMA provided herein on a monthly schedule sufficient to maintain decreased symptoms in a MMA patient suffering therefrom. In some embodiments, provide herein are methods for continuous therapy wherein a polynucleotide (e.g., mRNA) encoding an MCM polypeptide or a pharmaceutical composition thereof is administered to a subject in need thereof in accordance with the methods for treating MMA provided herein daily for a certain period of time. In some embodiments, a polynucleotide (e.g., mRNA) encoding an MCM polypeptide or a pharmaceutical composition thereof is administered continuously in subsequent 24 hour periods daily, weekly, monthly or yearly.

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[01116] Treatment periods for a course of therapy can span one week, two weeks, three weeks, four weeks, five weeks, six weeks, seven weeks, eight weeks, nine weeks, ten weeks, eleven weeks, twelve weeks, thirteen weeks, fourteen weeks, four months, five months, six months, seven months, eight months, nine months, ten months, eleven months, one year, two years, three years, four years, five years or longer. The treatment periods can be interrupted by periods of rest which can span a day, one week, two weeks, three weeks, four weeks, five weeks, six weeks, seven weeks, eight weeks, nine weeks, ten weeks, eleven weeks, twelve weeks, thirteen weeks, fourteen weeks, four months, five months, six months, seven months, eight months, nine months, ten months, eleven months, one year, two years, three years, four years, five years or longer. Such determinations can be made by one skilled in the art (e.g., a physician). In some embodiments, treatment is intermittent, with periods of treatment being followed by periods of no treatment. Continuous treatment can be interrupted by one or more days, months, weeks or years. Continuous treatment can also be followed by a rest period lasting one or more days, months, weeks or years, with continuous treatment then resuming after the rest period.

[01117] In a particular embodiment, a polynucleotide or a pharmaceutical composition thereof is administered in a dose of about 0.01-10 mg/kg. In a particular embodiment, a polynucleotide or a pharmaceutical composition thereof is administered in a dose of about 0.01 mg/kg, 0.02 mg/kg, 0.03 mg/kg, 0.04 mg/kg, 0.05 mg/kg, 0.06 mg/kg , 0.07 mg/kg, 0.08, mg/kg , 0.09 mg/kg , 0.1 mg/kg, about 0.2 mg/kg, about 0.3 mg/kg, about 0.4 mg/kg, about 0.5 mg/kg, about 0.6 mg/kg, about 0.7 mg/kg, about 0.8 mg/kg, 0.9 mg/kg, 1.0 mg/kg, about 1.1 mg/kg, 1.2 mg/kg, 1.3 mg/kg, about 1.4 mg/kg, 1.5 mg/kg, 1.6 mg/kg, about 1.7 mg/kg, 1.8 mg/kg, 1.9 mg/kg, about 2.0 mg/kg, 2.1 mg/kg, 2.2 mg/kg, about 2.3 mg/kg, 2.4 mg/kg, 2.5 mg/kg, 3.0 mg/kg, 3.5 mg/kg, 4.0 mg/kg or about 5.0 mg/kg. In a particular embodiment, a polynucleotide or a pharmaceutical composition thereof is administered in a dose of about 0.01-2 mg/kg. In a particular embodiment, a polynucleotide or a pharmaceutical composition thereof is administered in a dose of about 0.02-1 mg/kg. In a particular embodiment, a polynucleotide or a pharmaceutical composition thereof is administered in a dose of about 0.02-1 mg/kg. In a particular embodiment, a polynucleotide or a pharmaceutical composition thereof is administered in a dose of about 0.02-0.5 mg/kg. In a particular embodiment, a polynucleotide or a pharmaceutical composition thereof is administered in a dose of about 0.03-0.5 mg/kg. In a particular embodiment, a polynucleotide or a pharmaceutical composition thereof is administered

in a dose of about 0.04-0.5 mg/kg. In a particular embodiment, a polynucleotide or a pharmaceutical composition thereof is administered in a dose of about 0.05-0.5 mg/kg.

[01118] In a particular embodiment, a polynucleotide or a pharmaceutical composition thereof is administered in a dose of about 0.02-0.5 mg/kg. In a particular embodiment, a polynucleotide or a pharmaceutical composition thereof is administered in a dose of about 0.02-0.1 or 0.2 mg/kg. In a particular embodiment, a polynucleotide or a pharmaceutical composition thereof is administered in a dose of about 0.02-0.1 or 0.2 mg/kg. In a particular embodiment, a polynucleotide or a pharmaceutical composition thereof is administered in a dose of about 0.03-0.1 or 0.2 mg/kg. In a particular embodiment, a polynucleotide or a pharmaceutical composition thereof is administered in a dose of about 0.04-0.1 or 0.2 mg/kg. In a particular embodiment, a polynucleotide or a pharmaceutical composition thereof is administered in a dose of about 0.05-0.1 or 0.2 mg/kg.

[01119] In other embodiments, an effective dose for the polynucleotide of the disclosure is 0.1 mg/kg to 1.0 mg/kg, 0.1 mg/kg to 10 mg/kg, 0.1 mg/kg to 2 mg/kg, 0.1 mg/kg to 5 mg/kg, 1 mg/kg to 5 mg/kg, or 1 mg/kg to 3 mg/kg. In some embodiments, the effective dose is sufficient to reduce the plasma MMA level after the administration at least 70%, at least 75%, at least 80%, at least 85%, at least 90%, or at least 95% compared to the plasma MMA level prior to the administration. In other embodiments, the plasma MMA level is reduced about 75% to 85% compared to the plasma MMA level prior to the administration.

[01120] In other embodiments, the effective dose is siffucient to maintain the plasma MMA level after the administration lower than about 5 μmol/L, about 4.5 μmol/L, about 4 μmol/L, about 3.5 μmol/L, about 3 μmol/L, about 2.5 μmol/L, about 2 μmol/L, about 1.5 μmol/L, about 1 μmol/L, about 0.9 μmol/L, about 0.8 μmol/L, about 0.7 μmol/L, about 0.6 μmol/L, about 0.5 μmol/L, about 0.4 μmol/L, about 0.3 μmol/L, or 0.27 μmol/L.

[01121] In certain embodiments, the effective dose is sufficient to maintain the urinary MMA level less than 2000 mmol/mol creatinine, less than 1900 mmol/mol creatinine, less than 1800 mmol/mol creatinine, less than 1700 mmol/mol creatinine, less than 1600 mmol/mol creatinine, less than 1500 mmol/mol creatinine, less than 1400 mmol/mol creatinine, less than 1300 mmol/mol creatinine, less than 1200 mmol/mol creatinine, less than 1100 mmol/mol creatinine, less than 1000 mmol/mol creatinine, 900 mmol/mol creatinine, 800 mmol/mol creatinine, 700 mmol/mol creatinine, 600 mmol/mol creatinine, 500 mmol/mol creatinine, 400 mmol/mol creatinine, 300 mmol/mol creatinine, 200 mmol/mol creatinine, 100 mmol/mol creatinine, 90

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mmol/mol creatinine, 80 mmol/mol creatinine, 70 mmol/mol creatinine, 60 mmol/mol creatinine, 50 mmol/mol creatinine, 40 mmol/mol creatinine, 30 mmol/mol creatinine, 20 mmol/mol creatinine, 10 mmol/mol creatinine, 9 mmol/mol creatinine, 8 mmol/mol creatinine, 7 mmol/mol creatinine, 6 mmol/mol creatinine,5 mmol/mol creatinine, 4 mmol/mol creatinine, 3 mmol/mol creatinine, 2 mmol/mol creatinine, or 1 mmol/mol creatinine.

[01122] In some embodiments, a method for treating MMA presented herein involves the administration to a subject in need thereof of one or more doses of an effective amount of a polynucleotide (e.g., mRNA) encoding an MCM polypeptide or a pharmaceutical composition, wherein the effective amount may or may not be the same for each dose. In some embodiments, a first dose of a polynucleotide or pharmaceutical composition thereof is administered to a subject in need thereof for a first period of time, and subsequently, a second dose of a polynucleotide is administered to the subject for a second period of time. The first dose may be more than the second dose, or the first dose may be less than the second dose. A third dose of a polynucleotide also may be administered to a subject in need thereof for a third period of time.

[01123] The length of time that a subject in need thereof is administered a polynucleotide or a pharmaceutical composition thereof in accordance with the methods for treating MMA presented herein will be the time period that is determined to be efficacious. In some embodiments, a method for treating MMA presented herein involves the administration of a polynucleotide or a pharmaceutical composition thereof for a period of time until the severity and/or number of symptoms associated with MMA decrease.

[01124] It will be understood that the amounts of a polynucleotide or a pharmaceutical composition thereof administered to a patient in need thereof are or can be calculated based upon the actual weight of the patient in question or the average weight of the patient population in question.

Combination Therapy

[01125] Presented herein are combination therapies for the treatment of MMA which involve the administration of a polynucleotide (e.g., mRNA) encoding an MCM polypeptide in combination with one or more additional therapies to a subject in need thereof. In a specific embodiment, presented herein are combination therapies for the treatment of MMA which involve the administration of an effective amount of a polynucleotide (e.g., mRNA) encoding an MCM polypeptide in combination with an effective amount of another therapy to a subject in

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need thereof. Specific examples of such other therapies include, but are not limited to, carnitine supplements (such as L-carnitine), cobalamin supplements and antibiotics (such as metronidazole).

[01126] The combination therapies provided herein involve administrating to a subject to in need thereof a polynucleotide or a pharmaceutical composition thereof in combination with conventional, or known, therapies for MMA. Current therapies for MMA, include camitine supplements, cobalamin supplements and antibiotics. Other therapies for MMA or a condition associated therewith are aimed at controlling or relieving symptoms, e.g., anti-seizure medication. Accordingly, in some embodiments, the combination therapies provided herein involve administrating to a subject to in need thereof a pain reliever, a medication for epileptic seizures, or other therapy aimed at alleviating or controlling symptoms associated with MMA or a condition associated therewith.

[01127] In some embodiments, the methods for treating MMA provided herein comprise administering a polynucleotide (e.g., mRNA) encoding an MCM polypeptide as a single agent for a period of time prior to administering the polynucleotide in combination with an additional therapy. In some embodiments, the methods for treating MMA provided herein comprise administering an additional therapy alone for a period of time prior to administering a polynucleotide (e.g., mRNA) encoding an MCM polypeptide in combination with the additional therapy.

[01128] In some embodiments, the administration of a polynucleotide (e.g., mRNA) encoding an MCM polypeptide and one or more additional therapies in accordance with the methods presented herein have an additive effect relative the administration of the polynucleotide or said one or more additional therapies alone. In some embodiments, the administration of a polynucleotide (e.g., mRNA) encoding an MCM polypeptide and one or more additional therapies in accordance with the methods presented herein have a synergistic effect relative to the administration of the polynucleotide or said one or more additional therapies alone.

[01129] The combination of a polynucleotide (e.g., mRNA) encoding an MCM polypeptide and one or more additional therapies can be administered to a subject in the same pharmaceutical composition. Alternatively, a polynucleotide (e.g., mRNA) encoding an MCM polypeptide and one or more additional therapies can be administered concurrently to a subject in separate pharmaceutical compositions. A polynucleotide (e.g., mRNA) encoding an MCM polypeptide and one or more additional therapies can be administered sequentially to a subject in separate

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pharmaceutical compositions. A polynucleotide (e.g., mRNA) encoding an MCM polypeptide and one or more additional therapies may also be administered to a subject by the same or different routes of administration.

[01130] In some embodiments, the combination therapies provided herein involve administering to a subject in need thereof a polynucleotide (e.g., mRNA) encoding an MCM polypeptide or a pharmaceutical composition thereof in combination with one or more of the following: a camitine supplement (e.g., L-camitine), a cobalamin supplement and an antibiotic. In some embodiments, the combination therapies provided herein involve administering to a subject in need thereof a polynucleotide (e.g., mRNA) encoding an MCM polypeptide or a pharmaceutical composition thereof in combination with an organ transplant (e.g., a kidney, liver or kidney and liver transplant).

Clinical Objectives

[01131] Efficacy of a polynucleotide for treating MMA may be assessed by determining the effects of the polynucleotide on reduction of plasma methylmalonic acid. The efficacy of a polynucleotide for treating MMA may also be assessed by: (i) determining the effect on urinary levels of methylcitrate; (ii) determining the effect on plasma levels of propionlycarnitine; (iii) evaluating effects on erythrocyte odd long-chain fatty acid levels; (iv) determining effects on the urinary urea:methylmalonic acid ratio; (v) determining the effects on enzyme activity in cultured fibroblasts and lymphocytes from subjects with MMA, (vi) evaluating the effects on the developmental and cognitive ability of subjects; (vii) evaluating the effects on the dystonia rating scale; (viii) evaluating the effects on the occurrence of any metabolic decompensation episodes; (ix) evaluating the safety profile of the polynucleotide; (x) evaluating compliance with treatment with the polynucleotide; and (xi) determining the polynucleotide's plasma exposure over time.

Clinical Endpoints

[01132] A primary clinical endpoint for efficacy of a polynucleotide for treating MMA includes a reduction in plasma methylmalonic acid levels. Other clinical endpoints for the efficacy of a polynucleotide for treating MMA may include: a reduction in urinary methylmalonic acid levels;

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[01133] a reduction in urinary methylcitrate; a reduction in plasma propionylcarnitine; a reduction in erythrocyte odd long-chain fatty acid levels; an increase in the urea:methylmalonic acid ratio;

[01134] and pharmacokinetic parameters, e.g., time to maximum plasma concentration (T_{max}), C_{max}, AUC, terminal elimination half-life ($t_{1/2}$) based on a polynucleotide's plasma concentrations as assessed by a validated bioanalytical method.

Plasma methylmalonic acid Levels

[01135] Plasma methylmalonic acid levels may be used to indicate the effectiveness of a polynucleotide to increase the activity of the relevant enzyme or factor (*e.g.*, MCM). Normal plasma methylmalonic acid level is about <0.27 μmol/L (Fowler et al., 2008, J. Inherit. Metab. Dis. 31: 350-360). Plasma methylmalonic acid levels are elevated in patients with MMA, generally in the range of about 100 to about 1.000 μmol/L in cobalamin-non responsive patients and about 5 to about 100 μmol/L in cobalamin-responsive patients (Venditti, 2007, Gene Reviews). Methylmalonic acid is considered to be nephrotoxic, and central nervous system trapping of methylmalonic acid , propionyl-CoA, and 2 methylcitrate is considered to be the basis for chronic neurologic complications of MMA (Morath et al., 2008, J. Inherit. Metab. Dis. 31: 35-43). A decrease by >30% in plasma or urine methylmalonic acid levels has been considered by some to be a clinically relevant difference (Zwickler et al., 2008, J. Inherit. Metab. Dis. 31: 361-367).

[01136] Blood may be collected and plasma methylmalonic acid concentrations may be determined using a standard gas chromatography/mass spectroscopy (GC/MS) stable-isotope dilution method.

Urinary methylmalonic acid Levels

[01137] Urinary methylmalonic acid levels may be used to indicate the effectiveness of a polynucleotide to increase the activity of the relevant enzyme or factor (e.g., MCM). The normal urinary methylmalonic acid level is <4 mmol/mol creatinine (Venditti, 2007, Gene Reviews), and the level is significantly elevated in MMA. In general, the more severe types of MMA, mut^0 and cblB, have higher urinary methylmalonic acid levels (about 5,000 to >10.000 mmol/mol creatinine) compared to the less severe types, mut^- and cblA (<1,000 to >5,000 mol/mol creatinine) (Horster et al., 2007, Pediatr. Res. 62: 225-230; Fowler et al., 2008, J.

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Inherit. Metab. Dis. 31: 350-360). It has been observed that chronic renal failure does not occur in patients with urinary methylmalonic acid levels below –2.000 mmol/mol creatinine (Horster et al., 2007, Pediatr. Res. 62: 225-230).

[01138] Urine may be collected and urinary methylmalonic acid concentrations may be determined using a standard gas chromatography/mass spectroscopy (GC/MS) stable-isotope dilution method.

Plasma Propionylcarnitine, Urinary Methylcitrate, Erythrocyte OLCFAs, Urinary Urea:methylmalonic acid Ratio

[01139] Plasma propionylcamitine and urinary methylcitrate are methylmalonic acid metabolites and may be used to indicate the effectiveness of a polynucleotide (e.g., mRNA) encoding an MCM polypeptide to increase the activity of the relevant enzyme or factor (e.g., MCM). It has been suggested that plasma propionylcamitine may be a more useful measurement than urinary methylmalonic acid in the presence of renal insufficiency (Horster et al., 2007, Pediatr. Res. 62: 225-230). Urinary methylcitrate has been found to be elevated in the setting of elevated methylmalonic acid levels (Fowler et al., 2008, J. Inherit. Metab. Dis. 31: 350-360). Blood and urine may be collected and standard techniques may be used to determine plasma propionylcamitine levels and urinary methylcitrate levels, respectively.

[01140] OLCFAs are measured in erythrocyte membrane lipids and may be used to indicate the effectiveness of a polynucleotide (e.g., mRNA) encoding an MCM polypeptide to increase the activity of the relevant enzyme or factor (e.g., MCM). Erythrocyte OLCFAs values reflect both the severity of the disease and the quality of the dietary control in MMA (Merinero et al., 2008, J. Inherit. Metab. Dis. 31: 55-66). This parameter is indicative of the propionyl-CoA load of the cells and of long-term metabolic control in organic acidemias (Merinero et al., 2008, J. Inherit. Metab. Dis. 31: 55-66; Sperl et al., 2000, Eur. J. Pediatr. 159: 54-88). A standard method for determination of erythrocyte OLCFAs concentrations is available.

[01141] An increase in urinary urea:methylmalonic acid ratio following administration of a polynucleotide (e.g., mRNA) encoding an MCM polypeptide compared to baseline may indicate an increase in activity of the deficient enzyme or factor (MCM, cblA, or cblB). Protein catabolism leads to production of both urea and methylmalonic acid . The values of these catabolic products may fluctuate with dietary protein intake. If the source of methylmalonic acid is predominantly natural protein, in patients with no enzyme activity (e.g., mut^0patients) the ratio

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of urinary urea:methylmalonic acid is approximately 3.5. If there is residual enzyme activity (e.g., administration of vitamin B12 to cobalamin-sensitive patients) the ratio is generally >5. Patients receiving amino acid supplements will produce more urea than methylmalonic acid and will have a urea:MMA ratio>5. However, even in this category of patients the urea:MMA ratio will increase if the activity of the deficient enzyme or factor increases, (Valayannopoulos et al., Annual Symposium of the Society for the Study of Inborn Errors of Metabolism, Amsterdam, The Netherlands, September 2004).

VIII. Kits and Devices

Kits

[01142] The disclosure provides a variety of kits for conveniently and/or effectively using the claimed nucleotides of the present disclosure. Typically kits will comprise sufficient amounts and/or numbers of components to allow a user to perform multiple treatments of a subject(s) and/or to perform multiple experiments.

[01143] In one aspect, the present disclosure provides kits comprising the molecules (polynucleotides) of the disclosure.

[01144] Said kits can be for protein production, comprising a first polynucleotides comprising a translatable region. The kit can further comprise packaging and instructions and/or a delivery agent to form a formulation composition. The delivery agent can comprise a saline, a buffered solution, a lipidoid or any delivery agent disclosed herein.

[01145] In some embodiments, the buffer solution can include sodium chloride, calcium chloride, phosphate and/or EDTA. In another embodiment, the buffer solution can include, but is not limited to, saline, saline with 2mM calcium, 5% sucrose, 5% sucrose with 2mM calcium, 5% Mannitol, 5% Mannitol with 2mM calcium, Ringer's lactate, sodium chloride, sodium chloride with 2mM calcium and mannose (*See, e.g.,* U.S. Pub. No. 20120258046; herein incorporated by reference in its entirety). In a further embodiment, the buffer solutions can be precipitated or it can be lyophilized. The amount of each component can be varied to enable consistent, reproducible higher concentration saline or simple buffer formulations. The components can also be varied in order to increase the stability of modified RNA in the buffer solution over a period of time and/or under a variety of conditions. In one aspect, the present disclosure provides kits for protein production, comprising: a polynucleotide comprising a translatable region, provided in an amount effective to produce a desired amount of a protein encoded by the translatable

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region when introduced into a target cell; a second polynucleotide comprising an inhibitory nucleic acid, provided in an amount effective to substantially inhibit the innate immune response of the cell; and packaging and instructions.

[01146] In one aspect, the present disclosure provides kits for protein production, comprising a polynucleotide comprising a translatable region, wherein the polynucleotide exhibits reduced degradation by a cellular nuclease, and packaging and instructions.

[01147] In one aspect, the present disclosure provides kits for protein production, comprising a polynucleotide comprising a translatable region, wherein the polynucleotide exhibits reduced degradation by a cellular nuclease, and a mammalian cell suitable for translation of the translatable region of the first nucleic acid.

Devices

[01148] The present disclosure provides for devices that can incorporate polynucleotides that encode polypeptides of interest. These devices contain in a stable formulation the reagents to synthesize a polynucleotide in a formulation available to be immediately delivered to a subject in need thereof, such as a human patient

[01149] Devices for administration can be employed to deliver the polynucleotides of the present disclosure according to single, multi- or split-dosing regimens taught herein. Such devices are taught in, for example, International Application PCT/US2013/30062 filed March 9, 2013, the contents of which are incorporated herein by reference in their entirety.

[01150] Method and devices known in the art for multi-administration to cells, organs and tissues are contemplated for use in conjunction with the methods and compositions disclosed herein as embodiments of the present disclosure. These include, for example, those methods and devices having multiple needles, hybrid devices employing for example lumens or catheters as well as devices utilizing heat, electric current or radiation driven mechanisms.

[01151] According to the present disclosure, these multi-administration devices can be utilized to deliver the single, multi- or split doses contemplated herein. Such devices are taught for example in, International Application PCT/US2013/30062 filed March 9, 2013, the contents of which are incorporated herein by reference in their entirety.

[01152] In some embodiments, the polynucleotide is administered subcutaneously or intramuscularly via at least 3 needles to three different, optionally adjacent, sites simultaneously,

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or within a 60 minutes period (*e.g.,* administration to 4, 5, 6, 7, 8, 9, or 10 sites simultaneously or within a 60 minute period).

Methods and Devices utilizing catheters and/or lumens

[01153] Methods and devices using catheters and lumens can be employed to administer the polynucleotides of the present disclosure on a single, multi- or split dosing schedule. Such methods and devices are described in International Application PCT/US2013/30062 filed March 9, 2013 (Attorney Docket Number M300), the contents of which are incorporated herein by reference in their entirety.

Methods and Devices utilizing electrical current

[01154] Methods and devices utilizing electric current can be employed to deliver the polynucleotides of the present disclosure according to the single, multi- or split dosing regimens taught herein. Such methods and devices are described in International Application PCT/US2013/30062 filed March 9, 2013 (Attorney Docket Number M300), the contents of which are incorporated herein by reference in their entirety.

IX. Definitions

[01155] In order that the present disclosure can be more readily understood, certain terms are first defined. As used in this application, except as otherwise expressly provided herein, each of the following terms shall have the meaning set forth below. Additional definitions are set forth throughout the application.

[01156] The disclosure includes embodiments in which exactly one member of the group is present in, employed in, or otherwise relevant to a given product or process. The disclosure includes embodiments in which more than one, or all of the group members are present in, employed in, or otherwise relevant to a given product or process.

[01157] In this specification and the appended claims, the singular forms "a," "an" and "the" include plural referents unless the context clearly dictates otherwise. The terms "a" (or "an"), as well as the terms "one or more," and "at least one" can be used interchangeably herein. In certain aspects, the term "a" or "an" means "single." In other aspects, the term "a" or "an" includes "two or more" or "multiple."

[01158] Furthermore, "and/or" where used herein is to be taken as specific disclosure of each of the two specified features or components with or without the other. Thus, the term "and/or" as

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used in a phrase such as "A and/or B" herein is intended to include "A and B," "A or B," "A" (alone), and "B" (alone). Likewise, the term "and/or" as used in a phrase such as "A, B, and/or C" is intended to encompass each of the following aspects: A, B, and C; A, B, or C; A or C; A or B; B or C; A and C; A and B; B and C; A (alone); B (alone); and C (alone).

[01159] Unless defined otherwise, all technical and scientific terms used herein have the same meaning as commonly understood by one of ordinary skill in the art to which this disclosure is related. For example, the Concise Dictionary of Biomedicine and Molecular Biology, Juo, Pei-Show, 2nd ed., 2002, CRC Press; The Dictionary of Cell and Molecular Biology, 3rd ed., 1999, Academic Press; and the Oxford Dictionary Of Biochemistry And Molecular Biology, Revised, 2000, Oxford University Press, provide one of skill with a general dictionary of many of the terms used in this disclosure.

[01160] Wherever aspects are described herein with the language "comprising," otherwise analogous aspects described in terms of "consisting of" and/or "consisting essentially of" are also provided.

[01161] Units, prefixes, and symbols are denoted in their Système International de Unites (SI) accepted form. Numeric ranges are inclusive of the numbers defining the range. Where a range of values is recited, it is to be understood that each intervening integer value, and each fraction thereof, between the recited upper and lower limits of that range is also specifically disclosed, along with each subrange between such values. The upper and lower limits of any range can independently be included in or excluded from the range, and each range where either, neither or both limits are included is also encompassed within the disclosure. Where a value is explicitly recited, it is to be understood that values that are about the same quantity or amount as the recited value are also within the scope of the disclosure. Where a combination is disclosed, each subcombination of the elements of that combination is also specifically disclosed and is within the scope of the disclosure. Conversely, where different elements or groups of elements are individually disclosed, combinations thereof are also disclosed. Where any element of an disclosure is disclosed as having a plurality of alternatives, examples of that disclosure in which each alternative is excluded singly or in any combination with the other alternatives are also hereby disclosed; more than one element of an disclosure can have such exclusions, and all combinations of elements having such exclusions are hereby disclosed.

[01162] Nucleotides are referred to by their commonly accepted single-letter codes. Unless otherwise indicated, nucleic acids are written left to right in 5′ to 3′ orientation. Nucleotides are

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referred to herein by their commonly known one-letter symbols recommended by the IUPAC-IUB Biochemical Nomenclature Commission. Accordingly, A represents adenine, C represents cytosine, G represents guanine, T represents thymine, U represents uracil.

[01163] Amino acids are referred to herein by either their commonly known three letter symbols or by the one-letter symbols recommended by the IUPAC-IUB Biochemical Nomenclature Commission. Unless otherwise indicated, amino acid sequences are written left to right in amino to carboxy orientation.

[01164] At various places in the present specification, substituents of compounds of the present disclosure are disclosed in groups or in ranges. It is specifically intended that the present disclosure include each and every individual subcombination of the members of such groups and ranges

[01165] *About:* As used herein, the term "about" means +/- 10% of the recited value.

[01166] *Administered in combination:* As used herein, the term "administered in combination" or "combined administration" means that two or more agents are administered to a subject at the same time or within an interval such that there can be an overlap of an effect of each agent on the patient. In some embodiments, they are administered within about 60, 30, 15, 10, 5, or 1 minute of one another. In some embodiments, the administrations of the agents are spaced sufficiently closely together such that a combinatorial (*e.g.*, a synergistic) effect is achieved.

[01167] *Amino acid substitution:* The term "amino acid substitution" refers to replacing an amino acid residue present in a parent sequence (*e.g.*, a consensus sequence) with another amino acid residue. An amino acid can be substituted in a parent sequence, for example, via chemical peptide synthesis or through recombinant methods known in the art. Accordingly, a reference to a "substitution at position X" refers to the substitution of an amino acid present at position X with an alternative amino acid residue. In some aspects, substitution patterns can be described according to the schema AnY, wherein A is the single letter code corresponding to the amino acid naturally present at position n, and Y is the substituting amino acid residue. In other aspects, substitution patterns can be described according to the schema An(YZ), wherein A is the single letter code corresponding to the amino acid residue substituting the amino acid naturally present at position X, and Y and Z are alternative substituting amino acid residue, *i.e.,* In the context of the present disclosure, substitutions (even when they referred to as amino acid substitution) are conducted at the nucleic acid level, *i.e.,* substituting an amino acid residue with an alternative

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amino acid residue is conducted by substituting the codon encoding the first amino acid with a codon encoding the second amino acid.

[01168] *Animal:* As used herein, the term "animal" refers to any member of the animal kingdom. In some embodiments, "animal" refers to humans at any stage of development. In some embodiments, "animal" refers to non-human animals at any stage of development. In certain embodiments, the non-human animal is a mammal (*e.g.*, a rodent, a mouse, a rat, a rabbit, a monkey, a dog, a cat, a sheep, cattle, a primate, or a pig). In some embodiments, animals include, but are not limited to, mammals, birds, reptiles, amphibians, fish, and worms. In some embodiments, the animal is a transgenic animal, genetically-engineered animal, or a clone.

[01169] *Approximately:* As used herein, the term "approximately," as applied to one or more values of interest, refers to a value that is similar to a stated reference value. In certain embodiments, the term "approximately" refers to a range of values that fall within 25%, 20%, 19%, 18%, 17%, 16%, 15%, 14%, 13%, 12%, 11%, 10%, 9%, 8%, 7%, 6%, 5%, 4%, 3%, 2%, 1%, or less in either direction (greater than or less than) of the stated reference value unless otherwise stated or otherwise evident from the context (except where such number would exceed 100% of a possible value).

[01170] *Associated with:* As used herein with respect to a disease, the term "associated with" means that the symptom, measurement, characteristic, or status in question is linked to the diagnosis, development, presence, or progression of that disease. As association may, but need not, be causatively linked to the disease.

[01171] When used with respect to two or more moieties, the terms "associated with," "conjugated," "linked," "attached," and "tethered," when used with respect to two or more moieties, means that the moieties are physically associated or connected with one another, either directly or via one or more additional moieties that serves as a linking agent, to form a structure that is sufficiently stable so that the moieties remain physically associated under the conditions in which the structure is used, *e.g.*, physiological conditions. An "association" need not be strictly through direct covalent chemical bonding. It can also suggest ionic or hydrogen bonding or a hybridization based connectivity sufficiently stable such that the "associated" entities remain physically associated.

[01172] *Bifunctional:* As used herein, the term "bifunctional" refers to any substance, molecule or moiety that is capable of or maintains at least two functions. The functions can affect the same outcome or a different outcome. The structure that produces the function can be

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the same or different. For example, bifunctional modified RNAs of the present disclosure can encode a cytotoxic peptide (a first function) while those nucleosides that comprise the encoding RNA are, in and of themselves, cytotoxic (second function). In this example, delivery of the bifunctional modified RNA to a cancer cell would produce not only a peptide or protein molecule that can ameliorate or treat the cancer but would also deliver a cytotoxic payload of nucleosides to the cell should degradation, instead of translation of the modified RNA, occur.

[01173] *Biocompatible*: As used herein, the term "biocompatible" means compatible with living cells, tissues, organs or systems posing little to no risk of injury, toxicity or rejection by the immune system.

[01174] *Biodegradable*: As used herein, the term "biodegradable" means capable of being broken down into innocuous products by the action of living things.

[01175] *Biologically active*: As used herein, the phrase "biologically active" refers to a characteristic of any substance that has activity in a biological system and/or organism. For instance, a substance that, when administered to an organism, has a biological effect on that organism, is considered to be biologically active. In particular embodiments, a polynucleotide of the present disclosure can be considered biologically active if even a portion of the polynucleotide is biologically active or mimics an activity considered biologically relevant.

[01176] *Chimera*: As used herein, "chimera" is an entity having two or more incongruous or heterogeneous parts or regions.

[01177] *Conservative amino acid substitution:* A "conservative amino acid substitution" is one in which the amino acid residue is replaced with an amino acid residue having a similar side chain. Families of amino acid residues having similar side chains have been defined in the art, including basic side chains (*e.g.,* lysine, arginine, or histidine), acidic side chains (*e.g.,* aspartic acid or glutamic acid), uncharged polar side chains (*e.g.,* glycine, asparagine, glutamine, serine, threonine, tyrosine, or cysteine), nonpolar side chains (*e.g.,* alanine, valine, leucine, isoleucine, proline, phenylalanine, methionine, or tryptophan), beta-branched side chains (*e.g.,* threonine, valine, isoleucine) and aromatic side chains (*e.g.,* tyrosine, phenylalanine, tryptophan, or histidine). Thus, if an amino acid in a polypeptide is replaced with another amino acid from the same side chain family, the amino acid substitution is considered to be conservative. In another aspect, a string of amino acids can be conservatively replaced with a structurally similar string that differs in order and/or composition of side chain family members.

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[01178] Non-conservative amino acid substitutions include those in which (i) a residue having an electropositive side chain (*e.g.,* Arg, His or Lys) is substituted for, or by, an electronegative residue (*e.g.,* Glu or Asp), (ii) a hydrophilic residue (*e.g.,* Ser or Thr) is substituted for, or by, a hydrophobic residue (*e.g.,* Ala, Leu, Ile, Phe or Val), (iii) a cysteine or proline is substituted for, or by, any other residue, or (iv) a residue having a bulky hydrophobic or aromatic side chain (*e.g.,* Val, His, Ile or Trp) is substituted for, or by, one having a smaller side chain (*e.g.,* Ala or Ser) or no side chain (*e.g.,* Gly).

[01179] Other amino acid substitutions can be readily identified by workers of ordinary skill. For example, for the amino acid alanine, a substitution can be taken from any one of D-alanine, glycine, beta-alanine, L-cysteine and D-cysteine. For lysine, a replacement can be any one of D-lysine, arginine, D-arginine, homo-arginine, methionine, D-methionine, ornithine, or D-ornithine. Generally, substitutions in functionally important regions that can be expected to induce changes in the properties of isolated polypeptides are those in which (i) a polar residue, *e.g.,* serine or threonine, is substituted for (or by) a hydrophobic residue, *e.g.,* leucine, isoleucine, phenylalanine, or alanine; (ii) a cysteine residue is substituted for (or by) any other residue; (iii) a residue having an electropositive side chain, *e.g.,* lysine, arginine or histidine, is substituted for (or by) a residue having an electronegative side chain, *e.g.,* glutamic acid or aspartic acid; or (iv) a residue having a bulky side chain, *e.g.,* phenylalanine, is substituted for (or by) one not having such a side chain, *e.g.,* glycine. The likelihood that one of the foregoing non-conservative substitutions can alter functional properties of the protein is also correlated to the position of the substitution with respect to functionally important regions of the protein: some non-conservative substitutions can accordingly have little or no effect on biological properties.

[01180] *Conserved*: As used herein, the term "conserved" refers to nucleotides or amino acid residues of a polynucleotide sequence or polypeptide sequence, respectively, that are those that occur unaltered in the same position of two or more sequences being compared. Nucleotides or amino acids that are relatively conserved are those that are conserved amongst more related sequences than nucleotides or amino acids appearing elsewhere in the sequences.

[01181] In some embodiments, two or more sequences are said to be "completely conserved" if they are 100% identical to one another. In some embodiments, two or more sequences are said to be "highly conserved" if they are at least 70% identical, at least 80% identical, at least 90% identical, or at least 95% identical to one another. In some embodiments, two or more sequences are said to be "highly conserved" if they are about 70% identical, about 80% identical, about

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90% identical, about 95%, about 98%, or about 99% identical to one another. In some embodiments, two or more sequences are said to be "conserved" if they are at least 30% identical, at least 40% identical, at least 50% identical, at least 60% identical, at least 70% identical, at least 80% identical, at least 90% identical, or at least 95% identical to one another. In some embodiments, two or more sequences are said to be "conserved" if they are about 30% identical, about 40% identical, about 50% identical, about 60% identical, about 70% identical, about 80% identical, about 90% identical, about 95% identical, about 98% identical, or about 99% identical to one another. Conservation of sequence can apply to the entire length of an polynucleotide or polypeptide or can apply to a portion, region or feature thereof.

[01182] *Controlled Release:* As used herein, the term "controlled release" refers to a pharmaceutical composition or compound release profile that conforms to a particular pattern of release to effect a therapeutic outcome.

[01183] *Cyclic or Cyclized:* As used herein, the term "cyclic" refers to the presence of a continuous loop. Cyclic molecules need not be circular, only joined to form an unbroken chain of subunits. Cyclic molecules such as the engineered RNA or mRNA of the present disclosure can be single units or multimers or comprise one or more components of a complex or higher order structure.

[01184] *Cytotoxic*: As used herein, "cytotoxic" refers to killing or causing injurious, toxic, or deadly effect on a cell (*e.g.*, a mammalian cell (*e.g.*, a human cell)), bacterium, virus, fungus, protozoan, parasite, prion, or a combination thereof.

[01185] *Delivery:* As used herein, "delivery" refers to the act or manner of delivering a compound, substance, entity, moiety, cargo or payload.

[01186] *Delivery Agent*: As used herein, "delivery agent" refers to any substance that facilitates, at least in part, the *in vivo* delivery of a polynucleotide to targeted cells.

[01187] *Destabilized:* As used herein, the term "destable," "destabilize," or "destabilizing region" means a region or molecule that is less stable than a starting, wild-type or native form of the same region or molecule.

[01188] *Detectable label:* As used herein, "detectable label" refers to one or more markers, signals, or moieties that are attached, incorporated or associated with another entity that is readily detected by methods known in the art including radiography, fluorescence, chemiluminescence, enzymatic activity, absorbance and the like. Detectable labels include radioisotopes, fluorophores, chromophores, enzymes, dyes, metal ions, ligands such as biotin,

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avidin, streptavidin and haptens, quantum dots, and the like. Detectable labels can be located at any position in the peptides or proteins disclosed herein. They can be within the amino acids, the peptides, or proteins, or located at the N- or C- termini.

[01189] *Diastereomer:* As used herein, the term "diastereomer," means stereoisomers that are not mirror images of one another and are non-superimposable on one another.

[01190] *Digest*: As used herein, the term "digest" means to break apart into smaller pieces or components. When referring to polypeptides or proteins, digestion results in the production of peptides.

[01191] *Distal:* As used herein, the term "distal" means situated away from the center or away from a point or region of interest.

[01192] *Dosing regimen*: As used herein, a "dosing regimen" is a schedule of administration or physician determined regimen of treatment, prophylaxis, or palliative care.

[01193] *Effective Amount:* As used herein, the term "effective amount" of an agent is that amount sufficient to effect beneficial or desired results, for example, clinical results, and, as such, an "effective amount" depends upon the context in which it is being applied. The term "effective amount" can be used interchangeably with "effective dose," "therapeutically effective amount," or "therapeutically effective dose."

[01194] *Enantiomer:* As used herein, the term "enantiomer" means each individual optically active form of a compound of the disclosure, having an optical purity or enantiomeric excess (as determined by methods standard in the art) of at least 80% (*i.e.*, at least 90% of one enantiomer and at most 10% of the other enantiomer), at least 90%, or at least 98%.

[01195] *Encapsulate:* As used herein, the term "encapsulate" means to enclose, surround or encase.

[01196] *Encoded protein cleavage signal*: As used herein, "encoded protein cleavage signal" refers to the nucleotide sequence that encodes a protein cleavage signal.

[01197] *Engineered:* As used herein, embodiments of the disclosure are "engineered" when they are designed to have a feature or property, whether structural or chemical, that varies from a starting point, wild type or native molecule.

[01198] *Effective Amount:* As used herein, the term "effective amount" of an agent is that amount sufficient to effect beneficial or desired results, for example, clinical results, and, as such, an "effective amount" depends upon the context in which it is being applied. For example, in the context of administering an agent that treats high cholesterol, an effective amount of an

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agent is, for example, an amount sufficient to achieve treatment, as defined herein, of high cholesterol, as compared to the response obtained without administration of the agent.

[01199] *Exosome:* As used herein, "exosome" is a vesicle secreted by mammalian cells or a complex involved in RNA degradation.

[01200] *Expression*: As used herein, "expression" of a nucleic acid sequence refers to one or more of the following events: (1) production of an RNA template from a DNA sequence (*e.g.*, by transcription); (2) processing of an RNA transcript (*e.g.*, by splicing, editing, 5′ cap formation, and/or 3′ end processing); (3) translation of an RNA into a polypeptide or protein; and (4) post-translational modification of a polypeptide or protein.

[01201] *Feature:* As used herein, a "feature" refers to a characteristic, a property, or a distinctive element.

[01202] *Formulation*: As used herein, a "formulation" includes at least a polynucleotide and a delivery agent.

[01203] *Fragment:* A "fragment," as used herein, refers to a portion. For example, fragments of proteins can comprise polypeptides obtained by digesting full-length protein isolated from cultured cells.

[01204] *Functional*: As used herein, a "functional" biological molecule is a biological molecule in a form in which it exhibits a property and/or activity by which it is characterized.

[01205] *Homology*: As used herein, the term "homology" refers to the overall relatedness between polymeric molecules, *e.g.*, between nucleic acid molecules (*e.g.*, DNA molecules and/or RNA molecules) and/or between polypeptide molecules. In some embodiments, polymeric molecules are considered to be "homologous" to one another if their sequences are at least 25%, 30%, 35%, 40%, 45%, 50%, 55%, 60%, 65%, 70%, 75%, 80%, 85%, 90%, 95%, or 99% identical or similar. The term "homologous" necessarily refers to a comparison between at least two sequences (polynucleotide or polypeptide sequences). In accordance with the disclosure, two polynucleotide sequences are considered to be homologous if the polypeptides they encode are at least about 50%, 60%, 70%, 80%, 90%, 95%, or even 99% for at least one stretch of at least about 20 amino acids. In some embodiments, homologous polynucleotide sequences are characterized by the ability to encode a stretch of at least 4–5 uniquely specified amino acids. For polynucleotide sequences less than 60 nucleotides in length, homology is determined by the ability to encode a stretch of at least 4–5 uniquely specified amino acids. In accordance with the disclosure, two protein sequences are considered to be homologous if the proteins are at least

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about 50%, 60%, 70%, 80%, or 90% identical for at least one stretch of at least about 20 amino acids.

[01206] *Identity*: As used herein, the term "identity" refers to the overall relatedness between polymeric molecules, *e.g.*, between polynucleotide molecules (*e.g.*, DNA molecules and/or RNA molecules) and/or between polypeptide molecules. Percent identity can be calculated between two DNA molecules, between two RNA molecules, and between a DNA molecule and an RNA molecule. When DNA and RNA are compared, T is considered to be U (or vice versa).

[01207] Calculation of the percent identity of two polynucleotide sequences, for example, can be performed by aligning the two sequences for optimal comparison purposes (*e.g.*, gaps can be introduced in one or both of a first and a second nucleic acid sequences for optimal alignment and non-identical sequences can be disregarded for comparison purposes). In certain embodiments, the length of a sequence aligned for comparison purposes is at least 30%, at least 40%, at least 50%, at least 60%, at least 70%, at least 80%, at least 90%, at least 95%, or 100% of the length of the reference sequence. The nucleotides at corresponding nucleotide positions are then compared. When a position in the first sequence is occupied by the same nucleotide as the corresponding position in the second sequence, then the molecules are identical at that position. The percent identity between the two sequences is a function of the number of identical positions shared by the sequences, taking into account the number of gaps, and the length of each gap, which needs to be introduced for optimal alignment of the two sequences. The comparison of sequences and determination of percent identity between two sequences can be accomplished using a mathematical algorithm. For example, the percent identity between two nucleotide sequences can be determined using methods such as those described in Computational Molecular Biology, Lesk, A. M., ed., Oxford University Press, New York, 1988; Biocomputing: Informatics and Genome Projects, Smith, D. W., ed., Academic Press, New York, 1993; Sequence Analysis in Molecular Biology, von Heinje, G., Academic Press, 1987; Computer Analysis of Sequence Data, Part I, Griffin, A. M., and Griffin, H. G., eds., Humana Press, New Jersey, 1994; and Sequence Analysis Primer, Gribskov, M. and Devereux, J., eds., M Stockton Press, New York, 1991; each of which is incorporated herein by reference. For example, the percent identity between two nucleotide sequences can be determined using the algorithm of Meyers and Miller (CABIOS, 1989, 4:11-17), which has been incorporated into the ALIGN program (version 2.0) using a PAM120 weight residue table, a gap length penalty of 12 and a gap penalty of 4. The percent identity between two nucleotide sequences can, alternatively, be

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determined using the GAP program in the GCG software package using an NWSgapdna.CMP matrix. Methods commonly employed to determine percent identity between sequences include, but are not limited to those disclosed in Carillo, H., and Lipman, D., SIAM J Applied Math., 48:1073 (1988); incorporated herein by reference. Techniques for determining identity are codified in publicly available computer programs. Exemplary computer software to determine homology between two sequences include, but are not limited to, GCG program package, Devereux, J., *et al.*, *Nucleic Acids Research*, 12(1), 387 (1984)), BLASTP, BLASTN, and FASTA Altschul, S. F. *et al.*, *J. Molec. Biol.*, 215, 403 (1990)).

[01208] *Intact:* As used herein, in the context of a polypeptide, the term "intact" means retaining an amino acid corresponding to the wild-type protein, *e.g.*, not mutating or substituting the wild-type amino acid.

[01209] *Isomer:* As used herein, the term "isomer" means any tautomer, stereoisomer, enantiomer, or diastereomer of any compound of the disclosure. It is recognized that the compounds of the disclosure can have one or more chiral centers and/or double bonds and, therefore, exist as stereoisomers, such as double-bond isomers (*i.e.*, geometric E/Z isomers) or diastereomers (*e.g.*, enantiomers (*i.e.*, (+) or (-)) or cis/trans isomers). According to the disclosure, the chemical structures depicted herein, and therefore the compounds of the disclosure, encompass all of the corresponding stereoisomers, that is, both the stereomerically pure form (*e.g.*, geometrically pure, enantiomerically pure, or diastereomerically pure) and enantiomeric and stereoisomeric mixtures, *e.g.*, racemates. Enantiomeric and stereoisomeric mixtures of compounds of the disclosure can typically be resolved into their component enantiomers or stereoisomers by well-known methods, such as chiral-phase gas chromatography, chiral-phase high performance liquid chromatography, crystallizing the compound as a chiral salt complex, or crystallizing the compound in a chiral solvent. Enantiomers and stereoisomers can also be obtained from stereomerically or enantiomerically pure intermediates, reagents, and catalysts by well-known asymmetric synthetic methods.

[01210] *In vitro*: As used herein, the term "*in vitro*" refers to events that occur in an artificial environment, *e.g.*, in a test tube or reaction vessel, in cell culture, in a Petri dish, etc., rather than within an organism (*e.g.*, animal, plant, or microbe).

[01211] *In vivo*: As used herein, the term "*in vivo*" refers to events that occur within an organism (*e.g.*, animal, plant, or microbe or cell or tissue thereof).

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[01212] *Isolated*: As used herein, the term "isolated" refers to a substance or entity that has been separated from at least some of the components with which it was associated (whether in nature or in an experimental setting). Isolated substances can have varying levels of purity in reference to the substances from which they have been associated. Isolated substances and/or entities can be separated from at least about 10%, about 20%, about 30%, about 40%, about 50%, about 60%, about 70%, about 80%, about 90%, or more of the other components with which they were initially associated. In some embodiments, isolated agents are more than about 80%, about 85%, about 90%, about 91%, about 92%, about 93%, about 94%, about 95%, about 96%, about 97%, about 98%, about 99%, or more than about 99% pure. As used herein, a substance is "pure" if it is substantially free of other components. *Substantially isolated*: By "substantially isolated" is meant that the compound is substantially separated from the environment in which it was formed or detected. Partial separation can include, for example, a composition enriched in the compound of the present disclosure. Substantial separation can include compositions containing at least about 50%, at least about 60%, at least about 70%, at least about 80%, at least about 90%, at least about 95%, at least about 97%, or at least about 99% by weight of the compound of the present disclosure, or salt thereof.

[01213] A polynucleotide, vector, polypeptide, cell, or any composition disclosed herein that is "isolated" is a polynucleotide, vector, polypeptide, cell, or composition that is in a form not found in nature. Isolated polynucleotides, vectors, polypeptides, or compositions include those that have been purified to a degree that they are no longer in a form in which they are found in nature. In some aspects, a polynucleotide, vector, polypeptide, or composition that is isolated is substantially pure.

[01214] *Linker:* As used herein, a "linker" refers to a group of atoms, *e.g.,* 10-1,000 atoms, and can be comprised of the atoms or groups such as, but not limited to, carbon, amino, alkylamino, oxygen, sulfur, sulfoxide, sulfonyl, carbonyl, and imine. The linker can be attached to a modified nucleoside or nucleotide on the nucleobase or sugar moiety at a first end, and to a payload, *e.g.,* a detectable or therapeutic agent, at a second end. The linker can be of sufficient length as to not interfere with incorporation into a nucleic acid sequence. The linker can be used for any useful purpose, such as to form polynucleotide multimers (*e.g.,* through linkage of two or more chimeric polynucleotides molecules or IVT polynucleotides) or polynucleotides conjugates, as well as to administer a payload, as described herein. Examples of chemical groups that can be incorporated into the linker include, but are not limited to, alkyl, alkenyl, alkynyl,

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amido, amino, ether, thioether, ester, alkylene, heteroalkylene, aryl, or heterocyclyl, each of which can be optionally substituted, as described herein. Examples of linkers include, but are not limited to, unsaturated alkanes, polyethylene glycols (*e.g.,* ethylene or propylene glycol monomeric units, *e.g.,* diethylene glycol, dipropylene glycol, triethylene glycol, tripropylene glycol, tetraethylene glycol, or tetraethylene glycol), and dextran polymers and derivatives thereof., Other examples include, but are not limited to, cleavable moieties within the linker, such as, for example, a disulfide bond (-S-S-) or an azo bond (-N=N-), which can be cleaved using a reducing agent or photolysis. Non-limiting examples of a selectively cleavable bond include an amido bond can be cleaved for example by the use of tris(2-carboxyethyl)phosphine (TCEP), or other reducing agents, and/or photolysis, as well as an ester bond can be cleaved for example by acidic or basic hydrolysis.

[01215] *MCM Associated Disease:* As used herein, an "MCM-associated disease" or "MCM-associated disorder" refers to diseases or disorders, respectively, which results from aberrant MCM activity (*e.g.,* decreased activity or increased activity). As a non-limiting example, methylmalonic acidemia an MCM-associated disease.

[01216] *Mitochondrial transit peptide*: As used herein, the terms "mitochondrial transit peptide," "mitochondrial targeting peptide," and "mitochondrial targeting sequence" refer to an amino acid sequence (or a polynucleotide encoding such an amino acid sequence) that is a part of a larger polypeptide, where that sequence directs the transport or localization of the larger polypeptide to mitochondria.

[01217] *Modified:* As used herein "modified" refers to a changed state or structure of a molecule of the disclosure. Molecules can be modified in many ways including chemically, structurally, and functionally. In some embodiments, the mRNA molecules of the present disclosure are modified by the introduction of non-natural nucleosides and/or nucleotides, *e.g.,* as it relates to the natural ribonucleotides A, U, G, and C. Noncanonical nucleotides such as the cap structures are not considered "modified" although they differ from the chemical structure of the A, C, G, U ribonucleotides.

[01218] *Mucus*: As used herein, "mucus" refers to the natural substance that is viscous and comprises mucin glycoproteins.

[01219] *Naturally occurring:* As used herein, "naturally occurring" means existing in nature without artificial aid.

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[01220] *Non-human vertebrate:* As used herein, a "non-human vertebrate" includes all vertebrates except *Homo sapiens*, including wild and domesticated species. Examples of non-human vertebrates include, but are not limited to, mammals, such as alpaca, banteng, bison, camel, cat, cattle, deer, dog, donkey, gayal, goat, guinea pig, horse, llama, mule, pig, rabbit, reindeer, sheep water buffalo, and yak.

[01221] *Nucleic acid sequence:* The terms "nucleic acid sequence" and "nucleotide sequence" are used interchangeably and refer to a contiguous nucleic acid sequence. The sequence can be either single stranded or double stranded DNA or RNA, *e.g.,* an mRNA.

[01222] The term "nucleic acid," in its broadest sense, includes any compound and/or substance that comprises a polymer of nucleotides. These polymers are often referred to as polynucleotides. Exemplary nucleic acids or polynucleotides of the disclosure include, but are not limited to, ribonucleic acids (RNAs), deoxyribonucleic acids (DNAs), threose nucleic acids (TNAs), glycol nucleic acids (GNAs), peptide nucleic acids (PNAs), locked nucleic acids (LNAs, including LNA having a β- D-ribo configuration, α-LNA having an α-L-ribo configuration (a diastereomer of LNA), 2′-amino-LNA having a 2′-amino functionalization, and 2′-amino- α-LNA having a 2′-amino functionalization), ethylene nucleic acids (ENA), cyclohexenyl nucleic acids (CeNA) or hybrids or combinations thereof.

[01223] The phrase "nucleotide sequence encoding" and variants thereof refers to the nucleic acid (*e.g.,* an mRNA or DNA molecule) coding sequence that comprises a nucleotide sequence that encodes a polypeptide or functional fragment thereof as set forth herein. The coding sequence can further include initiation and termination signals operably linked to regulatory elements including a promoter and polyadenylation signal capable of directing expression in the cells of an individual or mammal to which the nucleic acid is administered. The coding sequence can further include sequences that encode signal peptides or targeting peptides, *e.g.,* mitochondrial transit peptides.

[01224] *Off-target:* As used herein, "off target" refers to any unintended effect on any one or more target, gene, or cellular transcript.

[01225] *Open reading frame:* As used herein, "open reading frame" or "ORF" refers to a sequence that does not contain a stop codon in a given reading frame.

[01226] *Operably linked:* As used herein, the phrase "operably linked" refers to a functional connection between two or more molecules, constructs, transcripts, entities, moieties or the like.

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[01227] *Optionally substituted:* Herein a phrase of the form "optionally substituted X" (*e.g.*, optionally substituted alkyl) is intended to be equivalent to "X, wherein X is optionally substituted" (*e.g.*, "alkyl, wherein said alkyl is optionally substituted"). It is not intended to mean that the feature "X" (*e.g.*, alkyl) *per se* is optional.

[01228] *Part*: As used herein, a "part" or "region" of a polynucleotide is defined as any portion of the polynucleotide that is less than the entire length of the polynucleotide.

[01229] *Peptide:* As used herein, "peptide" is less than or equal to 50 amino acids long, *e.g.*, about 5, 10, 15, 20, 25, 30, 35, 40, 45, or 50 amino acids long.

[01230] *Patient:* As used herein, "patient" refers to a subject who can seek or be in need of treatment, requires treatment, is receiving treatment, will receive treatment, or a subject who is under care by a trained professional for a particular disease or condition.

[01231] *Pharmaceutically acceptable*: The phrase "pharmaceutically acceptable" is employed herein to refer to those compounds, materials, compositions, and/or dosage forms that are, within the scope of sound medical judgment, suitable for use in contact with the tissues of human beings and animals without excessive toxicity, irritation, allergic response, or other problem or complication, commensurate with a reasonable benefit/risk ratio.

[01232] *Pharmaceutically acceptable excipients:* The phrase "pharmaceutically acceptable excipient," as used herein, refers any ingredient other than the compounds described herein (for example, a vehicle capable of suspending or dissolving the active compound) and having the properties of being substantially nontoxic and non-inflammatory in a patient. Excipients can include, for example: antiadherents, antioxidants, binders, coatings, compression aids, disintegrants, dyes (colors), emollients, emulsifiers, fillers (diluents), film formers or coatings, flavors, fragrances, glidants (flow enhancers), lubricants, preservatives, printing inks, sorbents, suspensing or dispersing agents, sweeteners, and waters of hydration. Exemplary excipients include, but are not limited to: butylated hydroxytoluene (BHT), calcium carbonate, calcium phosphate (dibasic), calcium stearate, croscarmellose, crosslinked polyvinyl pyrrolidone, citric acid, crospovidone, cysteine, ethylcellulose, gelatin, hydroxypropyl cellulose, hydroxypropyl methylcellulose, lactose, magnesium stearate, maltitol, mannitol, methionine, methylcellulose, methyl paraben, microcrystalline cellulose, polyethylene glycol, polyvinyl pyrrolidone, povidone, pregelatinized starch, propyl paraben, retinyl palmitate, shellac, silicon dioxide, sodium carboxymethyl cellulose, sodium citrate, sodium starch glycolate, sorbitol, starch (corn), stearic acid, sucrose, talc, titanium dioxide, vitamin A, vitamin E, vitamin C, and xylitol.

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[01233] *Pharmaceutically acceptable salts*: The present disclosure also includes pharmaceutically acceptable salts of the compounds described herein. As used herein, "pharmaceutically acceptable salts" refers to derivatives of the disclosed compounds wherein the parent compound is modified by converting an existing acid or base moiety to its salt form (*e.g.*, by reacting the free base group with a suitable organic acid). Examples of pharmaceutically acceptable salts include, but are not limited to, mineral or organic acid salts of basic residues such as amines; alkali or organic salts of acidic residues such as carboxylic acids; and the like. Representative acid addition salts include acetate, acetic acid, adipate, alginate, ascorbate, aspartate, benzenesulfonate, benzene sulfonic acid, benzoate, bisulfate, borate, butyrate, camphorate, camphorsulfonate, citrate, cyclopentanepropionate, digluconate, dodecylsulfate, ethanesulfonate, fumarate, glucoheptonate, glycerophosphate, hemisulfate, heptonate, hexanoate, hydrobromide, hydrochloride, hydroiodide, 2-hydroxy-ethanesulfonate, lactobionate, lactate, laurate, lauryl sulfate, malate, maleate, malonate, methanesulfonate, 2-naphthalenesulfonate, nicotinate, nitrate, oleate, oxalate, palmitate, pamoate, pectinate, persulfate, 3-phenylpropionate, phosphate, picrate, pivalate, propionate, stearate, succinate, sulfate, tartrate, thiocyanate, toluenesulfonate, undecanoate, valerate salts, and the like. Representative alkali or alkaline earth metal salts include sodium, lithium, potassium, calcium, magnesium, and the like, as well as nontoxic ammonium, quaternary ammonium, and amine cations, including, but not limited to ammonium, tetramethylammonium, tetraethylammonium, methylamine, dimethylamine, trimethylamine, triethylamine, ethylamine, and the like. The pharmaceutically acceptable salts of the present disclosure include the conventional non-toxic salts of the parent compound formed, for example, from non-toxic inorganic or organic acids. The pharmaceutically acceptable salts of the present disclosure can be synthesized from the parent compound that contains a basic or acidic moiety by conventional chemical methods. Generally, such salts can be prepared by reacting the free acid or base forms of these compounds with a stoichiometric amount of the appropriate base or acid in water or in an organic solvent, or in a mixture of the two; generally, nonaqueous media like ether, ethyl acetate, ethanol, isopropanol, or acetonitrile are used. Lists of suitable salts are found in *Remington's Pharmaceutical Sciences*, 17th ed., Mack Publishing Company, Easton, Pa., 1985, p. 1418, *Pharmaceutical Salts: Properties, Selection, and Use*, P.H. Stahl and C.G. Wermuth (eds.), Wiley-VCH, 2008, and Berge et al., *Journal of Pharmaceutical Science*, 66, 1-19 (1977), each of which is incorporated herein by reference in its entirety.

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[01234] *Pharmaceutically acceptable solvate*: The term "pharmaceutically acceptable solvate," as used herein, means a compound of the disclosure wherein molecules of a suitable solvent are incorporated in the crystal lattice. A suitable solvent is physiologically tolerable at the dosage administered. For example, solvates can be prepared by crystallization, recrystallization, or precipitation from a solution that includes organic solvents, water, or a mixture thereof. Examples of suitable solvents are ethanol, water (for example, mono-, di-, and tri-hydrates), *N*-methylpyrrolidinone (NMP), dimethyl sulfoxide (DMSO), *N*,*N*'-dimethylformamide (DMF), *N*,*N*'-dimethylacetamide (DMAC), 1,3-dimethyl-2-imidazolidinone (DMEU), 1,3-dimethyl-3,4,5,6-tetrahydro-2-(1H)-pyrimidinone (DMPU), acetonitrile (ACN), propylene glycol, ethyl acetate, benzyl alcohol, 2-pyrrolidone, benzyl benzoate, and the like. When water is the solvent, the solvate is referred to as a "hydrate."

[01235] *Pharmacokinetic:* As used herein, "pharmacokinetic" refers to any one or more properties of a molecule or compound as it relates to the determination of the fate of substances administered to a living organism. Pharmacokinetics is divided into several areas including the extent and rate of absorption, distribution, metabolism and excretion. This is commonly referred to as ADME where: (A) Absorption is the process of a substance entering the blood circulation; (D) Distribution is the dispersion or dissemination of substances throughout the fluids and tissues of the body; (M) Metabolism (or Biotransformation) is the irreversible transformation of parent compounds into daughter metabolites; and (E) Excretion (or Elimination) refers to the elimination of the substances from the body. In rare cases, some drugs irreversibly accumulate in body tissue.

[01236] *Physicochemical:* As used herein, "physicochemical" means of or relating to a physical and/or chemical property.

[01237] *Polynucleotide:* The term "polynucleotide" as used herein refers to polymers of nucleotides of any length, including ribonucleotides, deoxyribonucleotides, analogs thereof, or mixtures thereof. This term refers to the primary structure of the molecule. Thus, the term includes triple-, double- and single-stranded deoxyribonucleic acid ("DNA"), as well as triple-, double- and single-stranded ribonucleic acid ("RNA"). It also includes modified, for example by alkylation, and/or by capping, and unmodified forms of the polynucleotide. More particularly, the term "polynucleotide" includes polydeoxyribonucleotides (containing 2-deoxy-D-ribose), polyribonucleotides (containing D-ribose), including tRNA, rRNA, hRNA, siRNA and mRNA, whether spliced or unspliced, any other type of polynucleotide that is an N- or C-glycoside of a

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purine or pyrimidine base, and other polymers containing normucleotidic backbones, for example, polyamide (*e.g.,* peptide nucleic acids "PNAs") and polymorpholino polymers, and other synthetic sequence-specific nucleic acid polymers providing that the polymers contain nucleobases in a configuration that allows for base pairing and base stacking, such as is found in DNA and RNA. In particular aspects, the polynucleotide comprises an mRNA. In other aspect, the mRNA is a synthetic mRNA. In some aspects, the synthetic mRNA comprises at least one unnatural nucleobase. In some aspects, all nucleobases of a certain class have been replaced with unnatural nucleobases (*e.g.,* all uridines in a polynucleotide disclosed herein can be replaced with an unnatural nucleobase, *e.g.,* 5-methoxyuridine). In some aspects, the polynucleotide (*e.g.,* a synthetic RNA or a synthetic DNA) comprises only natural nucleobases, *i.e.,* A,C, T and U in the case of a synthetic DNA, or A, C, T, and U in the case of a synthetic RNA.

[01238] The skilled artisan will appreciate that the T bases in the codon maps disclosed herein are present in DNA, whereas the T bases would be replaced by U bases in corresponding RNAs. For example, a codon-nucleotide sequence disclosed herein in DNA form, *e.g.,* a vector or an in-vitro translation (IVT) template, would have its T bases transcribed as U based in its corresponding transcribed mRNA. In this respect, both sequence-optimized DNA sequences (comprising T) and their corresponding RNA sequences (comprising U) are considered sequence-optimized nucleotide sequence of the present disclosure. A skilled artisan would also understand that equivalent codon-maps can be generated by replaced one or more bases with non-natural bases. Thus, *e.g.,* a TTC codon (DNA map) would correspond to a UUC codon (RNA map), which in turn would correspond to a ΨΨC codon (RNA map in which U has been replaced with pseudouridine).

[01239] Standard A-T and G-C base pairs form under conditions that allow the formation of hydrogen bonds between the N3-H and C4-oxy of thymidine and the N1 and C6-NH2, respectively, of adenosine and between the C2-oxy, N3 and C4-NH2, of cytidine and the C2-NH2, N′—H and C6-oxy, respectively, of guanosine. Thus, for example, guanosine (2-amino-6-oxy-9-β-D-ribofuranosyl-purine) can be modified to form isoguanosine (2-oxy-6-amino-9-β-D-ribofuranosyl-purine). Such modification results in a nucleoside base that will no longer effectively form a standard base pair with cytosine. However, modification of cytosine (1-β-D-ribofuranosyl-2-oxy-4-amino-pyrimidine) to form isocytosine (1-β-D-ribofuranosyl-2-amino-4-oxy-pyrimidine-) results in a modified nucleotide that will not effectively base pair with guanosine but will form a base pair with isoguanosine (U.S. Pat. No. 5,681,702 to Collins et al.,

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hereby incorporated by reference in its entirety). Isocytosine is available from Sigma Chemical Co. (St. Louis, Mo.); isocytidine can be prepared by the method described by Switzer et al. (1993) Biochemistry 32:10489-10496 and references cited therein; 2′-deoxy-5-methyl-isocytidine can be prepared by the method of Tor et al., 1993, J. Am. Chem. Soc. 115:4461-4467 and references cited therein; and isoguanine nucleotides can be prepared using the method described by Switzer et al., 1993, supra, and Mantsch et al., 1993, Biochem. 14:5593-5601, or by the method described in U.S. Pat. No. 5,780,610 to Collins et al., each of which is hereby incorporated by reference in its entirety. Other nonnatural base pairs can be synthesized by the method described in Piccirilli et al., 1990, Nature 343:33-37, hereby incorporated by reference in its entirety, for the synthesis of 2,6-diaminopyrimidine and its complement (1-methylpyrazolo-[4,3]pyrimidine-5,7-(4H,6H)-dione. Other such modified nucleotide units that form unique base pairs are known, such as those described in Leach et al. (1992) J. Am. Chem. Soc. 114:3675-3683 and Switzer et al., supra.

[01240] *Polypeptide:* As used herein, "polypeptide" means a polymer of amino acid residues (natural or unnatural) linked together most often by peptide bonds. The term, as used herein, refers to proteins, polypeptides, and peptides of any size, structure, or function. Thus, polypeptides include gene products, naturally occurring polypeptides, synthetic polypeptides, homologs, orthologs, paralogs, fragments and other equivalents, variants, and analogs of the foregoing. A polypeptide can be a single molecule or can be a multi-molecular complex such as a dimer, trimer or tetramer. They can also comprise single chain or multichain polypeptides and can be associated or linked. Most commonly disulfide linkages are found in multichain polypeptides. The term polypeptide can also apply to amino acid polymers in which one or more amino acid residues are an artificial chemical analogue of a corresponding naturally occurring amino acid.

[01241] The term polypeptide encompasses an amino acid polymer that has been modified naturally or by intervention; for example, disulfide bond formation, glycosylation, lipidation, acetylation, phosphorylation, or any other manipulation or modification, such as conjugation with a labeling component. Also included within the definition are, for example, polypeptides containing one or more analogs of an amino acid (including, for example, unnatural amino acids such as homocysteine, ornithine, p-acetylphenylalanine, D-amino acids, and creatine), as well as other modifications known in the art.

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[01242] *Polypeptide variant*: As used herein, the term "polypeptide variant" refers to molecules that differ in their amino acid sequence from a native or reference sequence. The amino acid sequence variants can possess substitutions, deletions, and/or insertions at certain positions within the amino acid sequence, as compared to a native or reference sequence. Ordinarily, variants will possess at least about 50% identity (homology), at least about 60% identity, at least about 70% identity, at least about 80% identity, at least about 90% identity, at least about 95% identity, at least about 99% identity to a native or reference sequence. In some embodiments, they will be at least about 80%, or at least about 90% identical (homologous) to a native or reference sequence.

[01243] *Polypeptide per unit drug (PUD)*: As used herein, a PUD or product per unit drug, is defined as a subdivided portion of total daily dose, usually 1 mg, pg, kg, etc., of a product (such as a polypeptide) as measured in body fluid or tissue, usually defined in concentration such as pmol/mL, mmol/mL, etc. divided by the measure in the body fluid.

[01244] *Preventing*: As used herein, the term "preventing" refers to partially or completely delaying onset of an infection, disease, disorder and/or condition; partially or completely delaying onset of one or more symptoms, features, or clinical manifestations of a particular infection, disease, disorder, and/or condition; partially or completely delaying onset of one or more symptoms, features, or manifestations of a particular infection, disease, disorder, and/or condition; partially or completely delaying progression from an infection, a particular disease, disorder and/or condition; and/or decreasing the risk of developing pathology associated with the infection, the disease, disorder, and/or condition.

[01245] *Prodrug*: The present disclosure also includes prodrugs of the compounds described herein. As used herein, "prodrugs" refer to any substance, molecule or entity that is in a form predicate for that substance, molecule or entity to act as a therapeutic upon chemical or physical alteration. Prodrugs can by covalently bonded or sequestered in some way and that release or are converted into the active drug moiety prior to, upon or after administered to a mammalian subject. Prodrugs can be prepared by modifying functional groups present in the compounds in such a way that the modifications are cleaved, either in routine manipulation or *in vivo*, to the parent compounds. Prodrugs include compounds wherein hydroxyl, amino, sulfhydryl, or carboxyl groups are bonded to any group that, when administered to a mammalian subject, cleaves to form a free hydroxyl, amino, sulfhydryl, or carboxyl group respectively. Preparation and use of prodrugs is discussed in T. Higuchi and V. Stella, "Pro-drugs as Novel Delivery

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Systems," Vol. 14 of the A.C.S. Symposium Series, and in *Bioreversible Carriers in Drug Design*, ed. Edward B. Roche, American Pharmaceutical Association and Pergamon Press, 1987, both of which are hereby incorporated by reference in their entirety.

[01246] *Proliferate:* As used herein, the term "proliferate" means to grow, expand or increase or cause to grow, expand or increase rapidly. "Proliferative" means having the ability to proliferate. "Anti-proliferative" means having properties counter to or inapposite to proliferative properties.

[01247] *Prophylactic*: As used herein, "prophylactic" refers to a therapeutic or course of action used to prevent the spread of disease.

[01248] *Prophylaxis:* As used herein, a "prophylaxis" refers to a measure taken to maintain health and prevent the spread of disease. An "immune phrophylaxis" refers to a measure to produce active or passive immunity to prevent the spread of disease.

[01249] *Protein cleavage site*: As used herein, "protein cleavage site" refers to a site where controlled cleavage of the amino acid chain can be accomplished by chemical, enzymatic or photochemical means.

[01250] *Protein cleavage signal:* As used herein "protein cleavage signal" refers to at least one amino acid that flags or marks a polypeptide for cleavage.

[01251] *Protein of interest:* As used herein, the terms "proteins of interest" or "desired proteins" include those provided herein and fragments, mutants, variants, and alterations thereof.

[01252] *Proximal:* As used herein, the term "proximal" means situated nearer to the center or to a point or region of interest.

[01253] *Pseudouridine:* As used herein, pseudouridine refers to the C-glycoside isomer of the nucleoside uridine. A "pseudouridine analog" is any modification, variant, isoform or derivative of pseudouridine. For example, pseudouridine analogs include but are not limited to 1-carboxymethyl-pseudouridine, 1-propynyl-pseudouridine, 1-taurinomethyl-pseudouridine, 1-taurinomethyl-4-thio-pseudouridine, 1-methylpseudouridine ($m^1\psi$), 1-methyl-4-thio-pseudouridine ($m^1s^4\psi$), 4-thio-1-methyl-pseudouridine, 3-methyl-pseudouridine ($m^3\psi$), 2-thio-1-methyl-pseudouridine, 1-methyl-1-deaza-pseudouridine, 2-thio-1-methyl-1-deaza-pseudouridine, dihydropseudouridine, 2-thio-dihydropseudouridine, 2-methoxyuridine, 2-methoxy-4-thio-uridine, 4-methoxy-pseudouridine, 4-methoxy-2-thio-pseudouridine, N1-methyl-pseudouridine, 1-methyl-3-(3-amino-3-carboxypropyl)pseudouridine ($acp^3\ \psi$), and 2′-O-methyl-pseudouridine (ψm).

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[01254] *Purified:* As used herein, "purify," "purified," "purification" means to make substantially pure or clear from unwanted components, material defilement, admixture or imperfection.

[01255] *Repeated transfection:* As used herein, the term "repeated transfection" refers to transfection of the same cell culture with a polynucleotide a plurality of times. The cell culture can be transfected at least twice, at least 3 times, at least 4 times, at least 5 times, at least 6 times, at least 7 times, at least 8 times, at least 9 times, at least 10 times, at least 11 times, at least 12 times, at least 13 times, at least 14 times, at least 15 times, at least 16 times, at least 17 times at least 18 times, at least 19 times, at least 20 times, at least 25 times, at least 30 times, at least 35 times, at least 40 times, at least 45 times, at least 50 times or more.

[01256] *Sample:* As used herein, the term "sample" or "biological sample" refers to a subset of its tissues, cells or component parts (*e.g.,* body fluids, including but not limited to blood, mucus, lymphatic fluid, synovial fluid, cerebrospinal fluid, saliva, amniotic fluid, amniotic cord blood, urine, vaginal fluid and semen). A sample further can include a homogenate, lysate or extract prepared from a whole organism or a subset of its tissues, cells or component parts, or a fraction or portion thereof, including but not limited to, for example, plasma, serum, spinal fluid, lymph fluid, the external sections of the skin, respiratory, intestinal, and genitourinary tracts, tears, saliva, milk, blood cells, tumors, organs. A sample further refers to a medium, such as a nutrient broth or gel, which can contain cellular components, such as proteins or nucleic acid molecule.

[01257] *Signal Sequences:* As used herein, the phrase "signal sequences" refers to a sequence that can direct the transport or localization of a protein.

[01258] *Single unit dose*: As used herein, a "single unit dose" is a dose of any therapeutic administered in one dose/at one time/single route/single point of contact, *i.e.*, single administration event.

[01259] *Similarity*: As used herein, the term "similarity" refers to the overall relatedness between polymeric molecules, *e.g.*, between polynucleotide molecules (*e.g.*, DNA molecules and/or RNA molecules) and/or between polypeptide molecules. Calculation of percent similarity of polymeric molecules to one another can be performed in the same manner as a calculation of percent identity, except that calculation of percent similarity takes into account conservative substitutions as is understood in the art.

[01260] *Split dose*: As used herein, a "split dose" is the division of single unit dose or total daily dose into two or more doses.

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[01261] *Stable:* As used herein "stable" refers to a compound that is sufficiently robust to survive isolation to a useful degree of purity from a reaction mixture, and in some cases capable of formulation into an efficacious therapeutic agent.

[01262] *Stabilized:* As used herein, the term "stabilize," "stabilized," "stabilized region" means to make or become stable.

[01263] *Stereoisomer:* As used herein, the term "stereoisomer" refers to all possible different isomeric as well as conformational forms that a compound can possess (*e.g.,* a compound of any formula described herein), in particular all possible stereochemically and conformationally isomeric forms, all diastereomers, enantiomers and/or conformers of the basic molecular structure. Some compounds of the present disclosure can exist in different tautomeric forms, all of the latter being included within the scope of the present disclosure.

[01264] *Subject:* As used herein, the term "subject" or "patient" refers to any organism to which a composition in accordance with the disclosure can be administered, *e.g.*, for experimental, diagnostic, prophylactic, and/or therapeutic purposes. Typical subjects include animals (*e.g.*, mammals such as mice, rats, rabbits, non-human primates, and humans).

[01265] *Substantially*: As used herein, the term "substantially" refers to the qualitative condition of exhibiting total or near-total extent or degree of a characteristic or property of interest. One of ordinary skill in the biological arts will understand that biological and chemical phenomena rarely, if ever, go to completion and/or proceed to completeness or achieve or avoid an absolute result. The term "substantially" is therefore used herein to capture the potential lack of completeness inherent in many biological and chemical phenomena.

[01266] *Substantially equal*: As used herein as it relates to time differences between doses, the term means plus/minus 2%.

[01267] *Substantially simultaneously*: As used herein and as it relates to plurality of doses, the term means within 2 seconds.

[01268] *Suffering from*: An individual who is "suffering from" a disease, disorder, and/or condition has been diagnosed with or displays one or more symptoms of a disease, disorder, and/or condition.

[01269] *Susceptible to*: An individual who is "susceptible to" a disease, disorder, and/or condition has not been diagnosed with and/or can not exhibit symptoms of the disease, disorder, and/or condition but harbors a propensity to develop a disease or its symptoms. In some embodiments, an individual who is susceptible to a disease, disorder, and/or condition (for

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example, cancer) can be characterized by one or more of the following: (1) a genetic mutation associated with development of the disease, disorder, and/or condition; (2) a genetic polymorphism associated with development of the disease, disorder, and/or condition; (3) increased and/or decreased expression and/or activity of a protein and/or nucleic acid associated with the disease, disorder, and/or condition; (4) habits and/or lifestyles associated with development of the disease, disorder, and/or condition; (5) a family history of the disease, disorder, and/or condition; and (6) exposure to and/or infection with a microbe associated with development of the disease, disorder, and/or condition. In some embodiments, an individual who is susceptible to a disease, disorder, and/or condition will develop the disease, disorder, and/or condition. In some embodiments, an individual who is susceptible to a disease, disorder, and/or condition will not develop the disease, disorder, and/or condition.

[01270] *Sustained release:* As used herein, the term "sustained release" refers to a pharmaceutical composition or compound release profile that conforms to a release rate over a specific period of time.

[01271] *Synthetic*: The term "synthetic" means produced, prepared, and/or manufactured by the hand of man. Synthesis of polynucleotides or polypeptides or other molecules of the present disclosure can be chemical or enzymatic.

[01272] *Targeted Cells:* As used herein, "targeted cells" refers to any one or more cells of interest. The cells can be found *in vitro*, *in vivo*, *in situ* or in the tissue or organ of an organism. The organism can be an animal, for example a mammal, a human or a patient.

[01273] *Targeting sequence*: As used herein, the phrase "targeting sequence" refers to a sequence that can direct the transport or localization of a protein.

[01274] *Therapeutic Agent:* The term "therapeutic agent" refers to any agent that, when administered to a subject, has a therapeutic, diagnostic, and/or prophylactic effect and/or elicits a desired biological and/or pharmacological effect.

[01275] *Therapeutically effective amount:* As used herein, the term "therapeutically effective amount" means an amount of an agent to be delivered (*e.g.*, nucleic acid, drug, therapeutic agent, diagnostic agent, prophylactic agent, etc.) that is sufficient, when administered to a subject suffering from or susceptible to an infection, disease, disorder, and/or condition, to treat, improve symptoms of, diagnose, prevent, and/or delay the onset of the infection, disease, disorder, and/or condition.

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[01276] *Therapeutically effective outcome*: As used herein, the term "therapeutically effective outcome" means an outcome that is sufficient in a subject suffering from or susceptible to an infection, disease, disorder, and/or condition, to treat, improve symptoms of, diagnose, prevent, and/or delay the onset of the infection, disease, disorder, and/or condition.

[01277] *Total daily dose:* As used herein, a "total daily dose" is an amount given or prescribed in 24 hr. period. It can be administered as a single unit dose.

[01278] *Transcription factor:* As used herein, the term "transcription factor" refers to a DNA-binding protein that regulates transcription of DNA into RNA, for example, by activation or repression of transcription. Some transcription factors effect regulation of transcription alone, while others act in concert with other proteins. Some transcription factor can both activate and repress transcription under certain conditions. In general, transcription factors bind a specific target sequence or sequences highly similar to a specific consensus sequence in a regulatory region of a target gene. Transcription factors can regulate transcription of a target gene alone or in a complex with other molecules.

[01279] *Transcription*: As used herein, the term "transcription" refers to methods to introduce exogenous nucleic acids into a cell. Methods of transfection include, but are not limited to, chemical methods, physical treatments and cationic lipids or mixtures.

[01280] *Treating*: As used herein, the terms "treating" or "treatment" or "therapy" refers to partially or completely alleviating, ameliorating, improving, relieving, delaying onset of, inhibiting progression of, reducing severity of, and/or reducing incidence of one or more symptoms or features of a particular infection, disease, disorder, and/or condition. Treatment can be administered to a subject who does not exhibit signs of a disease, disorder, and/or condition and/or to a subject who exhibits only early signs of a disease, disorder, and/or condition for the purpose of decreasing the risk of developing pathology associated with the disease, disorder, and/or condition.

[01281] *Unmodified*: As used herein, "unmodified" refers to any substance, compound or molecule prior to being changed in any way. Unmodified may, but does not always, refer to the wild type or native form of a biomolecule. Molecules can undergo a series of modifications whereby each modified molecule can serve as the "unmodified" starting molecule for a subsequent modification.

[01282] *Viral protein*: As used herein, the phrase "viral protein" means any protein originating from a virus.

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X. Cross-reference to related applications

[01283] This application claims priority to U.S. Provisional Patent Application No. 62/269,089 filed December 17, 2015, entitled Polynucleotides Encoding Methylmalonyl-CoA Mutase; U.S. Provisional Patent Application No. 62/269,092 filed December 17, 2015, entitled Methods of Using MCM-Enconding Polynucleotides; U.S. Provisional Patent Application No. 62/273,112 filed December 30, 2015, entitled Polynucleotides Encoding Methylmalonyl-CoA Mutase; U.S. Provisional Patent Application No. 62/273,108 filed December 30, 2015, entitled Methods of Using MCM-Enconding Polynucleotides; U.S. Provisional Patent Application No. 62/274,727 filed January 4, 2016, entitled Polynucleotides Encoding Methylmalonyl-CoA Mutase; U.S. Provisional Patent Application No. 62/274,733 filed January 4, 2016, entitled Methods of Using MCM-Enconding Polynucleotides; U.S. Provisional Patent Application No. 62/274,722 filed January 4, 2016, entitled Polynucleotides Encoding Methylmalonyl-CoA Mutase; U.S. Provisional Patent Application No. 62/274,726 filed January 4, 2016, entitled Methods of Using MCM-Enconding Polynucleotides; U.S. Provisional Patent Application No. 62/338,478 filed Can 18, 2016, entitled Polynucleotides Encoding Methylmalonyl-CoA Mutase; U.S. Provisional Patent Application No. 62/338,456 filed Can 18, 2016, entitled Polynucleotides Encoding Methylmalonyl-CoA Mutase; and U.S. Provisional Patent Application No. 62/409,343 filed October 14, 2016, entitled Polynucleotides Encoding Methylmalonyl-CoA Mutase, the contents of each of which are herein incorporated by reference in its entirety.

XI. Reference to sequence listing submitted electronically

[01284] The content of the electronically submitted sequence listing (Name: "3529_052PC07_SeqListing_ST25.txt"; Size: 1,080,572 bytes; and date of creation: December 16, 2016) filed herewith the application is incorporated by reference in its entirety.

XII. Equivalents and Scope

[01285] Those skilled in the art will recognize, or be able to ascertain using no more than routine experimentation, many equivalents to the specific embodiments in accordance with the disclosure described herein. The scope of the present disclosure is not intended to be limited to the above Description, but rather is as set forth in the appended claims.

[01286] In the claims, articles such as "a," "an," and "the" can mean one or more than one unless indicated to the contrary or otherwise evident from the context. Claims or descriptions

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that include "or" between one or more members of a group are considered satisfied if one, more than one, or all of the group members are present in, employed in, or otherwise relevant to a given product or process unless indicated to the contrary or otherwise evident from the context. The disclosure includes embodiments in which exactly one member of the group is present in, employed in, or otherwise relevant to a given product or process. The disclosure includes embodiments in which more than one, or all of the group members are present in, employed in, or otherwise relevant to a given product or process.

[01287] It is also noted that the term "comprising" is intended to be open and permits but does not require the inclusion of additional elements or steps. When the term "comprising" is used herein, the term "consisting of" is thus also encompassed and disclosed.

[01288] Where ranges are given, endpoints are included. Furthermore, it is to be understood that unless otherwise indicated or otherwise evident from the context and understanding of one of ordinary skill in the art, values that are expressed as ranges can assume any specific value or subrange within the stated ranges in different embodiments of the disclosure, to the tenth of the unit of the lower limit of the range, unless the context clearly dictates otherwise.

[01289] In addition, it is to be understood that any particular embodiment of the present disclosure that falls within the prior art can be explicitly excluded from any one or more of the claims. Since such embodiments are deemed to be known to one of ordinary skill in the art, they can be excluded even if the exclusion is not set forth explicitly herein. Any particular embodiment of the compositions of the disclosure (*e.g.*, any nucleic acid or protein encoded thereby; any method of production; any method of use; etc.) can be excluded from any one or more claims, for any reason, whether or not related to the existence of prior art.

[01290] All cited sources, for example, references, publications, databases, database entries, and art cited herein, are incorporated into this application by reference, even if not expressly stated in the citation. In case of conflicting statements of a cited source and the instant application, the statement in the instant application shall control.

[01291] Section and table headings are not intended to be limiting.

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EXAMPLES

Example 1. Chimeric polynucleotide synthesis

Triphosphate route

[01292] Two regions or parts of a chimeric polynucleotide can be joined or ligated using triphosphate chemistry. According to this method, a first region or part of 100 nucleotides or less can be chemically synthesized with a 5' monophosphate and terminal 3'desOH or blocked OH. If the region is longer than 80 nucleotides, it can be synthesized as two strands for ligation.

[01293] If the first region or part is synthesized as a non-positionally modified region or part using *in vitro* transcription (IVT), conversion the 5'monophosphate with subsequent capping of the 3' terminus can follow. Monophosphate protecting groups can be selected from any of those known in the art.

[01294] The second region or part of the chimeric polynucleotide can be synthesized using either chemical synthesis or IVT methods. IVT methods can include an RNA polymerase that can utilize a primer with a modified cap. Alternatively, a cap of up to 80 nucleotides can be chemically synthesized and coupled to the IVT region or part.

[01295] It is noted that for ligation methods, ligation with DNA T4 ligase, followed by treatment with DNAse should readily avoid concatenation.

[01296] The entire chimeric polynucleotide need not be manufactured with a phosphate-sugar backbone. If one of the regions or parts encodes a polypeptide, then such region or part can comprise a phosphate-sugar backbone.

[01297] Ligation can then be performed using any known click chemistry, orthoclick chemistry, solulink, or other bioconjugate chemistries known to those in the art.

Synthetic route

[01298] The chimeric polynucleotide can be made using a series of starting segments. Such segments include:

(a) Capped and protected 5' segment comprising a normal 3'OH (SEG. 1)

(b) 5' triphosphate segment which can include the coding region of a polypeptide and comprising a normal 3'OH (SEG. 2)

(c) 5' monophosphate segment for the 3' end of the chimeric polynucleotide (*e.g.,* the tail) comprising cordycepin or no 3'OH (SEG. 3)

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[01299] After synthesis (chemical or IVT), segment 3 (SEG. 3) can be treated with cordycepin and then with pyrophosphatase to create the 5'monophosphate.

[01300] Segment 2 (SEG. 2) can then be ligated to SEG. 3 using RNA ligase. The ligated polynucleotide can then be purified and treated with pyrophosphatase to cleave the diphosphate. The treated SEG.2-SEG. 3 construct is then purified and SEG. 1 is ligated to the 5' terminus. A further purification step of the chimeric polynucleotide can be performed.

[01301] Where the chimeric polynucleotide encodes a polypeptide, the ligated or joined segments can be represented as: 5'UTR (SEG. 1), open reading frame or ORF (SEG. 2) and 3'UTR+PolyA (SEG. 3).

[01302] The yields of each step can be as much as 90-95%.

Example 2: PCR for cDNA Production

[01303] PCR procedures for the preparation of cDNA can be performed using 2x KAPA HIFI™ HotStart ReadyMix by Kapa Biosystems (Woburn, MA). This system includes 2x KAPA ReadyMix12.5 µl; Forward Primer (10 µM) 0.75 µl; Reverse Primer (10 µM) 0.75 µl; Template cDNA -100 ng; and dH_20 diluted to 25.0 µl. The PCR reaction conditions can be: at 95° C for 5 min. and 25 cycles of 98° C for 20 sec, then 58° C for 15 sec, then 72° C for 45 sec, then 72° C for 5 min. then 4° C to termination.

[01304] The reverse primer of the instant disclosure can incorporate a poly-T_{120} for a poly-A_{120} in the mRNA. Other reverse primers with longer or shorter poly(T) tracts can be used to adjust the length of the poly(A) tail in the polynucleotide mRNA.

[01305] The reaction can be cleaned up using Invitrogen's PURELINK™ PCR Micro Kit (Carlsbad, CA) per manufacturer's instructions (up to 5 µg). Larger reactions will require a cleanup using a product with a larger capacity. Following the cleanup, the cDNA can be quantified using the NANODROP™ and analyzed by agarose gel electrophoresis to confirm the cDNA is the expected size. The cDNA can then be submitted for sequencing analysis before proceeding to the *in vitro* transcription reaction.

Example 3. *In vitro* Transcription (IVT)

[01306] The *in vitro* transcription reactions can generate polynucleotides containing uniformly modified polynucleotides. Such uniformly modified polynucleotides can comprise a region or

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part of the polynucleotides of the disclosure. The input nucleotide triphosphate (NTP) mix can be made using natural and un-natural NTPs.

[01307] A typical *in vitro* transcription reaction can include the following:

1 Template cDNA—1.0 µg
2 10x transcription buffer (400 mM Tris-HCl pH 8.0, 190 mM $MgCl_2$, 50 mM DTT, 10 mM Spermidine)—2.0 µl
3 Custom NTPs (25mM each) —7.2 µl
4 RNase Inhibitor—20 U
5 T7 RNA polymerase —3000 U
6 dH_20—Up to 20.0 µl. and
7 Incubation at 37° C for 3 hr-5 hrs.

[01308] The crude IVT mix can be stored at 4° C overnight for cleanup the next day. 1 U of RNase-free DNase can then be used to digest the original template. After 15 minutes of incubation at 37° C, the mRNA can be purified using Ambion's MEGACLEAR™ Kit (Austin, TX) following the manufacturer's instructions. This kit can purify up to 500 µg of RNA. Following the cleanup, the RNA can be quantified using the NanoDrop and analyzed by agarose gel electrophoresis to confirm the RNA is the proper size and that no degradation of the RNA has occurred.

Example 4. Enzymatic Capping

[01309] Capping of a polynucleotide can be performed with a mixture includes: IVT RNA 60 µg-180µg and dH_20 up to 72 µl. The mixture can be incubated at 65° C for 5 minutes to denature RNA, and then can be transferred immediately to ice.

[01310] The protocol can then involve the mixing of 10x Capping Buffer (0.5 M Tris-HCl (pH 8.0), 60 mM KCl, 12.5 mM $MgCl_2$) (10.0 µl); 20 mM GTP (5.0 µl); 20 mM S-Adenosyl Methionine (2.5 µl); RNase Inhibitor (100 U); 2′-O-Methyltransferase (400U); Vaccinia capping enzyme (Guanylyl transferase) (40 U); dH_20 (Up to 28 µl); and incubation at 37° C for 30 minutes for 60 µg RNA or up to 2 hours for 180 µg of RNA.

[01311] The polynucleotide can then be purified using Ambion's MEGACLEAR™ Kit (Austin, TX) following the manufacturer's instructions. Following the cleanup, the RNA can be quantified using the NANODROP™ (ThermoFisher, Waltham, MA) and analyzed by agarose gel electrophoresis to confirm the RNA is the proper size and that no degradation of the RNA

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has occurred. The RNA product can also be sequenced by running a reverse-transcription-PCR to generate the cDNA for sequencing.

Example 5. PolyA Tailing Reaction

[01312] Without a poly-T in the cDNA, a poly-A tailing reaction must be performed before cleaning the final product. This can be done by mixing Capped IVT RNA (100 µl); RNase Inhibitor (20 U); 10x Tailing Buffer (0.5 M Tris-HCl (pH 8.0), 2.5 M NaCl, 100 mM $MgCl_2$)(12.0 µl); 20 mM ATP (6.0 µl); Poly-A Polymerase (20 U); dH_20 up to 123.5 µl and incubating at 37° C for 30 min. If the poly-A tail is already in the transcript, then the tailing reaction can be skipped and proceed directly to cleanup with Ambion's MEGACLEAR™ kit (Austin, TX) (up to 500 µg). Poly-A Polymerase is, in some cases, a recombinant enzyme expressed in yeast.

[01313] It should be understood that the processivity or integrity of the polyA tailing reaction does not always result in an exact size polyA tail. Hence polyA tails of approximately between 40-200 nucleotides, *e.g.*, about 40, 50, 60, 70, 80, 90, 91, 92, 93, 94, 95, 96, 97, 98, 99, 100, 101, 102, 103, 104, 105, 106, 107, 108, 109, 110, 150-165, 155, 156, 157, 158, 159, 160, 161, 162, 163, 164 or 165 are within the scope of the disclosure.

Example 6. Natural 5′ Caps and 5′ Cap Analogues

[01314] 5′-capping of polynucleotides can be completed concomitantly during the *in vitro*-transcription reaction using the following chemical RNA cap analogs to generate the 5′-guanosine cap structure according to manufacturer protocols: 3´-O-Me-m7G(5')ppp(5') G [the ARCA cap];G(5')ppp(5')A; G(5')ppp(5')G; m7G(5')ppp(5')A; m7G(5')ppp(5')G (New England BioLabs, Ipswich, MA). 5′-capping of modified RNA can be completed post-transcriptionally using a Vaccinia Virus Capping Enzyme to generate the "Cap 0" structure: m7G(5')ppp(5')G (New England BioLabs, Ipswich, MA). Cap 1 structure can be generated using both Vaccinia Virus Capping Enzyme and a 2′-O methyl-transferase to generate: m7G(5')ppp(5')G-2′-O-methyl. Cap 2 structure can be generated from the Cap 1 structure followed by the 2′-O-methylation of the 5′-antepenultimate nucleotide using a 2′-O methyl-transferase. Cap 3 structure can be generated from the Cap 2 structure followed by the 2′-O-methylation of the 5′-preantepenultimate nucleotide using a 2′-O methyl-transferase. Enzymes can be derived from a recombinant source.

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[01315] When transfected into mammalian cells, the modified mRNAs can have a stability of between 12-18 hours or more than 18 hours, *e.g.,* 24, 36, 48, 60, 72 or greater than 72 hours.

Example 7. Capping Assays

A. Protein Expression Assay

[01316] Polynucleotides encoding a polypeptide, containing any of the caps taught herein, can be transfected into cells at equal concentrations. After 6, 12, 24 and 36 hours post-transfection, the amount of protein secreted into the culture medium can be assayed by ELISA. Synthetic polynucleotides that secrete higher levels of protein into the medium would correspond to a synthetic polynucleotide with a higher translationally-competent Cap structure.

B. Purity Analysis Synthesis

[01317] Polynucleotides encoding a polypeptide, containing any of the caps taught herein, can be compared for purity using denaturing Agarose-Urea gel electrophoresis or HPLC analysis. Polynucleotides with a single, consolidated band by electrophoresis correspond to the higher purity product compared to polynucleotides with multiple bands or streaking bands. Synthetic polynucleotides with a single HPLC peak would also correspond to a higher purity product. The capping reaction with a higher efficiency would provide a more pure polynucleotide population.

C. Cytokine Analysis

[01318] Polynucleotides encoding a polypeptide, containing any of the caps taught herein, can be transfected into cells at multiple concentrations. After 6, 12, 24 and 36 hours post-transfection the amount of pro-inflammatory cytokines such as TNF-alpha and IFN-beta secreted into the culture medium can be assayed by ELISA. Polynucleotides resulting in the secretion of higher levels of pro-inflammatory cytokines into the medium would correspond to polynucleotides containing an immune-activating cap structure.

D. Capping Reaction Efficiency

[01319] Polynucleotides encoding a polypeptide, containing any of the caps taught herein, can be analyzed for capping reaction efficiency by LC-MS after nuclease treatment. Nuclease treatment of capped polynucleotides would yield a mixture of free nucleotides and the capped 5′-5-triphosphate cap structure detectable by LC-MS. The amount of capped product on the LC-MS spectra can be expressed as a percent of total polynucleotide from the reaction and would

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correspond to capping reaction efficiency. The cap structure with higher capping reaction efficiency would have a higher amount of capped product by LC-MS.

Example 8. Agarose Gel Electrophoresis of Modified RNA or RT PCR Products

[01320] Individual polynucleotides (200-400 ng in a 20 µl volume) or reverse transcribed PCR products (200-400 ng) can be loaded into a well on a non-denaturing 1.2% Agarose E-Gel (Invitrogen, Carlsbad, CA) and run for 12-15 minutes according to the manufacturer protocol.

Example 9. Nanodrop Modified RNA Quantification and UV Spectral Data

[01321] Modified polynucleotides in TE buffer (1 µl) can be used for Nanodrop UV absorbance readings to quantitate the yield of each polynucleotide from an chemical synthesis or *in vitro* transcription reaction.

Example 10. Formulation of Modified mRNA Using Lipidoids

[01322] Polynucleotides can be formulated for *in vitro* experiments by mixing the polynucleotides with the lipidoid at a set ratio prior to addition to cells. *In vivo* formulation can require the addition of extra ingredients to facilitate circulation throughout the body. To test the ability of these lipidoids to form particles suitable for *in vivo* work, a standard formulation process used for siRNA-lipidoid formulations can be used as a starting point. After formation of the particle, polynucleotide can be added and allowed to integrate with the complex. The encapsulation efficiency can be determined using a standard dye exclusion assays.

Example 11. Method of Screening for Protein Expression

A. Electrospray Ionization

[01323] A biological sample that can contain proteins encoded by a polynucleotide administered to the subject can be prepared and analyzed according to the manufacturer protocol for electrospray ionization (ESI) using 1, 2, 3 or 4 mass analyzers. A biologic sample can also be analyzed using a tandem ESI mass spectrometry system.

[01324] Patterns of protein fragments, or whole proteins, can be compared to known controls for a given protein and identity can be determined by comparison.

B. Matrix-Assisted Laser Desorption/Ionization

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[01325] A biological sample that can contain proteins encoded by one or more polynucleotides administered to the subject can be prepared and analyzed according to the manufacturer protocol for matrix-assisted laser desorption/ionization (MALDI).

[01326] Patterns of protein fragments, or whole proteins, can be compared to known controls for a given protein and identity can be determined by comparison.

C. Liquid Chromatography-Mass spectrometry-Mass spectrometry

[01327] A biological sample, which can contain proteins encoded by one or more polynucleotides, can be treated with a trypsin enzyme to digest the proteins contained within. The resulting peptides can be analyzed by liquid chromatography-mass spectrometry-mass spectrometry (LC/MS/MS). The peptides can be fragmented in the mass spectrometer to yield diagnostic patterns that can be matched to protein sequence databases via computer algorithms. The digested sample can be diluted to achieve 1 ng or less starting material for a given protein. Biological samples containing a simple buffer background (*e.g.,* water or volatile salts) are amenable to direct in-solution digest; more complex backgrounds (*e.g.,* detergent, non-volatile salts, glycerol) require an additional clean-up step to facilitate the sample analysis.

[01328] Patterns of protein fragments, or whole proteins, can be compared to known controls for a given protein and identity can be determined by comparison.

Example 12. Synthesis of mRNA Encoding MCM

[01329] The sequence optimized polynucleotides encoding MCM polypeptides, *i.e.*, SEQ ID NOs: 1-207, 732-765, and 772, are synthesized as described in Examples 1 to 12.

[01330] Further, mRNA's encoding both mouse MCM and human MCM were prepared for Examples 13-19 described below, and they were synthesized as described in Examples 1 to 12.

[01331] An mRNA encoding human MCM ("hMCM-mRNA") was constructed that encodes the naturally-occurring V671 mutation of MCM. The nucleotide sequence of hMCM-mRNA is provided in SEQ ID NO: 249. The hMCM-mRNA sequence includes both 5' and 3' UTR regions (SEQ ID NOs: 266 and 267, respectively):

5'UTR:TCAAGCTTTTGGACCCTCGTACAGAAGCTAATACGACTCACTAT
AGGGAAATAAGAGAGAAAAGAAGAGTAAGAAGAAATATAAGAGCCA
CC

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3'UTR:TGATAATAGGCTGGAGCCTCGGTGGCCATGCTTCTTGCCCCTTG
GGCCTCCCCCCAGCCCCTCCTCCCCTTCCTGCACCCGTACCCCCGTGGT
CTTTGAATAAAGTCTGAGTGGGCGGC

[01332] A mRNA encoding mouse MCM ("mMCM-mRNA") was also constructed using standard molecular biology techniques. The nucleotide sequence of mMCM-mRNA is provided in SEQ ID NO: 250, and it encodes mouse MCM (SEQ ID NO: 268). The mMCM-mRNA sequence includes the same 5' and 3' UTR regions as hMCM-mRNA.

[01333] Both hMCM-mRNA and mMCM-mRNA were prepared as modified mRNA. Specifically, during in vitro translation, modified mRNA was generated using 1-methyl-pseudoUTP to ensure that the mRNAs contained 100% 1-methyl-pseudouridine instead of uridine. Further, both hMCM-mRNA and mMCM-mRNA were synthesized with a primer that introduced a 100 nucleotide polyA-tail, and a Cap 1 structure was generated on both mRNAs using Vaccinia Virus Capping Enzyme and a 2′-O methyl-transferase to generate: m7G(5')ppp(5')G-2′-O-methyl.

Example 13. Detecting Endogenous MCM Expression *In Vitro*

[01334] MCM expression was characterized in a variety of cell lines, including cells derived from both mice and human sources. The cell lines tested included Hepa1-6 (mouse), HepG2 (human), SNU423 (human), and HeLa cells. Cell were cultured in standard conditions and cell extracts were obtained by placing the cells in lysis buffer. For comparison purposes, a mitochondrial extract from mouse liver was also prepared. To prepare the liver extract, whole liver was homogenized in an ice-cold sucrose-containing hypotonic buffer at neutral pH adjusted with 0.1 molarTrizma base-MOPS (3-(N-morpholino)propanesulfonic acid). The liver homogenates were centrifuged at 600g in a cold table-top centrifuge to remove the nuclear fraction. The mitochondrial fraction was then collected by centrifugation of the cleared lysates at 7000g.

[01335] To analyze MCM expression, 15 µg of each lysate was prepared in a 40µL volume with lithium dodecyl sulfate sample loading buffer and subjected to standard Western blot analysis. For detection of MCM, the antibody used was anti-methylmalonyl-CoA mutase (mouse polyclonal; Ab67869; ABCAM®) at a 1:1000 dilution. For detection of a load control, the antibody used was anti-citrase synthase (rabbit polyclonal; PA5-22126; Thermo-Fisher SCIENTIFIC®). In **FIG. 1**, the signal provided by anti-MCM is provided in green, while the

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anti-citrate synthase signal is provided in red. **FIG. 1** shows that MCM was found in all cell lines tested, including both mouse and human liver-derived cell lines. For all cell lines, the expression of MCM was in roughly the same proportion to the control citrate synthase signal, though less signal was observed in HeLa cells. **FIG. 1** also shows that the cell lines expressed MCM at a level comparable to mouse liver mitochondrial mitochondrial extract.

[01336] To examine the localization of endogenous MCM, immunofluorescence analysis was performed on HeLa cells. MCM expression was detected using anti-methylmalonyl-CoA mutase (mouse monoclonal; Ab67869; ABCAM®), mitochondria were detected using Mitotracker, and the nucleus was stained with DAPI. Image analysis was performed on a Zeiss ELYRA imaging system. As seen in **FIGS. 2(A)-(C)**, the HeLa immunofluorescent staining reveals extensive colocalization between mitochondria (red) and MCM immunofluorescence (green), with little to no colocalization between the nucleus (DAPI stain) and MCM. The finding that the majority of endogenous MCM localizes with mitochondria is consistent with MCM's known metabolic function and localization.

Example 14. *In Vitro* Expression of MCM in HeLa Cells

[01337] To measure in vitro expression of human MCM in HeLa cells, those cells were seeded on 12-well plates (BD Biosciences, San Jose, USA) one day prior to transfection. mRNA formulations comprising human MCM (SEQ ID NO: 249) or a GFP control (encoding SEQ ID NO: 269) were transfected using 800 ng mRNA and 2 µL Lipofectamin 2000 in 60 µL OPTI-MEM per well and incubated. After 24 hours, the cells in each well were lysed using a consistent amount of lysis buffer. For comparison purposes, mouse liver mitochondrial extract was also prepared as described in Example 13. Protein concentrations of each were determined using a BCA assay according to manufacturer's instructions. To analyze MCM expression, equal load of each lysate (24 µg) was prepared in a loading buffer and subjected to standard Western blot analysis. For detection of MCM, the antibody used was anti-methylmalonyl-CoA mutase (rabbit monoclonal; ab133672; Abcam®) at a 1:1000 dilution.

[01338] The resulting Western blot, shown in **FIG. 3**, demonstrates that introduction of a mRNA formulation comprising hMCM sequence (SEQ ID NO: 249) greatly increased the level of MCM expression in HeLa cells relative to cells transfected with a control construct. The MCM expression level observed after introduction of mRNA encoding MCM were even higher than the levels present in liver mitochondrial mitochondrial extract. While **FIG. 1** indicates that

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at least some endogenous MCM is present in HeLa cells, **FIG. 3** shows that the MCM expression levels far exceed that baseline after introduction of mRNAs comprising hMCM.

Example 15. *In Vitro* MCM Activity in HeLa Cells

[01339] While the Western blots of **FIG. 3** demonstrate that MCM is expressed after introduction of mRNA comprising an MCM sequence, **FIG. 3** does not address whether the exogenously-expressed MCM is active. To answer this question, an in vitro MCM activity assay was performed.

A. *Expression*

[01340] HeLa cells were transfected with mRNA formulations comprising human MCM (SEQ ID NO: 249) or a GFP control (encoding SEQ ID NO: 269) were transfected with Lipofectamin 2000 and lysed as described in Example 14 above. For comparison purposes, mouse liver mitochondrial extract was also prepared as described in Example 13 above.

B. *Activity Assay*

[01341] To assess whether exogenous MCM can function, an in vitro activity assay was performed using transfected HeLa cell lysates as the source of enzymatic activity. To begin, 60 µL of lysate containing 132 µg protein was mixed with 30 µL of MCM coenzyme adocobalimin (1 mM in distilled water) at 37°C for 5minutes. Equal amounts of DL-2-[methyl-^{14}C]-methylmalonyl-CoA (50-60 mCi per mmol; Cat ARC0847; American Radiolabeled Chemicals) were then added to each reaction, which was further incubated at 37°C for 10 minutes. The reaction was stopped by adding 50 µ L of 100 g/L TCA and vortexing. The reaction tubes were then centrifuged at 13,000 g for 1 min, and the supernatant was analyzed for the presence of [^{14}C]-succinyl-CoA using HPLC-based separation and quantification. Specifically, 20 µL of each activity reaction supernatant was analyzed using a HPLC system equipped with a Quaternary-Pump, a Multi-sampler, a Thermostated Column-Compartment, a Poroshell EC-C18 120 HPLC-column and a Radiometric Detector controlled by OpenLAB Chromatography Data System, all used according to the manufacturers' recommendations. Elusion was with a linear methanol gradient: 0-15 min (Solvent A: 95% 100mM acetic acid in 100 mM sodium phosphate buffer, pH 7.0) and 15-25 min (95% Solvent A with 5 % of an 18% v/v methanol/water solution) with a flow rate of 0.5 mL/min.

[01342] **FIG. 4** shows that there was very low to no MCM activity detected in control transfected HeLa cells. **FIG. 4** also shows, however, that transfection with mRNA encoding

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hMCM led to MCM activity of almost 0.2 mM/min/mg. The MCM activity of cell lysate generated by transfection with mRNA encoding hMCM was roughly half of that observed in mouse liver mitochondrial extract.

Example 16. Measuring *In Vitro* Expression of MCM

[01343] Hepa1-6 cells and fibroblasts from normal subject (NHDF) and MMA patients (GM50 and GM1673) were examined for their capacity to express exogenous MCM.

[01344] Cells were transfected with mRNA formulations comprising human MCM (SEQ ID NO: 249), mouse MCM (SEQ ID NO: 250), or a GFP control (encoding SEQ ID NO: 269) via electroporation using a standard protocol. Each construct was tested separately. After 24 hours incubation, cells were lysed and protein concentration in each lysate was measured by BCA assay. To analyze MCM expression, equal load of each lysate (26 µg) was prepared in a loading buffer and subjected to standard Western blot analysis. For detection of MCM, the antibody used was anti-methylmalonyl-CoA mutase (mouse monoclonal; Anti-MUT TRUEMAB Antibody Clone OTI2C8; OriGene®) at a 1:5000 dilution. For detection of a load control, the antibody used was anti-citrase synthase (rabbit polyclonal; MA5-17625; Pierce®).

[01345] **FIG. 5** shows that introduction of formulations containing a human MCM sequence (SEQ ID NO: 249) greatly increased the level of MCM expression in normal human cells and in cells from MMA patients, relative to cells transfected with a control construct. The increased MCM expression level observed after introduction of mRNA encoding hMCM were reflected in the appearance in **FIG. 5** of an MCM band in cells transfected with mRNA encoding hMCM. While no significant difference in MCM levels was noted after transfection with mouse MCM (SEQ ID NO: 250), this could be due to a specific interaction of the MCM antibody with only the human form of the enzyme.

[01346] **FIGS. 6A-6D** show co-localization of MCM and mitochondria in human fibroblasts transfected with eGFP or MCM mRNAs. To examine the localization of mRNA-encoded hMCM in mitochondria, 1 x 10^6 MCM-deficient patient fibroblasts (GM01673) were transfected with 1 µg of hMCM mRNA. 24 hours after transfection, the cells were incubated with 200 nM MitoTracker Red CMXRos (M7512, ThermoFisher Scientific) for 30 min to mark mitochondria and stained with anti-MCM mouse mAb (TA506873, Origene) to examine the cellular localization.). **FIGS. 6A** and **6C** are images taken of patient fibroblasts transfected with mRNA encoding eGFP. **FIGS. 6B** and **6D** are images taken of patient fibroblasts transfected with

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mRNA encoding hMCM. A co-localization of MCM and mitochondria was observed, suggesting expressed MCM proteins reside inside mitochondria.

Example 17. Measuring *In Vitro* MCM Activity

A. *Expression*

[01347] Hepa1-6 cells and fibroblasts from normal human subject (NHDF) and MMA patients (GM50 and GM1673) were cultured. Cells were transfected with mRNA formulations comprising human MCM (SEQ ID NO: 249), mouse MCM (SEQ ID NO: 250), or a GFP control (encoding SEQ ID NO: 269) via electroporation using a standard protocol.

B. *Activity Assay*

[01348] To assess whether exogenous MCM can function, an in vitro activity assay was performed using transfected cell lysates as the source of enzymatic activity. To begin, 60 µL of lysate containing 100 µg protein was mixed with 30 µL of MCM coenzyme adocobalimin (1 mM in distilled water) at 37°C for 5minutes. Equal amounts of DL-2-[methyl-^{14}C]-methylmalonyl-CoA (50-60 mCi per mmol; Cat ARC0847; American Radiolabeled Chemicals) were then added to each reaction, which was further incubated at 37°C for 10 minutes. The reaction was stopped by adding 50 µ L of 100 g/L TCA and vortexing. The reaction tubes were then centrifuged at 13,000 g for 1 min, and the supernatant was analyzed for the presence of [^{14}C]-succinyl-CoA using HPLC-based separation and quantification. Specifically, 20 µL of each activity reaction supernatant was analyzed using a HPLC system equipped with a Quaternary-Pump, a Multi-sampler, a Thermostated Column-Compartment, a Poroshell EC-C18 120 HPLC-column and a Radiometric Detector controlled by OpenLAB Chromatography Data System, all used according to the manufacturers' recommendations. Elusion was with a linear methanol gradient: 0-15 min (Solvent A: 95% 100mM acetic acid in 100 mM sodium phosphate buffer, pH 7.0) and 15-25 min (95% Solvent A with 5 % of an 18% v/v methanol/water solution) with a flow rate of 0.5 mL/min.

[01349] **FIG. 7** shows that, for each cell lines tested, transfection with mRNA's encoding either mouse MCM or human MCM increased the level of MCM activity in all cell types tested. Thus this data demonstrates that transfection of mRNA encoding MCM leads to the expression of active MM enzyme in Hepa1-6 cells, fibroblasts from normal human subjects, and fibroblasts from MMA patients. Further, human MCM increased MCM activity to a greater degree than did mouse MCM when transfected into Hepa1-6 cells.

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Example 18. Increased *In Vivo* MCM expression

[01350] To assess the ability of MCM-containing mRNA's to facilitate MCM expression *in vivo*, mRNA encoding human MCM (SEQ ID NO: 249) was introduced into C57B/L6 mice. C57B/L6 mice were injected intravenously with either control mRNA (NT-FIX) or hMCM mRNA at 0.5 mg/kg. The mRNA was formulated in lipid nanoparticles for delivery into the mice. Mice were sacrificed after 24 or 48 hrs. and MCM protein levels in liver lysates were determined by capillary electrophoresis (CE). Citrate synthase expression was examined for use as a loading control. For control NT-FIX injections, 4 mice were tested for each time point. For hMCM mRNA injections, 6 mice were tested for each time point.

[01351] As shown in **FIGS. 8A and 8B**, MCM expression was drastically increased in all mice injected with mRNA encoding human MCM. The MCM expression peaked at the 24 hour time point, and was still higher than control mice at 48 hours. Relatively low levels of variance were observed between mice of each experimental condition, indicating that treatment with mRNA encoding MCM is capable of reliably inducing expression of MCM.

Example 19. Human MCM Mutant Constructs

[01352] According to the present disclosure, the polynucleotide can comprise at least a first region of linked nucleosides encoding human MCM. Exemplary human MCM protein sequences of the present disclosure are listed in **Table 3** above.

Example 20. MMA Levels and Body Weight Change in MCK mouse model

[01353] A MCK mouse model of MMA (Mut-/-;$Tg^{INS\text{-}MCK\text{-}Mut}$) is known in the literature and lacks exon 3 of the MCM allele, which encodes the substate-binding pocket of MCM. Manoli 2013 (*PNAS* 110(33):13552-13557 (2013); and Harrington et al., "Stable Isotope Breath Tests to Assess Metabolite Flux in Methylmalonic Acidemia (MMA)", American Society of Human Genetics, Abstract, 2014, which are incorporated herein by reference in their entireties. The MCM knockout mice exhibit a semipenetrant neonatal lethal phenotype, with most mice perishing in the early neonatal period. This mouse model is described in WO 2014/143884 A2, hereby incorporated by reference in its entirety. Because the severe phenotype associated with the knockout makes study difficult, researchers have prepared partial rescues of the MCM knockout mice by transgenic rescue with tissue-specific expression or expression of mutants that mimic those mutations associated with human MMA. For example, transgenic mice that express

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MCM in the knockout background under the control of the muscle-specific creatine kinase promoter ("the MCK mice") survive but still display severe metabolic perturbations and growth abnormalities.

[01354] The effectiveness of mRNA encoding human MCM was assessed in the MCK mouse model of MMA (Mut-/-;$Tg^{INS\text{-}MCK\text{-}Mut}$), N=3-4. MCK mice were injected intravenously with either control mRNA (NT-FIX) or codon optimized human MCM mRNA at 0.16 mg/kg. Five (5) injections were done with MCM mRNA (**SEQ ID NO: 734, FIG. 9**) at 0.16 mg/kg; and two injections were done with MCM mRNA (**SEQ ID NO: 735, FIG. 10**) at 0.2 mg/kg. The mRNA was formulated in lipid nanoparticles (Compound 18) for delivery into the mice via tail vein injection. Plasma was collected twice a week, 3 and 6 days after dosing. Plasma MMA was determined by LC-MS/MS. Body weight was measured twice a week at time of dosing. Mice were not sacrificed at the end of this study and were used for other studies. On the third scheduled injection (day 15), one of the mice that had previously been administered control mRNA was switched to being administered hMCM mRNA and the other mouse administered control mRNA was found dead. This testing demonstrated that repeat intravenous dosing of hMCM mRNA corrected biochemical and growth abnormalities in an animal model of Methylmalonic acidemia (MMA-emia).

[01355] Although expression of MCM in skeletal muscle rescues MCK mice from neonatal lethality, these mice display severe metabolic perturbations and growth retardation that resembles clinical characteristics observed in methylmalonic acidemia patients. In the present example, repeat IV dosing of Compound 18 LNP-encapsulated hMCM mRNA (fully modified with mo5U) was investigated to determine whether mRNA therapy can correct biochemical and growth abnormalities. MCK mice were administered weekly IV injections of 0.16 mg/kg hMCM mRNA (encoding SEQ ID NO: 734) or a vehicle control (non-translating factor IX, NTFIX) mRNA. MCK mice that received hMCM mRNA injections showed decreased plasma MMA levels 3 and 6 days following each dose throughout the entire treatment period (**FIG. 16A**). Importantly, treated MCK mice also showed increased weight gain which was correlated to decreased plasma MMA levels (**FIG. 16B**). In contrast, MCK mice that received vehicle mRNA control (NTFIX) showed neither reduction in plasma MMA levels nor increase in body weight following 2 doses (**FIG. 16A**). Indeed, after 2 IV doses of NTFIX injections, one of the MCK mice died likely due to metabolic decompensation although the cause of death is unknown. To present further loss of MCK mouse, the vehicle control (NTFIX) mRNA treated

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mouse was switched to hMCM mRNA therapy. Interestingly, once that MCK mouse started to receive hMCM mRNA treatment, plasma MMA levels of this mouse quickly decreased from 835 μM to 153 μM within 3 days (**FIG. 16A**). Moreover, this mouse gained 4.8 g in body weight in just one week following crossover to hMCM mRNA therapy. After the fifth IV dose, the MCK mice were given a 10 day washout period (**FIG. 16B**). Interestingly, there was a partial rebound of plasma MMA to 955+/-SD μM in these mice 10 days following their last hMCM mRNA injection (**FIG. 16A**). Moreover, during this washout period, decreased body weight was observed in these mice (0.13+/-SD to 2.8+/-SD g) from day 6 to day 10 (**FIG. 16B**). When MCK mice were re-dosed with 0.2 mg/kg IV hMCM mRNA (encoding SEQ ID NO: 734) after the 10 day washout, plasma MMA levels decreased to 226+/- μM and body weight increased from 1.38+/- g to 3.81+/- g in 4 days. These data demonstrates that LNP-formulated hMCM mRNA is efficacious in lowering plasma MMA levels and simultaneously increasing body weight in this methylmalonic acidemia mouse model of the more severe Mut0 subtype.

Example 21. Expression of MCM in Liver of Wild-type Mice Dosed with Codon Optimized MCM human mRNA Compared to Endogenous MCM in Normal Mouse and Human Liver

[01356] To assess MCM expression *in vivo*, codon optimized MCM human mRNA (**SEQ ID NO: 734**) was introduced into wild-type CD1 mice. CD1 mice were injected intravenously with a single dose of codon optimized MCM mRNA (**SEQ ID NO: 734**) at 0.2 mg/kg. The mRNA was formulated in lipid nanoparticles (Compound 18) for delivery into the mice via tail vein injection (N=3). Mice were sacrificed 24 hours after dosing, and MCM protein levels in liver lysates were determined by LC-MS/MS. As shown in **FIG. 17**, dosing at 0.2 mg/kg in wild-type mice resulted in abundant expression of human MCM, higher than endogenous MCM found in human and normal mouse livers.

Example 22. MCM Expression in Liver of mice administered codon optimized MCM mRNA

[01357] LNP encapsulates hMUT mRNA and distributes the mRNA to the liver, where it is subsequently translated to its functional protein. The half-life of the mRNA and protein product are critical determinants of the pharmacokinetics of mRNA-based therapeutics. To understand the kinetics of hMUT mRNA, the LNP, and the encoded MUT protein, we performed a PK study in wild type CD1 mice in which mice were administered a single IV bolus of 0.5 mg/kg hMUT mRNA or vehicle control (NTFIX) mRNA. Our data showed that 2 hours after administration,

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939 ng/g LNP was detected in livers and by 6 hours, LNP concentrations decreased by almost 98.5% (**FIG. 18A**). At 16 hours, LNP concentrations are not detectable in the liver suggesting that the LNP is highly degradable and is rapidly cleared in liver. hMUT mRNA was also cleared quickly as shown in **FIG. 18B**, with a precipitous drop of hMut mRNA levels at 6 hours following a single IV hMUT mRNA administration (**FIG. 18B**). Over 98% Mut mRNA was cleared 48 hours after administration. In contrast, human MUT protein is rapidly expressed and showed a significantly longer half-life (**FIG. 18C**). Human MUT protein is detectable 2 hours and peaks at 16 hours after hMUT IV mRNA administration (**FIG. 18C**). Our data suggested that the half-life if expressed human Mut is approximately 1.6 days. The data show a decline in mRNA levels in the liver with levels reaching baseline by about 2 days. The sustained expression of MCM protein out to 5 days following a single administration of MCM-encoding mRNA demonstrates potential advantages in treating MMA patients with weekly dosing being a potentially acceptable dosing regimen to achieve therapeutically effective doses in humans.

Example 23. Lipid Nanoparticle Quantification and Kidney, Liver and Spleen Analysis

[01358] *In vivo* analysis of lipid nanoparticles quanification, in situ hybridization for kidney, and bDNA for spleen is assessed. Codon optimized MCM mRNA (**SEQ ID NO: 735**) is administered to CD1 mice. CD1 mice are injected intravenously with either control mRNA (NT-FIX) or codon optimized MCM mRNA at 0.5 mg/kg. The mRNA was formulated in lipid nanoparticles (Compound 18) for delivery into the mice via tail vein injection. Mice (N=3/time point) are sacrificed after 2, 6, 16, 24, 48, 72, 120, or 168 hours. Lipid nanoparticles are quanified at elarly time points (2, 6, and 16 hours). ISH of kidney and bDNA of liver and spleen are analyzed and compared to untreated CD1 mice.

Example 24. *In Vivo* Delivery of mRNA encoding MCM

[01359] To assess methods of delivering MCM *in vivo*, codon optimized MCM human mRNA, i.e., mRNA1, mRNA2, mRNA3, mRNA4, and mRNA5 (**SEQ ID NOs: 775, 776, 777, 734 and 778, respectively**) or a vehicle control (non-translating factor IX, NTFIX) mRNA was introduced into wild-type CD1 mice. The mice were injected intravenously with a single dose of mRNA at 0.2 mg/kg. The mRNA was formulated for delivery into the mice via tail vein injection (N=3 per formulation). Compositions were formulated with either MC3 or Compound 18. Mice were sacrificed 24 hours after dosing, and MCM protein levels in liver lysates were determined

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by Western blot. **FIG. 19A** is a Western blot with equal loading of each lysate. **FIG. 19B** is a quantification of the expression patterns in the Western blot of **FIG. 19A**. As shown in **FIGS. 19A** and **19B**, both MC3 formulations and Compound 18 formulations were effective in facilitating delivery and expression of mRNA encoding MCM. Delivering mRNAs encoding MCM in wild-type mice resulted in expression of human MCM at levels much higher than that of endogenous MCM in control mice.

Example 24. In vivo MMA level and Body Weight Effect on MCK mice

[01360] Two MCK mice were administered weekly IV injections of 0.2 mg/kg hMCM mRNA and the other two received a vehicle control (non-translating factor IX, NTFIX) mRNA at 0.2 mg/kg. The study encompasses 2 doses. The MCK mice that received hMCM mRNA injections showed decreased plasma MMA levels 3 days following each dose (**FIG. 20A**). Importantly, treated MCK mice also showed significantly increased body weight which was correlated to decreased plasma MMA levels. See **FIG. 20B**. In contrast, the MCK mouse that received vehicle mRNA control (NTFIX) showed no significant reduction in plasma MMA levels nor increase in body weight following 2 doses. One MCK mouse received the vehicle control died.

[01361] Certain exemplary mRNA sequences are shown below:

hMCM mRNA (SEQ ID NO: 769)	TCAAGCTTTTGGACCCTCGTACAGAAGCTAATACGACTCACTATAGGGAAATAAGAGAGAAAAGAAGAGTAAGA AGAAATATAAGAGCCACCATGCTGCGGGCCAAGAACCAGCTGTTCCTGCTGAGCCCTCACTACCTGCGGCAGGT GAAGGAGAGCAGCGGCAGCCGGCTGATCCAGCAGCGGCTGCTGCACCAGCAGCAGCCCCTGCACCCCGAGTGGG CCGCCCTGGCCAAGAAGCAGCTGAAGGGCAAGAACCCCGAGGACCTGATCTGGCACACGCCCGAGGGCATCAGC ATCAAGCCCCTGTACAGCAAGCGGGACACCATGGACCTGCCCGAGGAGCTGCCCGGCGTGAAGCCCTTCACCCG GGGCCCCTACCCCACCATGTACACCTTCCGGCCCTGGACCATCCGGCAGTACGCCGGCTTCAGCACCGTGGAGG AGAGCAACAAGTTCTACAAGGACAACATCAAGGCCGGCCAGCAGGGCCTGAGCGTGGCCTTCGACCTGGCCACC CACCGGGGCTACGACAGCGACAACCCACGGGTGCGGGGCGACGTGGGCATGGCCGGCGTGGCCATCGACACCGT GGAGGACACCAAGATCCTGTTCGACGGCATCCCTCTGGAGAAGATGAGCGTGAGCATGACCATGAACGGCGCCG TGATCCCCGTGCTGGCCAACTTCATCGTGACCGGCGAGGAGCAGGGCGTGCCCAAGGAGAAGCTGACCGGCACC ATCCAGAACGACATCCTGAAGGAGTTCATGGTGCGGAACACCTACATCTTCCCTCCCGAGCCCAGCATGAAGAT CATCGCCGACATCTTCGAGTACACCGCCAAGCACATGCCCAAGTTCAACAGCATCAGCATCAGCGGCTACCACA TGCAGGAGGCCGGCGCCGACGCCATCCTGGAGCTGGCCTACACCCTGGCCGACGGCCTGGAGTACAGCCGGACC GGCCTGCAGGCCGGCCTGACCATCGACGAGTTCGCGCCCCGGCTGAGCTTCTTCTGGGGCATCGGCATGAACTT CTACATGGAGATCGCCAAGATGCGGGCCGGCCGGCGGCTGTGGGCCCACCTGATCGAGAAGATGTTCCAGCCCA AGAACAGCAAGAGCCTGCTGCTGCGGGCCCACTGCCAGACCAGCGGCTGGAGCCTGACCGAGCAGGACCCCTAC AACAACATCGTGCGGACCGCCATCGAGGCCATGGCCGCCGTGTTCGGCGGCACCCAGAGCCTGCACACCAACAG CTTCGACGAGGCCCTGGGCCTGCCCACCGTGAAGAGCGCCCGGATCGCCCGGAACACCCAGATCATCATCCAGG AGGAGAGCGGCATCCCCAAGGTGGCCGACCCCTGGGGCGGCAGCTACATGATGGAGTGCCTGACCAACGACGTG TACGACGCCGCCCTGAAGCTGATCAACGAGATCGAGGAGATGGGCGGCATGGCCAAGGCCGTGGCCGAGGGCAT CCCCAAGCTGCGGATCGAGGAGTGCGCCGCCCGGCGGCAGGCCCGGATCGACAGCGGCAGCGAGGTGATCGTGG GCGTGAACAAGTACCAGCTGGAGAAGGAGGACGCCGTGGAGGTGCTGGCCATCGACAACACCAGCGTGCGGAAC CGGCAGATCGAGAAGCTGAAGAAGATCAAGAGCAGCCGGGACCAGGCCCTGGCCGAGCGGTGCCTGGCCGCCCT GACCGAGTGCGCCGCCAGCGGCGACGGCAACATCCTGGCCCTGGCCGTGGACGCCAGCCGGGCCCGGTGCACCG TGGGCGAGATCACCGACGCCCTGAAGAAGGTGTTCGGCGAGCACAAGGCCAACGACCGGATGGTGAGCGGCGCC TACCGGCAGGAGTTCGGCGAGAGCAAGGAGATCACCAGCGCCATCAAGCGGGTGCACAAGTTCATGGAGCGGGA GGGCCGGCGGCCCCGGCTGCTGGTGGCCAAGATGGGCCAGGACGGCCACGACCGGGGCGCCAAGGTGATCGCCA CCGGCTTCGCCGACCTGGGCTTCGACGTGGACATCGGCCCACTGTTCCAGACGCCCCGGGAGGTGGCCCAGCAG GCCGTGGACGCCGACGTGCACGCCGTGGGCGTGAGCACCCTGGCCGCCGGCCACAAGACCCTGGTGCCCGAGCT GATCAAGGAGCTGAACAGCCTGGGCCGGCCCGACATCCTGGTGATGTGCGGCGGCGTGATCCCGCCCCAGGACT

	ACGAGTTCCTGTTCGAGGTGGGCGTGAGCAACGTGTTCGGCCCCGGCACCCGGATCCCCAAGGCCGCCGTGCAG GTGCTGGACGACATCGAGAAGTGCCTGGAGAAGAAGCAGCAGAGCGTGTGATAATAGTCCATAAAGTAGGAAAC ACTACAGCTGGAGCCTCGGTGGCCATGCTTCTTGCCCCTTGGGCCTCCCCCCAGCCCCTCCTCCCCTTCCTGCA CCCGTACCCCCCGCATTATTACTCACGGTACGAGTGGTCTTTGAATAAAGTCTGAGTGGGCGGC
hMCM mRNA (SEQ ID NO: 770)	TCAAGCTTTTGGACCCTCGTACAGAAGCTAATACGACTCACTATAGGGAAATAAGAGAGAAAAGAAGAGTAAGA AGAAATATAAGAGCCACCATGCTGCGGGCCAAGAACCAGCTGTTCCTGCTGAGCCCCCACTACCTGCGGCAGGT GAAGGAGAGCAGCGGCAGCCGGCTGATCCAGCAGCGCCTCCTCCACCAGCAGCAGCCCCTCCACCCCGAGTGGG CCGCCCTCGCCAAGAAGCAGCTCAAGGGCAAGAACCCCGAGGACCTCATCTGGCACACCCCCGAGGGCATCTCC ATCAAGCCCCTCTACTCCAAGCGCGACACCATGGACCTCCCCGAGGAGCTCCCCGGCGTCAAGCCCTTCACCCG CGGCCCCTACCCCACCATGTACACCTTCCGCCCCTGGACCATCCGCCAGTACGCCGGCTTCTCCACCGTCGAGG AGTCCAACAAGTTCTACAAGGACAACATCAAGGCCGGCCAGCAGGGCCTCTCCGTCGCCTTCGACCTCGCCACC CACCGCGGCTACGACTCCGACAACCCCCGCGTCCGCGGCGACGTCGGCATGGCCGGCGTCGCCATCGACACCGT CGAGGACACCAAGATCCTCTTCGACGGCATCCCCCTCGAGAAGATGTCCGTCTCCATGACCATGAACGGCGCCG TCATCCCCGTCCTCGCCAACTTCATCGTCACCGGCGAGGAGCAGGGCGTCCCCAAGGAGAAGCTCACCGGCACC ATCCAGAACGACATCCTCAAGGAGTTCATGGTCCGCAACACCTACATCTTCCCCCCCGAGCCCTCCATGAAGAT CATCGCCGACATCTTCGAGTACACCGCCAAGCACATGCCCAAGTTCAACTCCATCTCCATCTCCGGCTACCACA TGCAGGAGGCCGGCGCCGACGCCATCCTCGAGCTCGCCTACACCCTCGCCGACGGCCTCGAGTACTCCCGCACC GGCCTCCAGGCCGGCCTCACCATCGACGAGTTCGCCCCCCCGCCTCTCCTTCTTCTGGGGCATCGGCATGAACTT CTACATGGAGATCGCCAAGATGCGCGCCGGCCGCCGCCTCTGGGCCCACCTCATCGAGAAGATGTTCCAGCCCA AGAACTCCAAGTCCCTCCTCCTCCGCGCCCACTGCCAGACCTCCGGCTGGTCCCTCACCGAGCAGGACCCCTAC AACAACATCGTCCGCACCGCCATCGAGGCCATGGCCGCCGTCTTCGGCGGCACCCAGTCCCTCCACACCAACTC CTTCGACGAGGCCCTCGGCCTCCCCACCGTCAAGTCCGCCCGCATCGCCCGCAACACCCAGATCATCATCCAGG AGGAGTCCGGCATCCCCAAGGTCGCCGACCCCTGGGGCGGCTCCTACATGATGGAGTGCCTCACCAACGACGTC TACGACGCCGCCCTCAAGCTCATCAACGAGATCGAGGAGATGGGCGGCATGGCCAAGGCCGTCGCCGAGGGCAT CCCCAAGCTCCGCATCGAGGAGTGCGCCGCCCGCCGCCAGGCCCGCATCGACTCCGGCTCCGAGGTCATCGTCG GCGTCAACAAGTACCAGCTCGAGAAGGAGGACGCCGTCGAGGTCCTCGCCATCGACAACACCTCCGTCCGCAAC CGCCAGATCGAGAAGCTCAAGAAGATCAAGTCCTCCCGCGACCAGGCCCTCGCCGAGCGCTGCCTCGCCGCCCT CACCGAGTGCGCCGCCTCCGGCGACGGCAACATCCTCGCCCTCGCCGTCGACGCCTCCCGCGCCCGCTGCACCG TCGGCGAGATCACCGACGCCCTCAAGAAGGTCTTCGGCGAGCACAAGGCCAACGACCGCATGGTCTCCGGCGCC TACCGCCAGGAGTTCGGCGAGTCCAAGGAGATCACCTCCGCCATCAAGCGCGTCCACAAGTTCATGGAGCGCGA GGGCCGCCGCCCCCGCCTCCTCGTCGCCAAGATGGGCCAGGACGGCCACGACCGCGGCGCCAAGGTCATCGCCA CCGGCTTCGCCGACCTCGGCTTCGACGTCGACATCGGCCCCCTCTTCCAGACCCCCCGCGAGGTCGCCCAGCAG GCCGTCGACGCCGACGTCCACGCCGTCGGCGTCTCCACCCTCGCCGCCGGCCACAAGACCCTCGTCCCCGAGCT CATCAAGGAGCTCAACTCCCTCGGCCGCCCCGACATCCTCGTCATGTGCGGCGGCGTCATCCCCCCCCCAGGACT ACGAGTTCCTCTTCGAGGTCGGCGTCTCCAACGTCTTCGGCCCCGGCACCCGCATCCCCAAGGCCGCCGTCCAG GTCCTCGACGACATCGAGAAGTGCCTCGAGAAGAAGCAGCAGTCCGTCTGATAATAGGCTGGAGCCTCGGTGGC CATGCTTCTTGCCCCTTGGGCCTCCCCCCAGCCCCTCCTCCCCTTCCTGCACCCGTACCCCCCGCATTATTACT CACGGTACGAGTGGTCTTTGAATAAAGTCTGAGTGGGCGGC
hMCM ORF (SEQ ID NO: 775)	ATGTTAAGAGCTAAGAATCAGCTTTTTTTACTTTCACCTCATTACCTGAGGCAGGTAAAAGAATCATCAGGCTC CAGGCTCATACAGCAACGACTTCTACACCAGCAACAGCCCCTTCACCCAGAATGGGCTGCCCTGGCTAAAAAGC AGCTGAAAGGCAAAAACCCAGAAGACCTAATATGGCACACCCCGGAAGGGATCTCTATAAAACCCTTGTATTCC AAGAGAGATACTATGGACTTACCTGAAGAACTTCCAGGAGTGAAGCCATTCACACGTGGACCATATCCTACCAT GTATACCTTTAGGCCCTGGACCATCCGCCAGTATGCTGGTTTTAGTACTGTGGAAGAAAGCAATAAGTTCTATA AGGACAACATTAAGGCTGGTCAGCAGGGATTATCAGTTGCCTTTGATCTGGCGACACATCGTGGCTATGATTCA GACAACCCTCGAGTTCGTGGTGATGTTGGAATGGCTGGAGTTGCTATTGACACTGTGGAAGATACCAAAATTCT TTTTGATGGAATTCCTTTAGAAAAAATGTCAGTTTCCATGACTATGAATGGAGCAGTTATTCCAGTTCTTGCAA ATTTTATAGTAACTGGAGAAGAACAAGGTGTACCTAAAGAGAAACTTACTGGTACCATCCAAAATGATATACTA AAGGAATTTATGGTTCGAAATACATACATTTTTCCTCCAGAACCATCCATGAAAATTATTGCTGACATATTTGA ATATACAGCAAAGCACATGCCAAAATTTAATTCAATTTCAATTAGTGGATACCATATGCAGGAAGCAGGGGCTG ATGCCATTCTGGAGCTGGCCTATACTTTAGCAGATGGATTGGAGTACTCTAGGACTGGACTCCAGGCTGGCCTG ACAATTGATGAATTTGCACCAAGGTTGTCTTTCTTCTGGGGAATTGGAATGAATTTCTATATGGAAATAGCAAA GATGAGAGCTGGTAGAAGACTCTGGGCTCACTTAATAGAGAAAATGTTTCAGCCTAAAAACTCAAAATCTCTTC TTCTAAGAGCACACTGTCAGACATCTGGATGGTCACTTACTGAGCAGGATCCCTACAATAATATTGTCCGTACT GCAATAGAAGCAATGGCAGCAGTATTTGGAGGGACTCAGTCTTTGCACACAAATTCTTTTGATGAAGCTTTGGG TTTGCCAACTGTGAAAAGTGCTCGAATTGCCAGGAACACACAAATCATCATTCAAGAAGAATCTGGGATTCCCA AAGTGGCTGATCCTTGGGGAGGTTCTTACATGATGGAATGTCTCACAAATGATGTTTATGATGCTGCTTTAAAG CTCATTAATGAAATTGAAGAAATGGGTGGAATGGCCAAAGCTGTAGCTGAGGGAATACCTAAACTTCGAATTGA AGAATGTGCTGCCCGAAGACAAGCTAGAATAGATTCTGGTTCTGAAGTAATTGTTGGAGTAAATAAGTACCAGT TGGAAAAAGAAGACGCTGTAGAAGTTCTGGCAATTGATAATACTTCAGTGCGAAACAGGCAGATTGAAAAACTT AAGAAGATCAAATCCAGCAGGGATCAAGCTTTGGCTGAACGTTGCCTTGCTGCACTAACCGAATGTGCTGCTAG CGGAGATGGAAATATCCTGGCTCTTGCAGTGGATGCATCTCGGGCAAGATGTACAGTGGGAGAAATCACAGATG CCCTGAAAAAGGTATTTGGTGAACATAAAGCGAATGATCGAATGGTGAGTGGAGCATATCGCCAGGAATTTGGA GAAAGTAAAGAGATAACATCTGCTATCAAGAGGGTTCATAAATTCATGGAACGTGAAGGTCGCAGACCTCGTCT

	TCTTGTAGCAAAAATGGGACAAGATGGCCATGACAGAGGAGCAAAAGTTATTGCTACAGGATTTGCTGATCTTG GTTTTGATGTGGACATAGGCCCTCTTTTCCAGACTCCTCGTGAAGTGGCCCAGCAGGCTGTGGATGCGGATGTG CATGCTGTGGGCGTAAGCACCCTCGCTGCTGGTCATAAAACCCTAGTTCCTGAACTCATCAAAGAACTTAACTC CCTTGGACGGCCAGATATTCTTGTCATGTGTGGAGGGGTGATACCACCTCAGGATTATGAATTTCTGTTTGAAG TTGGTGTTTCCAATGTATTTGGTCCTGGGACTCGAATTCCAAAGGCTGCCGTTCAGGTGCTTGATGATATTGAG AAGTGTTTGGAAAAGAAGCAGCAATCTGTA
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	GCTTCGACGTCGACATCGGCCCCCTCTTCCAGACCCCCCGCGAGGTCGCCCAGCAGGCCGTCGACGCCGACGTC CACGCCGTCGGCGTCTCCACCCTCGCCGCCGGCCACAAGACCCTCGTCCCCGAGCTCATCAAGGAGCTCAACTC CCTCGGCCGCCCCGACATCCTCGTCATGTGCGGCGGCGTCATCCCCCCCCCAGGACTACGAGTTCCTCTTCGAGG TCGGCGTCTCCAACGTCTTCGGCCCCGGCACCCGCATCCCCAAGGCCGCCGTCCAGGTCCTCGACGACATCGAG AAGTGCCTCGAGAAGAAGCAGCAGTCCGTC
hMCM ORF (SEQ ID NO: 778)	ATGCTGCGGGCCAAGAACCAGCTGTTCCTGCTGAGCCCCCACTACCTGCGGCAGGTGAAGGAGAGCAGCGGCAG CCGGCTGATCCAGCAGCGCCTCCTCCACCAGCAGCAGCCCCTCCACCCCGAGTGGGCCGCCCTCGCCAAGAAGC AGCTCAAGGGCAAGAACCCCGAGGACCTCATCTGGCACACCCCCGAGGGCATCTCCATCAAGCCCCTCTACTCC AAGCGCGACACCATGGACCTCCCCGAGGAGCTCCCCGGCGTCAAGCCCTTCACCCGCGGCCCCTACCCCACCAT GTACACCTTCCGCCCCTGGACCATCCGCCAGTACGCCGGCTTCTCCACCGTCGAGGAGTCCAACAAGTTCTACA AGGACAACATCAAGGCCGGCCAGCAGGGCCTCTCCGTCGCCTTCGACCTCGCCACCCACCGCGGCTACGACTCC GACAACCCCCGCGTCCGCGGCGACGTCGGCATGGCCGGCGTCGCCATCGACACCGTCGAGGACACCAAGATCCT CTTCGACGGCATCCCCCTCGAGAAGATGTCCGTCTCCATGACCATGAACGGCGCCGTCATCCCCGTCCTCGCCA ACTTCATCGTCACCGGCGAGGAGCAGGGCGTCCCCAAGGAGAAGCTCACCGGCACCATCCAGAACGACATCCTC AAGGAGTTCATGGTCCGCAACACCTACATCTTCCCCCCCGAGCCCTCCATGAAGATCATCGCCGACATCTTCGA GTACACCGCCAAGCACATGCCCAAGTTCAACTCCATCTCCATCTCCGGCTACCACATGCAGGAGGCCGGCGCCG ACGCCATCCTCGAGCTCGCCTACACCCTCGCCGACGGCCTCGAGTACTCCCGCACCGGCCTCCAGGCCGGCCTC ACCATCGACGAGTTCGCCCCCCGCCTCTCCTTCTTCTGGGGCATCGGCATGAACTTCTACATGGAGATCGCCAA GATGCGCGCCGGCCGCCGCCTCTGGGCCCACCTCATCGAGAAGATGTTCCAGCCCAAGAACTCCAAGTCCCTCC TCCTCCGCGCCCACTGCCAGACCTCCGGCTGGTCCCTCACCGAGCAGGACCCCTACAACAACATCGTCCGCACC GCCATCGAGGCCATGGCCGCCGTCTTCGGCGGCACCCAGTCCCTCCACACCAACTCCTTCGACGAGGCCCTCGG CCTCCCCACCGTCAAGTCCGCCCGCATCGCCCGCAACACCCAGATCATCATCCAGGAGGAGTCCGGCATCCCCA AGGTCGCCGACCCCTGGGGCGGCTCCTACATGATGGAGTGCCTCACCAACGACGTCTACGACGCCGCCCTCAAG CTCATCAACGAGATCGAGGAGATGGGCGGCATGGCCAAGGCCGTCGCCGAGGGCATCCCCAAGCTCCGCATCGA GGAGTGCGCCGCCCGCCGCCAGGCCCGCATCGACTCCGGCTCCGAGGTCATCGTCGGCGTCAACAAGTACCAGC TCGAGAAGGAGGACGCCGTCGAGGTCCTCGCCATCGACAACACCTCCGTCCGCAACCGCCAGATCGAGAAGCTC AAGAAGATCAAGTCCTCCCGCGACCAGGCCCTCGCCGAGCGCTGCCTCGCCGCCCTCACCGAGTGCGCCGCCTC CGGCGACGGCAACATCCTCGCCCTCGCCGTCGACGCCTCCCGCGCCCGCTGCACCGTCGGCGAGATCACCGACG CCCTCAAGAAGGTCTTCGGCGAGCACAAGGCCAACGACCGCATGGTCTCCGGCGCCTACCGCCAGGAGTTCGGC GAGTCCAAGGAGATCACCTCCGCCATCAAGCGCGTCCACAAGTTCATGGAGCGCGAGGGCCGCCGCCCCCGCCT CCTCGTCGCCAAGATGGGCCAGGACGGCCACGACCGCGGCGCCAAGGTCATCGCCACCGGCTTCGCCGACCTCG GCTTCGACGTCGACATCGGCCCCCTCTTCCAGACCCCCCGCGAGGTCGCCCAGCAGGCCGTCGACGCCGACGTC CACGCCGTCGGCGTCTCCACCCTCGCCGCCGGCCACAAGACCCTCGTCCCCGAGCTCATCAAGGAGCTCAACTC CCTCGGCCGCCCCGACATCCTCGTCATGTGCGGCGGCGTCATCCCCCCCCCAGGACTACGAGTTCCTCTTCGAGG TCGGCGTCTCCAACGTCTTCGGCCCCGGCACCCGCATCCCCAAGGCCGCCGTCCAGGTCCTCGACGACATCGAG AAGTGCCTCGAGAAGAAGCAGCAGTCCGTC

Other Embodiments

[01362] It is to be understood that the words that have been used are words of description rather than limitation, and that changes can be made within the purview of the appended claims without departing from the true scope and spirit of the disclosure in its broader aspects.

[01363] While the present disclosure has been described at some length and with some particularity with respect to the several described embodiments, it is not intended that it should be limited to any such particulars or embodiments or any particular embodiment, but it is to be construed with references to the appended claims so as to provide the broadest possible interpretation of such claims in view of the prior art and, therefore, to effectively encompass the intended scope of the disclosure.

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[01364] All publications, patent applications, patents, and other references mentioned herein are incorporated by reference in their entirety. In case of conflict, the present specification, including definitions, will control. In addition, section headings, the materials, methods, and examples are illustrative only and not intended to be limiting.

DEFINITION

[01365] In this specification, the term "comprising" is intended to denote the inclusion of a stated integer or integers, but not necessarily the exclusion of any other integer, depending on the context in which that the term is used. This applies to variants of that term such as "comprising" or "comprises".

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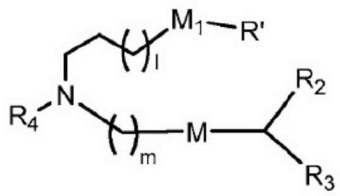
CLAIMS

1. A lipid nanoparticle composition comprising:

a polynucleotide comprising an open reading frame (ORF) encoding a methylmalonyl-CoA mutase (MCM) polypeptide; and

a compound that is of Formula (IA):



(IA),

or a salt thereof, wherein

l is selected from 1, 2, 3, 4, and 5;

m is selected from 5, 6, 7, 8, and 9

M_1 is a bond or M';

R_4 is unsubstituted C_{1-3} alkyl, or $–(CH_2)_nQ$, in which n is 1, 2, 3, 4 or 5 and Q is OH, -NHC(S)N$(R)_2$, or –NHC(O)N$(R)_2$;

M and M' are independently selected from – C(O)O, OC(O), C(O)N(R'), P(O)(OR')O, an aryl group, and a heteroaryl group;

R_2 and R_3 are independently selected from the group consisting of H, C_{1-14} alkyl, and C_{2-14} alkenyl;

each R is independently selected from the group consisting of C_{1-3} alkyl, C_{2-3} alkenyl, and H;

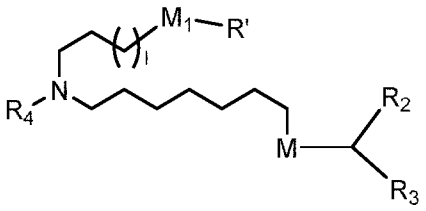
each R' is independently selected from the group consisting of C_{1-18} alkyl, C_{2-18} alkenyl, -R*YR", -YR", and H;

each R" is independently selected from the group consisting of C_{3-14} alkyl and C_{3-14} alkenyl;

each R* is independently selected from the group consisting of C_{1-12} alkyl and C_{2-12} alkenyl; and

each Y is independently a C_{3-6} carbocycle.

2. The lipid nanoparticle composition of claim 1, wherein the compound is of Formula (II):

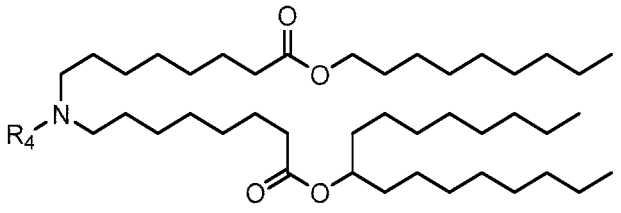


(II),

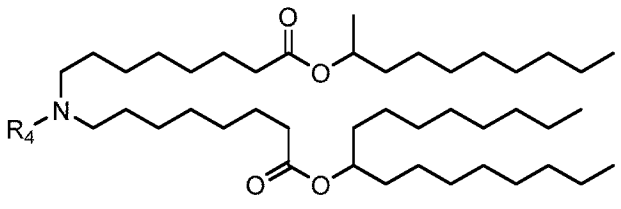
or a salt thereof, wherein

R_4 is unsubstituted C_{1-3} alkyl, or $-(CH_2)_nQ$, in which n is 2, 3, or 4 and Q is OH, $-NHC(S)N(R)_2$, or $-NHC(O)N(R)_2$.

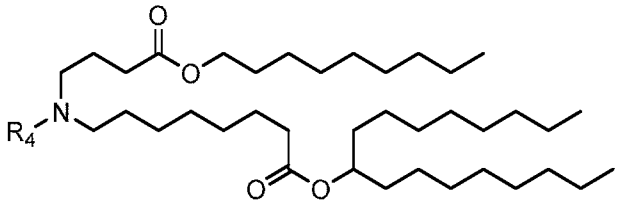
3. The lipid nanoparticle composition of claim 1, wherein the compound is of Formula (IIa), (IIb), (IIc), or (IIe):



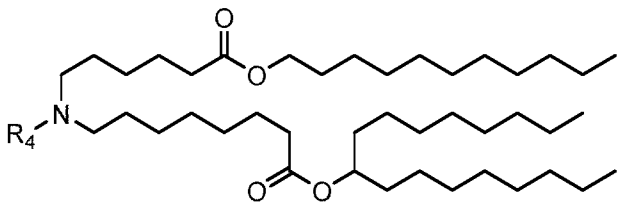
(IIa),



(IIb),



(IIc), or



(IIe),

or a salt thereof.

4. The lipid nanoparticle composition of claim 1, wherein M and M' are independently –C(O)O- or –OC(O)-.

5. The lipid nanoparticle composition of claim 1, wherein:

(i) R_2 and R_3 are the same, optionally wherein R_2 and R_3 are C_8 alkyl; or

(ii) R_2 and R_3 are different.

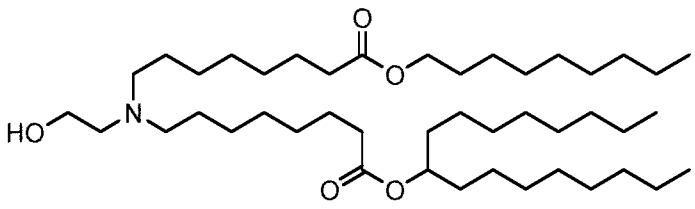
6. The lipid nanoparticle composition of claim 2, wherein:

(i) n is 2;

(ii) R' is selected from: C_4 alkyl and C_4 alkenyl, C_5 alkyl and C_5 alkenyl, C_6 alkyl and C_6 alkenyl, C_7 alkyl and C_7 alkenyl, C_9 alkyl and C_9 alkenyl, C_{11} alkyl and C_{11} alkenyl, C_{12} alkyl, C_{12} alkenyl, C_{13} alkyl, C_{13} alkenyl, C_{14} alkyl, C_{14} alkenyl, C_{15} alkyl, C_{15} alkenyl, C_{16} alkyl, C_{16} alkenyl, C_{17} alkyl, C_{17} alkenyl, C_{18} alkyl, and C_{18} alkenyl; or

(iii) l is selected from 3, 4, and 5.

7. The lipid nanoparticle composition of claim 1, wherein the compound is of the formula:



(Compound 18)

or a salt thereof.

8. The lipid nanoparticle composition of any one of claims 1 to 7, further comprising a phospholipid, a structural lipid, and a PEG lipid.

9. The lipid nanoparticle composition of claim 8, wherein:

(i) the phospholipid is selected from the group consisting of:

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1,2-dilinoleoyl-sn-glycero-3-phosphocholine (DLPC),

1,2-dimyristoyl-sn-glycero-phosphocholine (DMPC),

1,2-dioleoyl-sn-glycero-3-phosphocholine (DOPC),

1,2-dipalmitoyl-sn-glycero-3-phosphocholine (DPPC),

1,2-distearoyl-sn-glycero-3-phosphocholine (DSPC),

1,2-diundecanoyl-sn-glycero-phosphocholine (DUPC),

1-palmitoyl-2-oleoyl-sn-glycero-3-phosphocholine (POPC),

1,2-di-O-octadecenyl-*sn*-glycero-3-phosphocholine (18:0 Diether PC),

1-oleoyl-2-cholesterylhemisuccinoyl-*sn*-glycero-3-phosphocholine (OChemsPC),

1-hexadecyl-sn-glycero-3-phosphocholine (C16 Lyso PC),

1,2-dilinolenoyl-sn-glycero-3-phosphocholine,

1,2-diarachidonoyl-sn-glycero-3-phosphocholine,

1,2-didocosahexaenoyl-sn-glycero-3-phosphocholine,

1,2-dioleoyl-sn-glycero-3-phosphoethanolamine (DOPE),

1,2-diphytanoyl-sn-glycero-3-phosphoethanolamine (ME 16:0 PE),

1,2-distearoyl-sn-glycero-3-phosphoethanolamine,

1,2-dilinoleoyl-sn-glycero-3-phosphoethanolamine,

1,2-dilinolenoyl-sn-glycero-3-phosphoethanolamine,

1,2-diarachidonoyl-sn-glycero-3-phosphoethanolamine,

1,2-didocosahexaenoyl-sn-glycero-3-phosphoethanolamine,

1,2-dioleoyl-sn-glycero-3-phospho-rac-(1-glycerol) sodium salt (DOPG),

sphingomyelin, and

any mixtures thereof;

(ii) the structural lipid is cholesterol, fecosterol, sitosterol, ergosterol, campesterol, stigmasterol, brassicasterol, tomatidine, ursolic acid, alpha-tocopherol, or any mixture thereof; and/or

(iii) the PEG lipid is a PEG-modified phosphatidylethanolamine, a PEG-modified phosphatidic acid, a PEG-modified ceramide, a PEG-modified dialkylamine, a PEG-modified diacylglycerol, a PEG-modified dialkylglycerol, or any mixture thereof.

10. The lipid nanoparticle composition of any one of claims 1 to 9, wherein the MCM polypeptide comprises an amino acid sequence at least about 95%, at least about 96%, at least

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about 97%, at least about 98%, at least about 99%, or about 100% identical to SEQ ID NO:208, and wherein the MCM polypeptide retains methylmalonyl-CoA mutase activity.

11. The lipid nanoparticle composition of any one of claims 1 to 9, wherein the MCM polypeptide comprises the amino acid sequence set forth in SEQ ID NO:208, SEQ ID NO:209, SEQ ID NO:210, SEQ ID NO:211, SEQ ID NO:212, or SEQ ID NO:213.

12. The lipid nanoparticle composition of any one of claims 1 to 11, wherein the ORF has at least 98%, at least 99%, or 100% sequence identity to nucleotide 1 to nucleotide 2250 of SEQ ID NO: 732, wherein the ORF encodes an MCM polypeptide.

13. The lipid nanoparticle composition of any one of claims 1 to 12, wherein the polynucleotide is a messenger RNA (mRNA).

14. The lipid nanoparticle composition of claim 13, wherein:

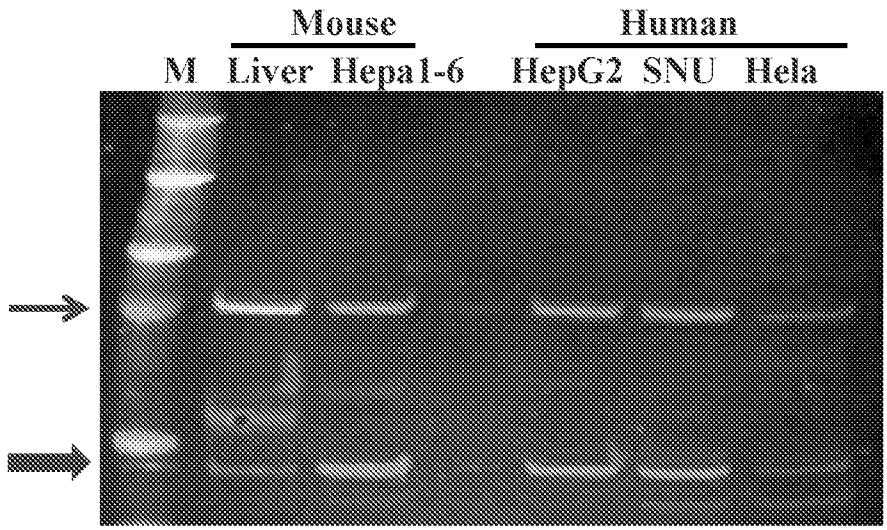
(i) the mRNA comprises a 5' untranslated region (UTR) comprising the nucleotide sequence of SEQ ID NO:215; or

(ii) the mRNA comprises the miR-142-3p binding site depicted in SEQ ID NO:722.

15. A method for treating and/or preventing methylmalonic acidemia in a human subject, comprising administering to the human subject the lipid nanoparticle composition of any one of claims 1 to 14.

16. Use of a lipid nanoparticle composition according to any one of claims 1 to 14 in the manufacture of a medicament used to treat and/or prevent methylmalonic acidemia in a human subject.

FIG. 1



Mouse α–Methymalonyl-CoA mutase (⟶)
Rabbit α–Citrate synthetase (➡)

FIG. 2A

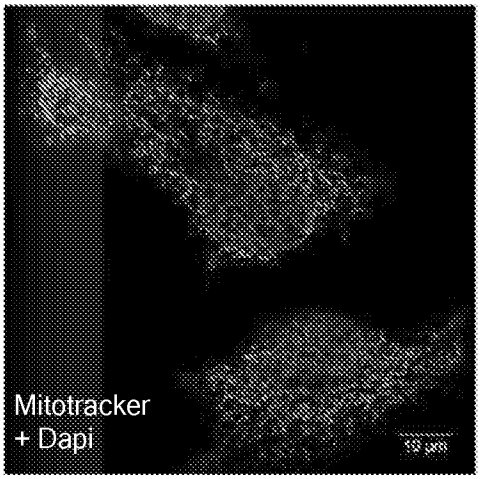


FIG. 2B

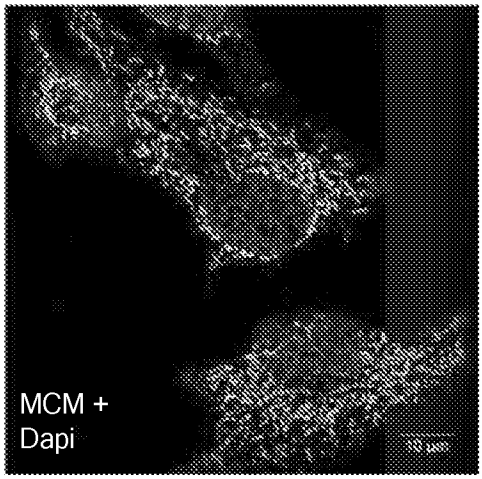
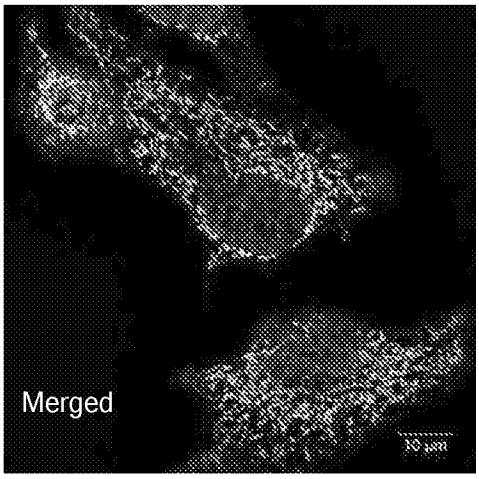


FIG. 2C



KEY

hMCM:	green
Mitotracker:	red
DAPI:	blue

FIG. 3

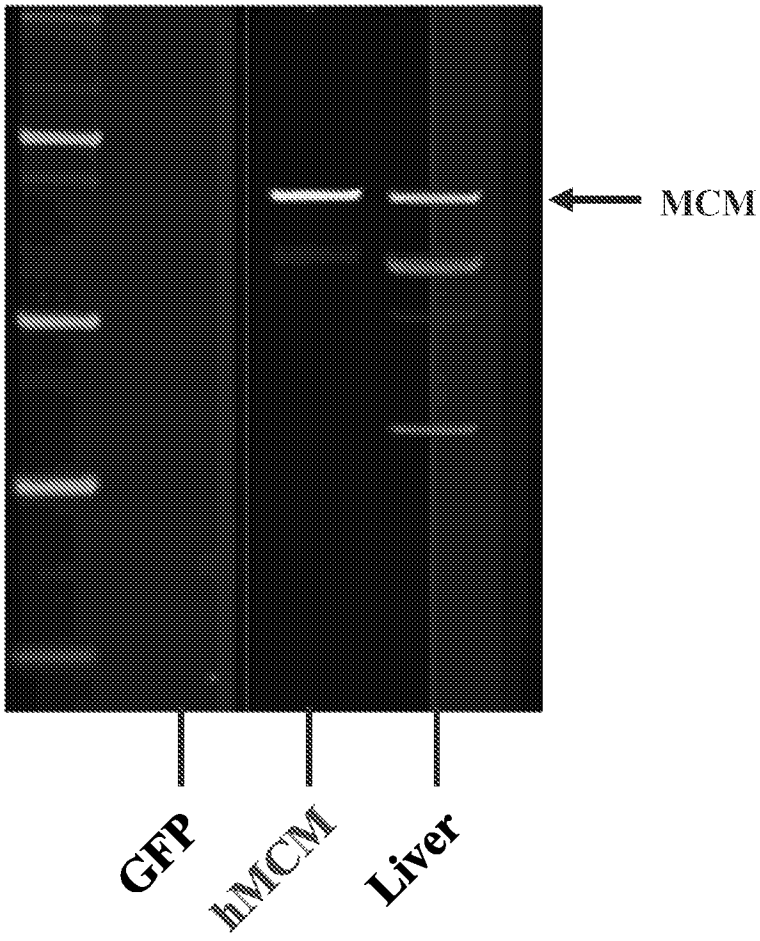


FIG. 4

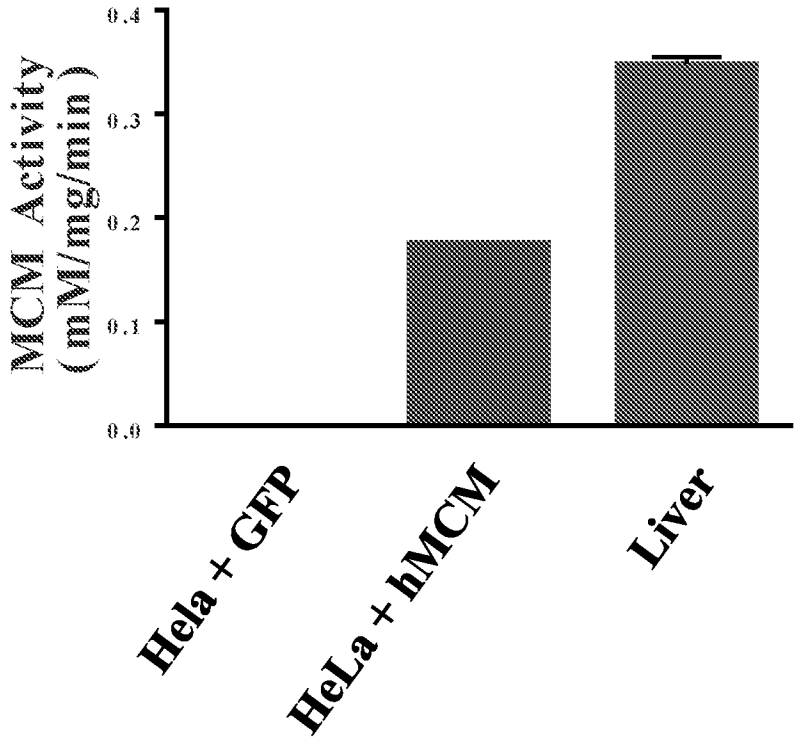
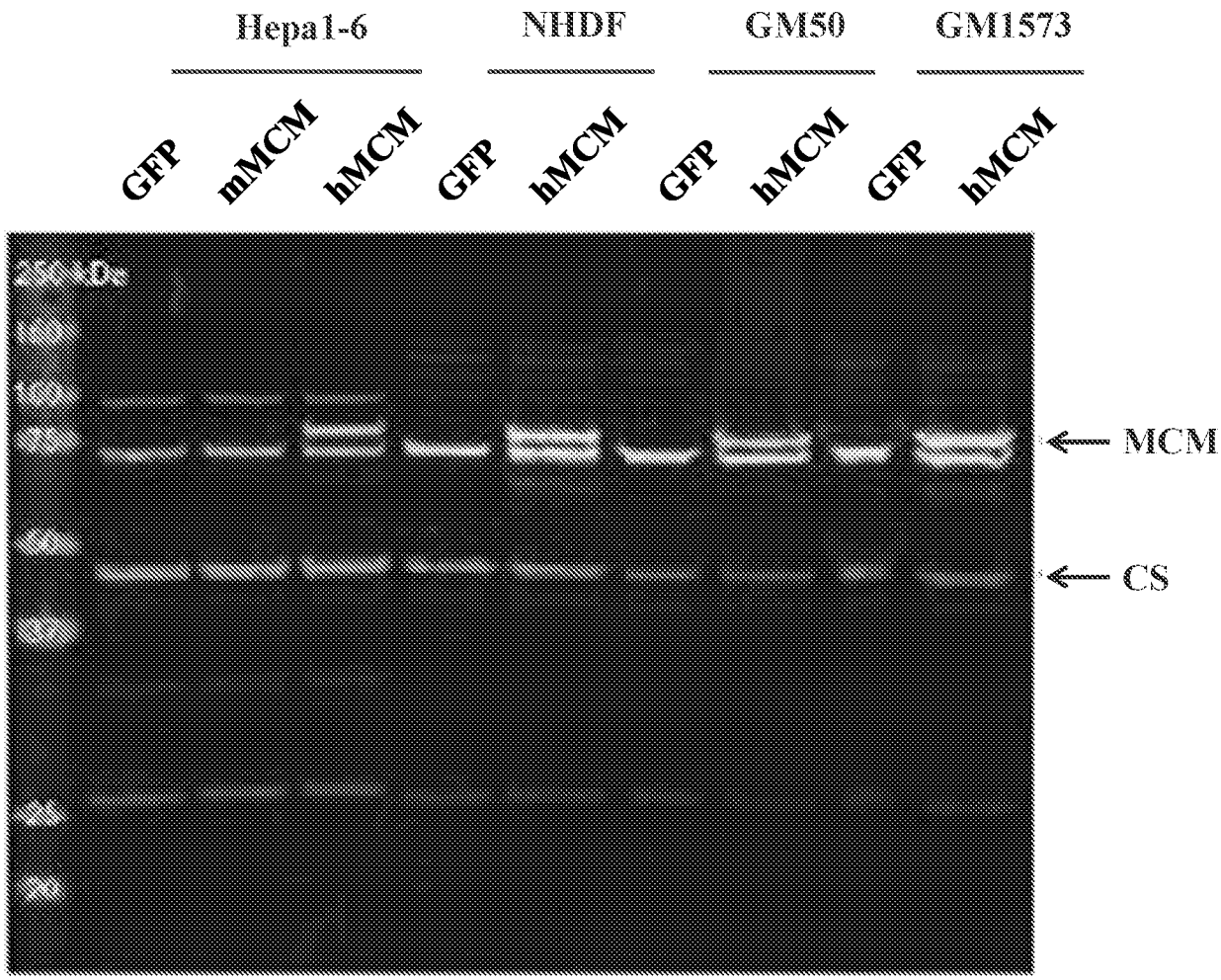


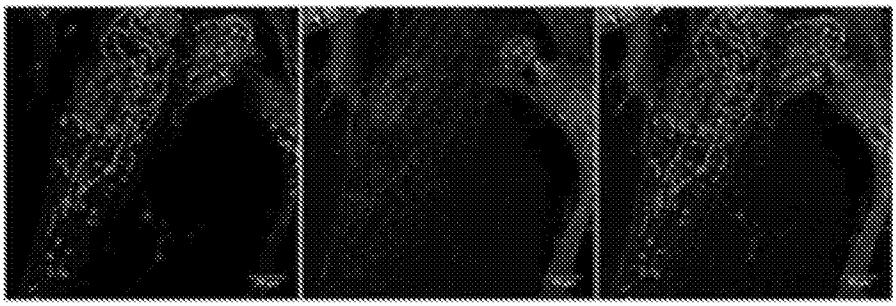
FIG. 5



MCM: Mouse α-Methymalonyl-CoA mutase (TA505873_2C8)
CS: Rabbit α-Citrate synthetase

FIG. 6A

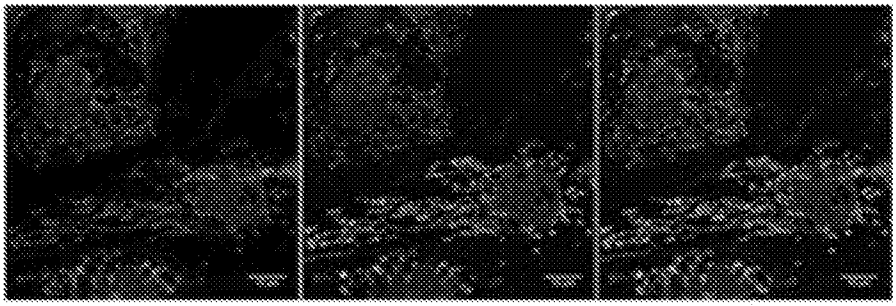
eGFP-transfected normal human fibroblasts



MitoTracker DAPI | MCM DAPI | Merged

FIG. 6B

MUT-transfected normal human fibroblasts



MitoTracker DAPI | MCM DAPI | Merged

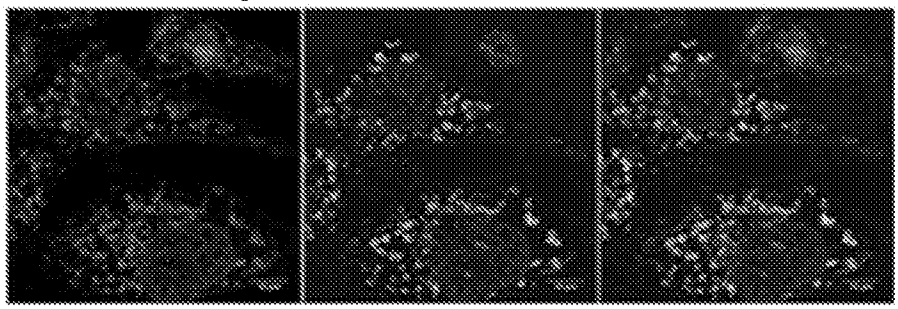
FIG. 6C

eGFP-transfected patient fibroblasts

MitoTracker DAPI | MCM DAPI | Merged

FIG. 6D

MUT-transfected patient fibroblasts



MitoTracker DAPI | MCM DAPI | Merged

FIG. 7

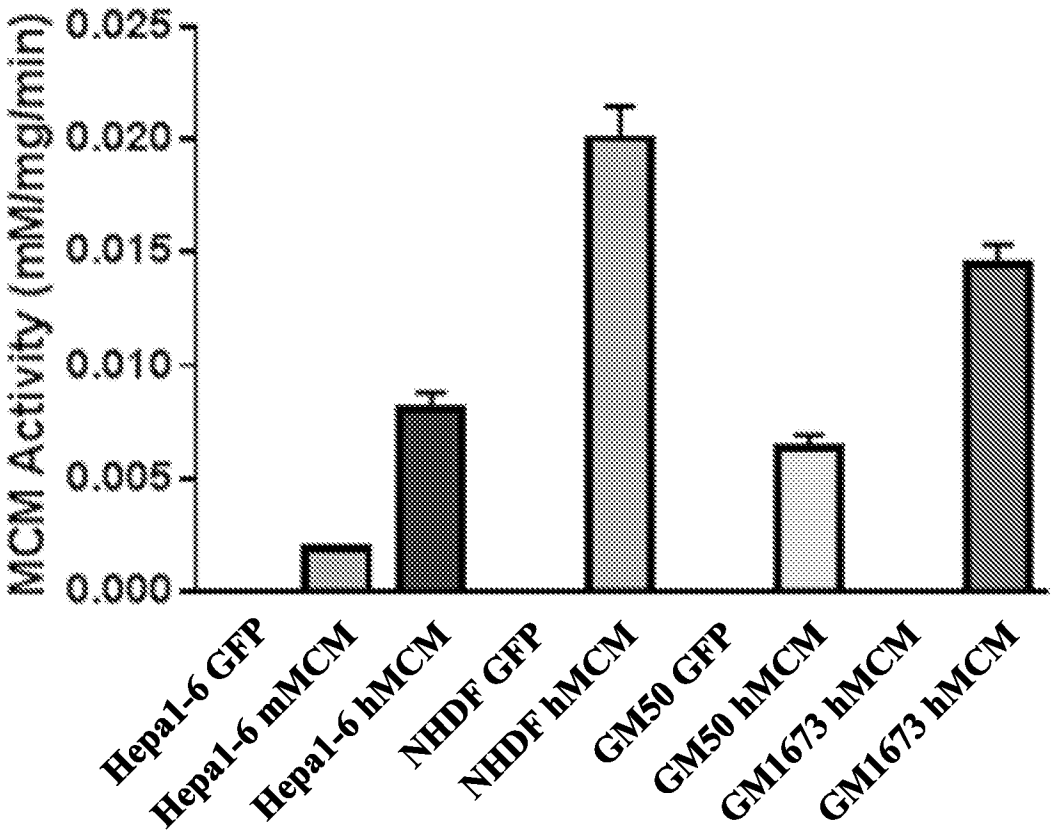

MCM Activity (mM/mg/min)
0.025
0.020
0.015
0.010
0.005
0.000
Hepa1-6 GFP
Hepa1-6 mMCM
Hepa1-6 hMCM
NHDF GFP
NHDF hMCM
GM50 GFP
GM50 hMCM
GM1673 hMCM
GM1673 hMCM

FIG. 8A

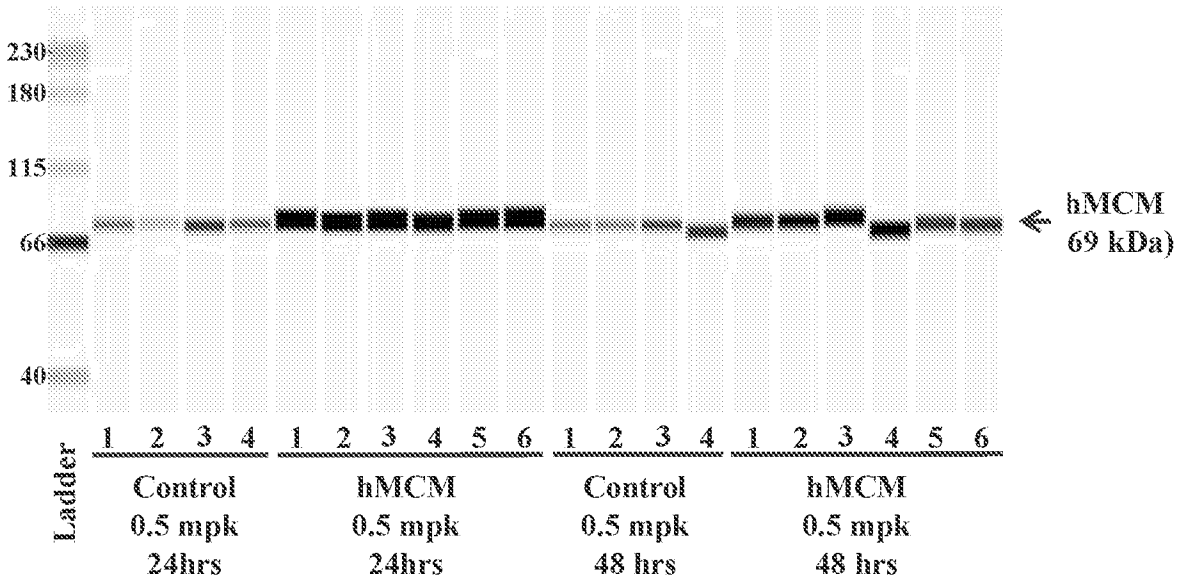

230
180
115
66
40
hMCM
69 kDa)
Ladder
1 2 3 4 1 2 3 4 5 6 1 2 3 4 1 2 3 4 5 6
Control
0.5 mpk
24hrs
hMCM
0.5 mpk
24hrs
Control
0.5 mpk
48 hrs
hMCM
0.5 mpk
48 hrs

FIG. 8B

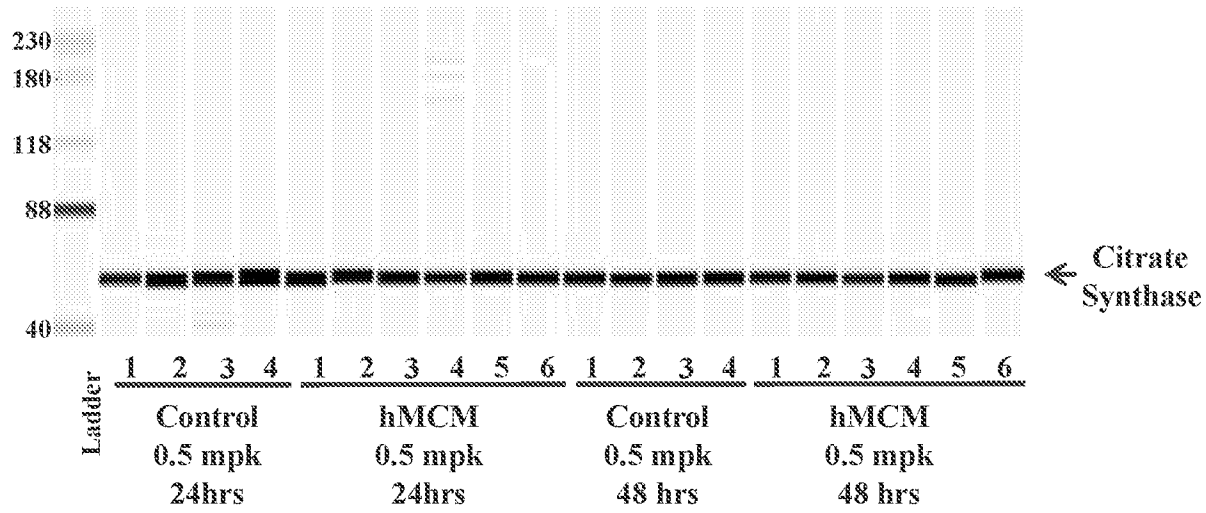

230
180
118
88
40
Citrate
Synthase
Ladder
1 2 3 4 1 2 3 4 5 6 1 2 3 4 1 2 3 4 5 6
Control
0.5 mpk
24hrs
hMCM
0.5 mpk
24hrs
Control
0.5 mpk
48 hrs
hMCM
0.5 mpk
48 hrs

FIG. 9

ATGCTGCGGGCCAAGAACCAGCTGTTCCTGCTGAGCCCTCACTACCTGCGGCAGGTGAA
GGAGAGCAGCGGCAGCCGGCTGATCCAGCAGCGGCTGCTGCACCAGCAGCAGCCCCTGC
ACCCCGAGTGGGCCGCCCTGGCCAAGAAGCAGCTGAAGGGCAAGAACCCCGAGGACCTG
ATCTGGCACACGCCCGAGGGCATCAGCATCAAGCCCCTGTACAGCAAGCGGGACACCAT
GGACCTGCCCGAGGAGCTGCCCGGCGTGAAGCCCTTCACCCGGGGCCCCTACCCCACCA
TGTACACCTTCCGGCCCTGGACCATCCGGCAGTACGCCGGCTTCAGCACCGTGGAGGAG
AGCAACAAGTTCTACAAGGACAACATCAAGGCCGGCCAGCAGGGCCTGAGCGTGGCCTT
CGACCTGGCCACCCACCGGGGCTACGACAGCGACAACCCACGGGTGCGGGGCGACGTGG
GCATGGCCGGCGTGGCCATCGACACCGTGGAGGACACCAAGATCCTGTTCGACGGCATC
CCTCTGGAGAAGATGAGCGTGAGCATGACCATGAACGGCGCCGTGATCCCCGTGCTGGC
CAACTTCATCGTGACCGGCGAGGAGCAGGGCGTGCCCAAGGAGAAGCTGACCGGCACCA
TCCAGAACGACATCCTGAAGGAGTTCATGGTGCGGAACACCTACATCTTCCCTCCCGAG
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CAACAGCATCAGCATCAGCGGCTACCACATGCAGGAGGCCGGCGCCGACGCCATCCTGG
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CTGACCATCGACGAGTTCGCGCCCCGGCTGAGCTTCTTCTGGGGCATCGGCATGAACTT
CTACATGGAGATCGCCAAGATGCGGGCCGGCCGGCGGCTGTGGGCCCACCTGATCGAGA
AGATGTTCCAGCCCAAGAACAGCAAGAGCCTGCTGCTGCGGGCCCACTGCCAGACCAGC
GGCTGGAGCCTGACCGAGCAGGACCCCTACAACAACATCGTGCGGACCGCCATCGAGGC
CATGGCCGCCGTGTTCGGCGGCACCCAGAGCCTGCACACCAACAGCTTCGACGAGGCCC
TGGGCCTGCCCACCGTGAAGAGCGCCCGGATCGCCCGGAACACCCAGATCATCATCCAG
GAGGAGAGCGGCATCCCCAAGGTGGCCGACCCCTGGGGCGGCAGCTACATGATGGAGTG
CCTGACCAACGACGTGTACGACGCCGCCCTGAAGCTGATCAACGAGATCGAGGAGATGG
GCGGCATGGCCAAGGCCGTGGCCGAGGGCATCCCCAAGCTGCGGATCGAGGAGTGCGCC
GCCCGGCGGCAGGCCCGGATCGACAGCGGCAGCGAGGTGATCGTGGGCGTGAACAAGTA
CCAGCTGGAGAAGGAGGACGCCGTGGAGGTGCTGGCCATCGACAACACCAGCGTGCGGA
ACCGGCAGATCGAGAAGCTGAAGAAGATCAAGAGCAGCCGGGACCAGGCCCTGGCCGAG
CGGTGCCTGGCCGCCCTGACCGAGTGCGCCGCCAGCGGCGACGGCAACATCCTGGCCCT
GGCCGTGGACGCCAGCCGGGCCCGGTGCACCGTGGGCGAGATCACCGACGCCCTGAAGA
AGGTGTTCGGCGAGCACAAGGCCAACGACCGGATGGTGAGCGGCGCCTACCGGCAGGAG
TTCGGCGAGAGCAAGGAGATCACCAGCGCCATCAAGCGGGTGCACAAGTTCATGGAGCG
GGAGGGCCGGCGGCCCCGGCTGCTGGTGGCCAAGATGGGCCAGGACGGCCACGACCGGG
GCGCCAAGGTGATCGCCACCGGCTTCGCCGACCTGGGCTTCGACGTGGACATCGGCCCA
CTGTTCCAGACGCCCCGGGAGGTGGCCCAGCAGGCCGTGGACGCCGACGTGCACGCCGT
GGGCGTGAGCACCCTGGCCGCCGGCCACAAGACCCTGGTGCCCGAGCTGATCAAGGAGC
TGAACAGCCTGGGCCGGCCCGACATCCTGGTGATGTGCGGCGGCGTGATCCCGCCCCAG
GACTACGAGTTCCTGTTCGAGGTGGGCGTGAGCAACGTGTTCGGCCCCGGCACCCGGAT
CCCCAAGGCCGCCGTGCAGGTGCTGGACGACATCGAGAAGTGCCTGGAGAAGAAGCAGC
AGAGCGTG

SEQ ID NO: 732

FIG. 10

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ATCTGGCACACGCCCGAGGGCATCTCCATCAAGCCCCTCTACTCCAAGCGCGACACCAT
GGACCTCCCCGAGGAGCTCCCCGGCGTCAAGCCCTTCACCCGCGGCCCCTACCCCACCA
TGTACACCTTCCGCCCCTGGACCATCCGCCAGTACGCCGGCTTCTCCACCGTCGAGGAG
TCCAACAAGTTCTACAAGGACAACATCAAGGCCGGCCAGCAGGGCCTCTCCGTCGCCTT
CGACCTCGCCACCCACCGCGGCTACGACTCCGACAACCCGCGCGTCCGCGGCGACGTCG
GCATGGCCGGCGTCGCCATCGACACCGTCGAGGACACCAAGATCCTCTTCGACGGCATC
CCTCTCGAGAAGATGTCCGTCTCCATGACCATGAACGGCGCCGTCATCCCCGTCCTCGC
CAACTTCATCGTCACCGGCGAGGAGCAGGGCGTCCCCAAGGAGAAGCTCACCGGCACCA
TCCAGAACGACATCCTCAAGGAGTTCATGGTCCGCAACACCTACATCTTCCCTCCCGAG
CCCTCCATGAAGATCATCGCCGACATCTTCGAGTACACCGCCAAGCACATGCCCAAGTT
CAACTCCATCTCCATCTCCGGCTACCACATGCAGGAGGCCGGCGCCGACGCCATCCTCG
AGCTCGCCTACACCCTCGCCGACGGCCTCGAGTACTCCCGCACCGGCCTCCAGGCCGGC
CTCACCATCGACGAGTTCGCGCCCCGCCTCTCCTTCTTCTGGGGCATCGGCATGAACTT
CTACATGGAGATCGCCAAGATGCGCGCCGGCCGCCGCCTCTGGGCCCACCTCATCGAGA
AGATGTTCCAGCCCAAGAACTCCAAGTCCCTCCTCCTCCGCGCCCACTGCCAGACCTCC
GGCTGGTCCCTCACCGAGCAGGACCCCTACAACAACATCGTCCGCACCGCCATCGAGGC
CATGGCCGCCGTCTTCGGCGGCACCCAGTCCCTCCACACCAACTCCTTCGACGAGGCCC
TCGGCCTCCCCACCGTCAAGTCCGCCCGCATCGCCCGCAACACCCAGATCATCATCCAG
GAGGAGTCCGGCATCCCCAAGGTCGCCGACCCCTGGGGCGGCTCCTACATGATGGAGTG
CCTCACCAACGACGTCTACGACGCCGCCCTCAAGCTCATCAACGAGATCGAGGAGATGG
GCGGCATGGCCAAGGCCGTCGCCGAGGGCATCCCCAAGCTCCGCATCGAGGAGTGCGCC
GCCCGCCGCCAGGCCCGCATCGACTCCGGCTCCGAGGTCATCGTCGGCGTCAACAAGTA
CCAGCTCGAGAAGGAGGACGCCGTCGAGGTCCTCGCCATCGACAACACCTCCGTCCGCA
ACCGCCAGATCGAGAAGCTCAAGAAGATCAAGTCCTCCCGCGACCAGGCCCTCGCCGAG
CGCTGCCTCGCCGCCCTCACCGAGTGCGCCGCCTCCGGCGACGGCAACATCCTCGCCCT
CGCCGTCGACGCCTCCCGCGCCCGCTGCACCGTCGGCGAGATCACCGACGCCCTCAAGA
AGGTCTTCGGCGAGCACAAGGCCAACGACCGCATGGTCTCCGGCGCCTACCGCCAGGAG
TTCGGCGAGTCCAAGGAGATCACCTCCGCCATCAAGCGCGTCCACAAGTTCATGGAGCG
CGAGGGCCGCCGCCCCGCGCCTCCTCGTCGCCAAGATGGGCCAGGACGGCCACGACCGCG
GCGCCAAGGTCATCGCCACCGGCTTCGCCGACCTCGGCTTCGACGTCGACATCGGCCCA
CTCTTCCAGACGCCCCGCGAGGTCGCCCAGCAGGCCGTCGACGCCGACGTCCACGCCGT
CGGCGTCTCCACCCTCGCCGCCGGCCACAAGACCCTCGTCCCCGAGCTCATCAAGGAGC
TCAACTCCCTCGGCCGCCCCGACATCCTCGTCATGTGCGGCGGCGTCATCCCTCCCCAG
GACTACGAGTTCCTCTTCGAGGTCGGCGTCTCCAACGTCTTCGGCCCCGGCACCCGCAT
CCCCAAGGCCGCCGTCCAGGTCCTCGACGACATCGAGAAGTGCCTCGAGAAGAAGCAGC
AGTCCGTC

SEQ ID NO: 733

FIG. 11

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GGAGAGCAGCGGCAGCCGGCTGATCCAGCAGCGGCTGCTGCACCAGCAGCAGCCCCTGC
ACCCCGAGTGGGCCGCCCTGGCCAAGAAGCAGCTGAAGGGCAAGAACCCCGAGGACCTG
ATCTGGCACACCCCCGAGGGCATCAGCATCAAGCCCCTGTACAGCAAGCGGGACACCAT
GGACCTGCCCGAGGAGCTGCCCGGCGTGAAGCCCTTCACCCGGGGCCCCTACCCCACCA
TGTACACCTTCCGGCCCTGGACCATCCGGCAGTACGCCGGCTTCAGCACCGTGGAGGAG
AGCAACAAGTTCTACAAGGACAACATCAAGGCCGGCCAGCAGGGCCTGAGCGTGGCCTT
CGACCTGGCCACCCACCGGGGCTACGACAGCGACAACCCCCGGGTGCGGGGCGACGTGG
GCATGGCCGGCGTGGCCATCGACACCGTGGAGGACACCAAGATCCTGTTCGACGGCATC
CCCCTGGAGAAGATGAGCGTGAGCATGACCATGAACGGCGCCGTGATCCCCGTGCTGGC
CAACTTCATCGTGACCGGCGAGGAGCAGGGCGTGCCCAAGGAGAAGCTGACCGGCACCA
TCCAGAACGACATCCTGAAGGAGTTCATGGTGCGGAACACCTACATCTTCCCCCCCGAG
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CAACAGCATCAGCATCAGCGGCTACCACATGCAGGAGGCCGGCGCCGACGCCATCCTGG
AGCTGGCCTACACCCTGGCCGACGGCCTGGAGTACAGCCGGACCGGCCTGCAGGCCGGC
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CTACATGGAGATCGCCAAGATGCGGGCCGGCCGGCGGCTGTGGGCCCACCTGATCGAGA
AGATGTTCCAGCCCAAGAACAGCAAGAGCCTGCTGCTGCGGGCCCACTGCCAGACCAGC
GGCTGGAGCCTGACCGAGCAGGACCCCTACAACAACATCGTGCGGACCGCCATCGAGGC
CATGGCCGCCGTGTTCGGCGGCACCCAGAGCCTGCACACCAACAGCTTCGACGAGGCCC
TGGGCCTGCCCACCGTGAAGAGCGCCCGGATCGCCCGGAACACCCAGATCATCATCCAG
GAGGAGAGCGGCATCCCCAAGGTGGCCGACCCCTGGGGCGGCAGCTACATGATGGAGTG
CCTGACCAACGACGTGTACGACGCCGCCCTGAAGCTGATCAACGAGATCGAGGAGATGG
GCGGCATGGCCAAGGCCGTGGCCGAGGGCATCCCCAAGCTGCGGATCGAGGAGTGCGCC
GCCCGGCGGCAGGCCCGGATCGACAGCGGCAGCGAGGTGATCGTGGGCGTGAACAAGTA
CCAGCTGGAGAAGGAGGACGCCGTGGAGGTGCTGGCCATCGACAACACCAGCGTGCGGA
ACCGGCAGATCGAGAAGCTGAAGAAGATCAAGAGCAGCCGGGACCAGGCCCTGGCCGAG
CGGTGCCTGGCCGCCCTGACCGAGTGCGCCGCCAGCGGCGACGGCAACATCCTGGCCCT
GGCCGTGGACGCCAGCCGGGCCCGGTGCACCGTGGGCGAGATCACCGACGCCCTGAAGA
AGGTGTTCGGCGAGCACAAGGCCAACGACCGGATGGTGAGCGGCGCCTACCGGCAGGAG
TTCGGCGAGAGCAAGGAGATCACCAGCGCCATCAAGCGGGTGCACAAGTTCATGGAGCG
GGAGGGCCGGCGGCCCCGGCTGCTGGTGGCCAAGATGGGCCAGGACGGCCACGACCGGG
GCGCCAAGGTGATCGCCACCGGCTTCGCCGACCTGGGCTTCGACGTGGACATCGGCCCC
CTGTTCCAGACCCCCCGGGAGGTGGCCCAGCAGGCCGTGGACGCCGACGTGCACGCCGT
GGGCGTGAGCACCCTGGCCGCCGGCCACAAGACCCTGGTGCCCGAGCTGATCAAGGAGC
TGAACAGCCTGGGCCGGCCCGACATCCTGGTGATGTGCGGCGGCGTGATCCCCCCCCAG
GACTACGAGTTCCTGTTCGAGGTGGGCGTGAGCAACGTGTTCGGCCCCGGCACCCGGAT
CCCCAAGGCCGCCGTGCAGGTGCTGGACGACATCGAGAAGTGCCTGGAGAAGAAGCAGC
AGAGCGTG

SEQ ID NO: 734

FIG. 12

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ATCCCGAGTGGGCAGCTCTGGCCAAGAAACAGTTGAAGGGCAAGAACCCCGAGGACCTG
ATTTGGCATACCCCCGAGGGCATCAGCATCAAGCCTCTGTACTCCAAGCGCGACACCAT
GGACCTCCCCGAGGAACTGCCCGGGGTGAAACCATTTACACGCGGCCCCTACCCCACCA
TGTACACCTTCCGGCCATGGACGATTAGGCAGTACGCTGGCTTCAGCACGGTGGAGGAG
AGCAATAAGTTCTACAAGGACAACATCAAGGCAGGGCAGCAGGGGCTTAGCGTGGCCTT
TGACCTGGCCACACACCGGGGGTACGACAGCGACAATCCCAGGGTGCGGGGCGACGTTG
GCATGGCCGGCGTTGCTATCGATACCGTGGAGGATACGAAGATACTGTTTGACGGGATC
CCCCTGGAGAAAATGAGCGTGAGCATGACAATGAACGGCGCTGTGATCCCTGTCCTCGC
TAACTTCATCGTTACCGGCGAGGAACAGGGAGTACCTAAGGAAAAGCTGACTGGAACTA
TTCAGAATGACATTCTCAAGGAATTCATGGTCAGGAACACTTATATCTTTCCCCCTGAA
CCGTCTATGAAAATCATAGCAGACATTTTTGAGTATACCGCCAAGCACATGCCCAAGTT
TAACAGCATCTCCATCTCTGGCTACCACATGCAGGAGGCAGGCGCCGACGCTATTCTGG
AGCTGGCGTACACTCTCGCCGACGGACTGGAGTACTCTCGCACTGGACTCCAGGCCGGG
CTGACCATCGATGAGTTCGCACCGAGGCTGTCCTTCTTCTGGGGCATTGGAATGAACTT
TTACATGGAGATCGCTAAGATGCGAGCAGGCCGGAGACTGTGGGCCCACCTGATTGAAA
AAATGTTCCAACCTAAGAATTCCAAGAGCCTGCTGTTGAGAGCCCACTGCCAGACCAGC
GGCTGGTCGCTGACCGAGCAGGACCCCTACAATAACATAGTGCGGACCGCTATTGAAGC
CATGGCCGCCGTTTTTGGCGGCACTCAGAGCCTGCACACCAACAGCTTTGACGAGGCCC
TGGGCCTGCCCACTGTGAAGAGTGCCAGAATCGCCAGGAATACCCAGATTATCATTCAG
GAGGAGTCAGGAATACCCAAAGTGGCCGACCCCTGGGGGGGTAGCTACATGATGGAGTG
CCTGACAAACGACGTGTACGATGCCGCCCTCAAGCTGATCAACGAGATCGAGGAAATGG
GCGGCATGGCCAAGGCTGTTGCCGAAGGCATCCCCAAGCTCCGGATTGAAGAGTGTGCG
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CCAGCTGGAAAAGGAAGATGCTGTGGAGGTGCTGGCCATCGACAACACCTCCGTTCGGA
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GGCCGTGGACGCTTCTAGGGCAAGATGCACAGTGGGCGAGATCACAGACGCTCTGAAGA
AGGTCTTCGGCGAGCATAAAGCCAACGACCGGATGGTGAGCGGAGCATACCGGCAGGAG
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CTTTTCCAGACACCTCGGGAGGTGGCTCAACAGGCTGTGGATGCCGACGTCCACGCAGT
GGGCGTGAGCACCCTGGCCGCCGGCCACAAGACCCTGGTGCCCGAGTTAATCAAGGAGT
TGAATTCACTGGGCAGACCTGACATCCTGGTGATGTGCGGCGGCGTCATCCCCCCGCAG
GATTACGAGTTCCTGTTCGAGGTGGGAGTGAGCAACGTGTTCGGTCCTGGCACACGGAT
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AGTCCGTG

SEQ ID NO: 151

FIG. 13

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GGAGAGCTCAGGGAGCCGGCTCATCCAGCAGAGACTGCTCCATCAGCAGCAGCCGCTGC
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ATTTGGCACACCCCAGAGGGCATTAGCATCAAGCCTCTCTATAGCAAGAGAGACACCAT
GGACCTCCCCGAGGAGCTGCCCGGCGTGAAGCCTTTCACCCGTGGCCCCTACCCAACCA
TGTACACATTCAGGCCCTGGACTATCCGGCAGTACGCGGGCTTCTCTACCGTGGAGGAG
TCCAACAAGTTCTACAAGGACAATATTAAAGCTGGCCAGCAGGGACTGAGCGTGGCCTT
CGATTTGGCCACCCACAGAGGATACGACAGCGACAACCCCAGGGTGAGGGGCGACGTTG
GAATGGCCGGCGTGGCCATTGATACTGTCGAGGACACCAAGATCCTGTTCGATGGGATA
CCCCTCGAAAAAATGTCTGTGTCCATGACAATGAATGGGGCCGTGATCCCAGTGTTGGC
CAATTTTATCGTGACAGGAGAGGAGCAGGGCGTGCCCAAGGAGAAGCTGACCGGCACCA
TCCAGAACGACATCTTGAAAGAATTCATGGTTAGAAATACCTACATCTTTCCTCCCGAA
CCCAGCATGAAGATCATCGCCGATATCTTCGAGTATACCGCCAAACACATGCCCAAATT
CAACTCCATTAGCATATCCGGATACCATATGCAGGAGGCTGGCGCCGACGCCATCCTGG
AGCTGGCGTACACCCTGGCCGATGGCCTGGAATATTCTAGGACCGGCCTGCAGGCTGGA
CTCACAATCGATGAGTTCGCCCCCCGCCTGAGCTTCTTCTGGGGCATCGGCATGAACTT
CTACATGGAGATCGCTAAGATGAGAGCGGGACGCCGCCTGTGGGCTCACCTGATCGAAA
AAATGTTCCAACCTAAGAATAGCAAGTCTCTGCTCCTGCGGGCACACTGTCAAACCTCC
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CATGGCGGCCGTGTTCGGGGGCACCCAGTCACTCCACACCAATAGCTTCGACGAGGCCC
TGGGCTTGCCTACTGTCAAGTCTGCCAGGATCGCCAGGAACACTCAGATTATCATCCAG
GAGGAGAGCGGCATTCCTAAGGTAGCTGACCCCTGGGGGGGAAGCTACATGATGGAATG
CCTCACCAACGACGTGTACGATGCCGCCCTGAAGCTGATTAATGAGATCGAGGAAATGG
GGGGCATGGCCAAGGCTGTAGCCGAGGGAATCCCCAAGCTGAGAATCGAGGAGTGCGCC
GCCAGGCGGCAGGCCCGCATCGATAGTGGCAGCGAGGTGATCGTGGGCGTTAACAAGTA
CCAGCTCGAGAAGGAAGACGCCGTAGAGGTGTTGGCAATCGACAATACCTCCGTGAGAA
ATAGGCAGATCGAGAAGCTAAAGAAGATAAAGAGCAGCCGGGACCAGGCTCTGGCAGAA
CGGTGCCTGGCCGCCCTCACTGAATGCGCCGCTTCTGGCGATGGCAACATTCTGGCCCT
TGCCGTCGATGCCAGCCGGGCCCGATGCACTGTGGGAGAGATCACAGACGCTCTGAAGA
AGGTGTTCGGCGAGCATAAAGCAAACGATAGAATGGTGTCCGGCGCCTACAGGCAGGAG
TTTGGCGAGAGCAAGGAGATCACATCTGCTATTAAGAGAGTGCATAAGTTCATGGAGAG
AGAGGGACGGCGGCCTAGACTGCTGGTAGCAAAGATGGGCCAGGACGGCCACGATCGGG
GAGCAAAGGTCATTGCTACCGGGTTCGCCGACCTGGGCTTCGACGTGGACATTGGCCCC
CTCTTCCAGACCCCCCGCGAAGTTGCTCAGCAGGCTGTGGATGCTGACGTGCACGCTGT
GGGCGTCAGCACACTGGCCGCTGGACATAAGACCCTGGTTCCCGAGCTGATCAAGGAGC
TGAATAGCCTGGGTCGGCCAGACATCCTCGTGATGTGCGGGGGTGTGATCCCCCCTCAG
GATTACGAGTTCCTGTTCGAGGTTGGAGTCTCTAATGTGTTCGGCCCCGGAACAAGAAT
CCCGAAGGCCGCTGTGCAAGTCCTGGACGACATCGAAAAGTGCCTCGAGAAGAAGCAGC
AGTCTGTG

SEQ ID NO: 152

FIG. 14

ATGCTGAGGGCCAAGAACCAGCTGTTCCTCCTGTCTCCTCACTACCTGAGACAGGTGAA
GGAGTCCAGCGGTAGCAGACTGATCCAGCAGAGGCTGCTTCACCAGCAGCAGCCCCTCC
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GTATGGCCGGCGTGGCCATCGACACTGTTGAGGACACCAAAATCCTATTTGACGGCATA
CCCCTGGAAAAGATGTCCGTGAGCATGACAATGAATGGCGCTGTGATCCCCGTGCTCGC
TAACTTCATCGTGACCGGCGAGGAGCAGGGTGTCCCTAAGGAGAAACTTACCGGCACAA
TCCAGAACGACATTCTCAAGGAGTTTATGGTGCGCAACACCTACATTTTCCCCCCAGAG
CCTAGCATGAAGATCATTGCCGACATCTTCGAGTACACCGCCAAGCATATGCCAAAGTT
TAACTCCATTTCAATCTCTGGCTACCATATGCAGGAAGCTGGCGCTGACGCCATCTTAG
AGCTGGCCTACACCTTGGCCGACGGCCTCGAATACAGCAGGACCGGCCTTCAGGCCGGT
CTGACCATTGACGAATTTGCACCCAGACTGAGCTTCTTCTGGGGCATCGGCATGAACTT
CTATATGGAGATCGCTAAAATGAGAGCCGGCCGGAGACTGTGGGCTCACCTGATCGAGA
AAATGTTTCAACCCAAGAACTCCAAAAGCCTTCTGCTCAGGGCCCATTGTCAAACCTCT
GGATGGAGCCTGACTGAGCAGGACCCGTATAACAACATCGTCAGGACCGCCATCGAGGC
CATGGCTGCGGTGTTTGGCGGAACCCAGTCCTTACACACAAATAGCTTTGACGAAGCCC
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CTTGACCAACGATGTGTACGATGCTGCTCTGAAGCTGATTAACGAGATTGAGGAGATGG
GAGGCATGGCTAAGGCTGTCGCGGAGGGCATCCCTAAGCTGAGAATCGAGGAGTGCGCC
GCCCGCCGGCAGGCCAGGATTGACAGCGGATCTGAGGTGATCGTGGGGGTGAACAAGTA
CCAGCTGGAGAAGGAGGACGCCGTTGAGGTTCTGGCTATCGACAACACCAGCGTCAGAA
ACAGGCAGATCGAGAAGCTGAAGAAAATCAAAAGCAGCAGAGACCAGGCCCTGGCAGAA
AGATGCCTGGCTGCCCTGACCGAGTGCGCTGCTAGCGGAGACGGGAACATCCTGGCTCT
GGCCGTCGACGCTTCCAGAGCCAGGTGTACCGTCGGCGAGATCACCGACGCCCTGAAGA
AAGTGTTCGGCGAGCACAAGGCCAACGACCGCATGGTGTCCGGCGCCTACAGGCAGGAG
TTCGGCGAGTCCAAGGAGATTACCTCCGCCATCAAACGGGTGCACAAATTCATGGAGAG
AGAGGGCAGACGGCCACGCTTGCTCGTGGCCAAGATGGGGCAGGACGGCCACGATAGGG
GCGCTAAGGTTATCGCTACAGGCTTTGCTGATCTGGGCTTCGACGTGGACATCGGCCCC
CTGTTTCAGACCCCTAGAGAGGTAGCTCAGCAGGCCGTCGACGCCGACGTGCACGCCGT
GGGCGTCAGCACACTGGCAGCCGGACACAAGACCCTCGTGCCCGAGCTTATCAAGGAAC
TGAACTCCTTGGGGCGGCCCGACATCCTCGTCATGTGCGGCGGAGTGATTCCCCCCCAG
GACTATGAGTTCCTGTTCGAGGTCGGCGTAAGCAACGTCTTTGGCCCCGGAACTCGGAT
CCCCAAGGCCGCAGTACAGGTGCTGGACGACATCGAAAAGTGCCTGGAGAAGAAGCAAC
AGTCTGTG

SEQ ID NO: 153

FIG. 15

ATGCTGCGCGCTAAAAACCAACTATTCCTGCTGTCCCCCCATTACCTGAGACAGGTGAA
GGAGAGCTCCGGAAGCAGGCTGATCCAACAGAGACTTCTGCACCAGCAGCAGCCCCTGC
ATCCCGAGTGGGCCGCTCTGGCTAAGAAACAACTGAAGGGAAAGAACCCCGAGGACCTG
ATCTGGCACACCCCAGAGGGCATATCCATCAAGCCCCTGTATTCTAAGAGGGACACTAT
GGACCTGCCCGAGGAGCTCCCCGGCGTCAAGCCTTTCACACGCGGACCTTACCCCACAA
TGTACACATTCCGACCATGGACCATTAGGCAGTACGCAGGATTCAGCACCGTTGAGGAG
TCCAATAAATTCTATAAGGACAATATTAAGGCCGGACAACAGGGCCTGAGTGTGGCATT
CGACCTGGCCACACACAGAGGTTACGACTCCGATAATCCTAGGGTGAGAGGCGACGTGG
GCATGGCTGGAGTGGCCATCGATACCGTCGAGGACACAAAGATCCTGTTCGACGGCATC
CCCTTGGAGAAAATGTCCGTGAGCATGACCATGAACGGCGCCGTGATTCCCGTGCTGGC
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CCCTCCATGAAGATCATCGCCGACATCTTCGAGTACACCGCCAAGCACATGCCCAAGTT
CAACTCCATCAGTATTAGCGGCTATCACATGCAGGAGGCCGGCGCCGACGCCATCCTGG
AACTGGCCTACACACTGGCCGACGGTCTGGAGTACAGCAGAACCGGCCTGCAAGCAGGC
CTGACCATCGACGAGTTCGCCCCTCGACTGAGCTTCTTCTGGGGCATTGGCATGAACTT
TTACATGGAGATCGCCAAAATGCGCGCTGGCAGGCGACTCTGGGCCCACCTGATAGAAA
AAATGTTCCAGCCCAAGAACTCCAAGTCCCTGCTCCTCAGGGCCCACTGTCAGACTAGC
GGCTGGAGCCTCACCGAGCAGGACCCATATAATAACATTGTAAGAACAGCCATCGAGGC
CATGGCCGCAGTGTTCGGAGGGACCCAGAGCCTGCATACCAACAGCTTCGATGAGGCCC
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AGGTGTTCGGAGAGCACAAGGCCAACGACAGAATGGTGTCTGGCGCATATAGACAGGAG
TTCGGCGAGAGCAAGGAGATTACGAGCGCCATCAAGAGAGTGCACAAGTTCATGGAGAG
GGAGGGCAGGAGACCACGGCTGCTGGTTGCCAAGATGGGCCAAGACGGTCACGACAGAG
GGGCTAAAGTGATTGCCACCGGCTTCGCCGACCTGGGCTTCGACGTGGACATCGGTCCA
CTGTTCCAGACCCCTAGGGAGGTGGCGCAGCAGGCCGTGGACGCCGACGTGCACGCCGT
CGGCGTGAGCACACTGGCTGCCGGCCACAAGACACTAGTTCCTGAGCTGATCAAGGAAC
TCAACAGCCTGGGCCGGCCTGATATACTGGTGATGTGCGGGGGGGTGATCCCCCCTCAG
GATTACGAGTTTCTGTTTGAGGTGGGCGTGTCCAACGTCTTCGGCCCCGGGACCAGAAT
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SEQ ID NO: 154

FIG. 16A

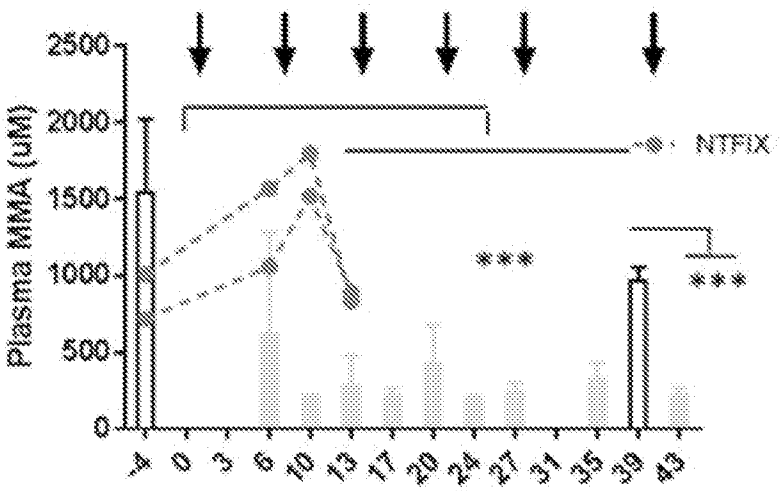


FIG. 16B

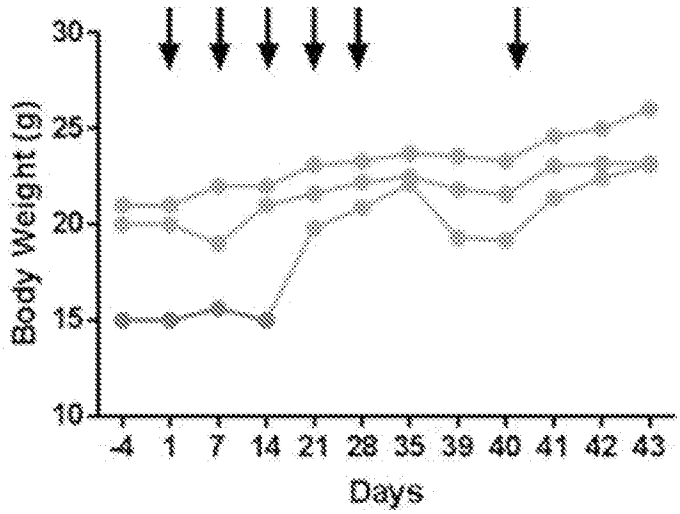
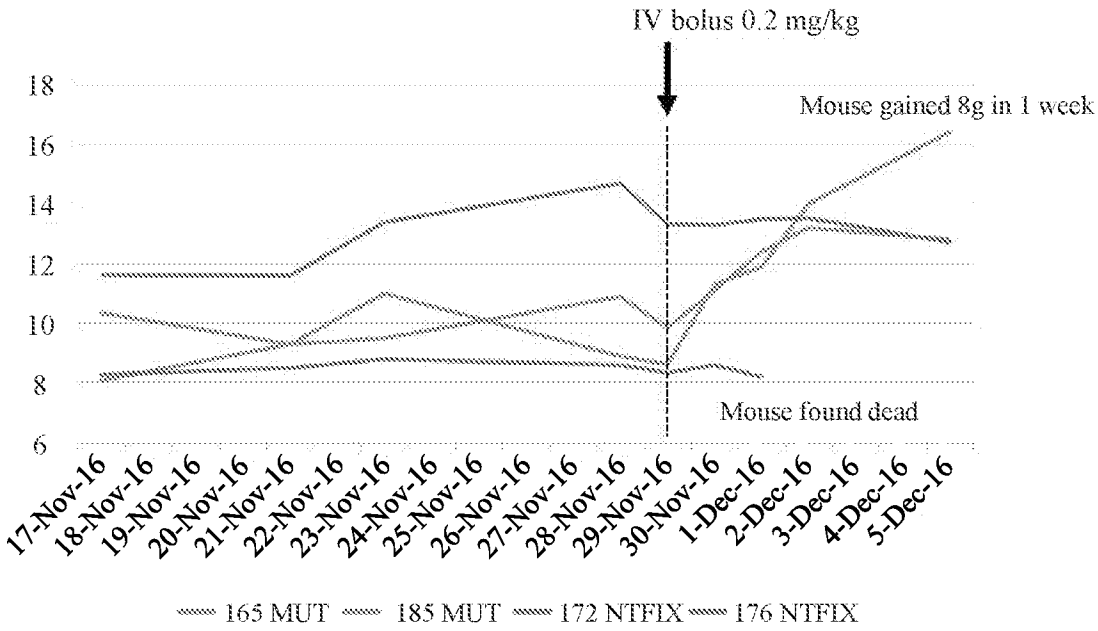


FIG. 16C



Study Design: Weekly IV injections (hMUT or NTFIX mRNA) into MCK mice

FIG. 17

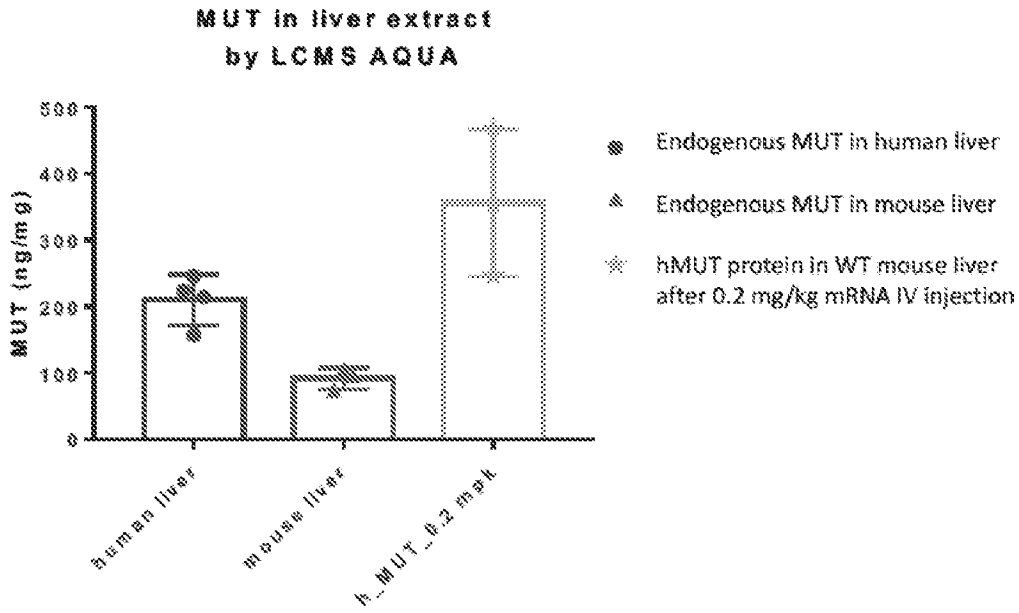

MUT in liver extract
by LCMS AQUA
MUT (ng/mg)
500
400
300
200
100
0
human liver
mouse liver
h_MUT_0.2 mg/k
Endogenous MUT in human liver
Endogenous MUT in mouse liver
hMUT protein in WT mouse liver
after 0.2 mg/kg mRNA IV injection

FIG. 18A

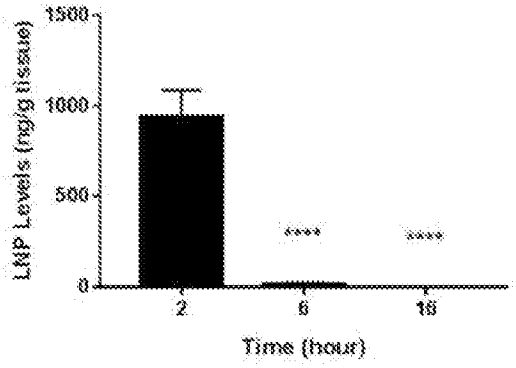


FIG. 18B

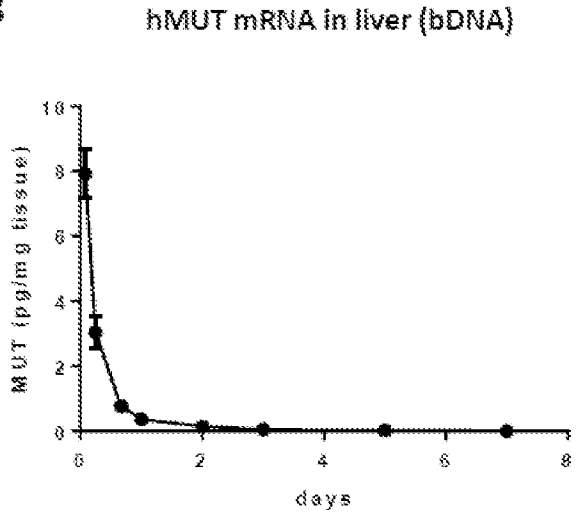


FIG. 18C

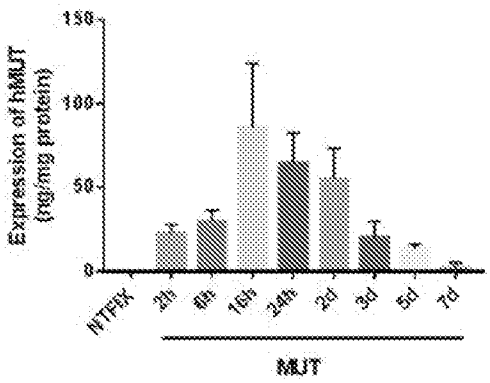


FIG. 19A

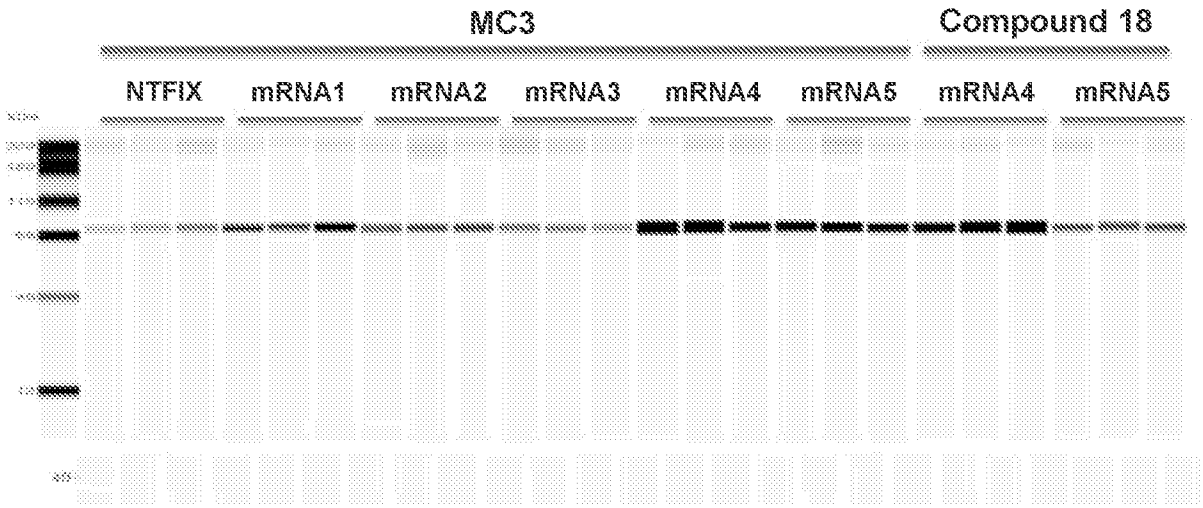


FIG. 19B

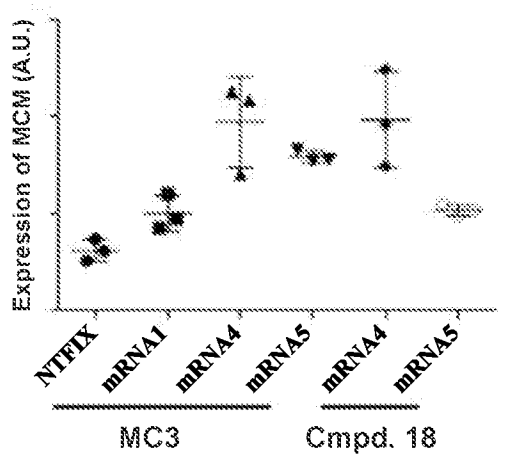


FIG. 20A

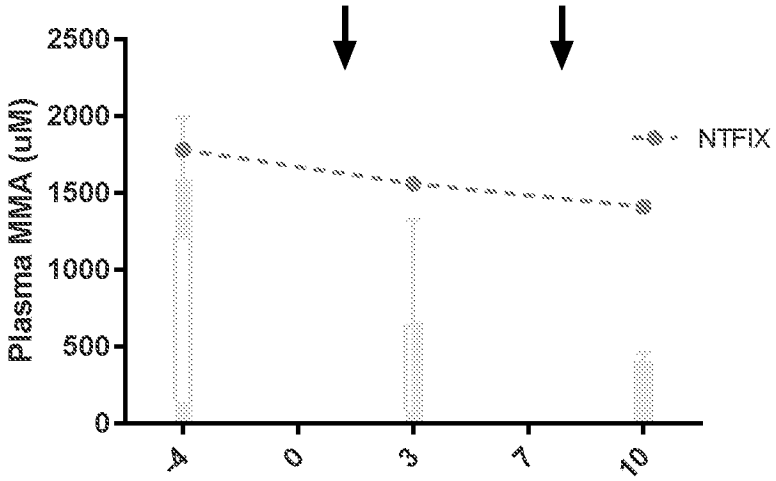
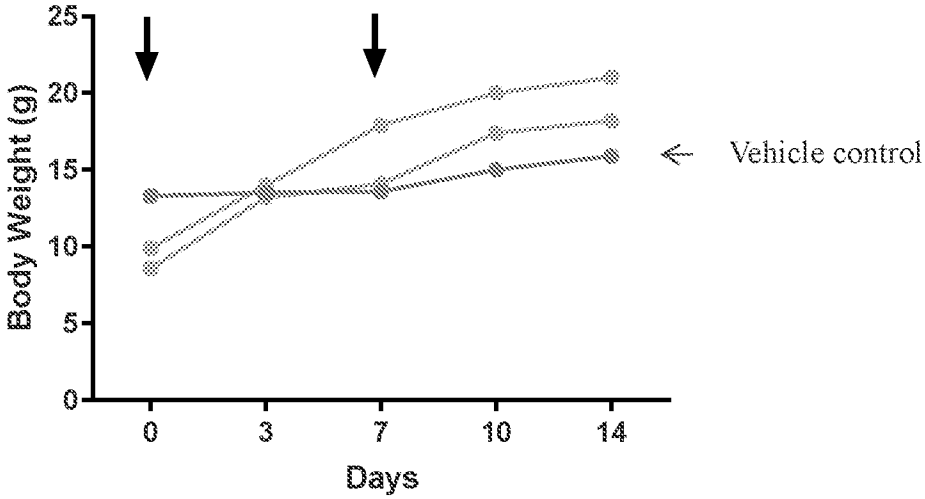


FIG. 20B



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<151> 2016-05-18

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<151> 2016-10-17

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<170> PatentIn version 3.5

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<213> Artificial Sequence

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ccagagtggg cagccctggc caaaaagcag ctgaagggga agaatcctga ggacttgata 180

tggcacacac ctgagggaat cagtatcaaa cctctgtatt caaaaaggga cactatggac 240

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actttcagac cgtggactat tcggcagtat gcaggattta gtactgtcga agagtccaat 360

aagttctata aggacaatat caaggccggc cagcaggggc tgtctgtagc cttcgatcta 420

gctactcaca ggggctacga ttctgacaat ccccgggtca ggggagacgt cggtatggcg 480

ggagtggcga ttgatactgt ggaagatact aagattttgt ttgatggaat cccactggaa 540

aagatgagtg tttcaatgac gatgaatggt gccgtcatac cagtactcgc gaacttcatt 600

gttacggggg aggaacaagg tgtgcccaag gagaagctca ccgggacaat acaaaatgat 660

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atcaagcggg tacataagtt catggagaga gagggccggc gcccccgtct tctggtcgcc 1860

aagatgggcc aggatggaca cgaccgcggc gctaaggtaa ttgccaccgg tttcgcagat 1920

ctcggtttcg atgtggatat cggtcctctg tttcaaaccc cccgggaggt cgctcaacaa 1980

gccgttgatg ccgacgtgca tgcagtcggc gtgtctaccc tggccgcggg gcataaaaca 2040

ctcgtgccag agctcataaa ggagctgaat agcttaggta gacctgatat acttgttatg 2100

tgcggagggg ttatccctcc gcaggactac gagtttctgt tcgaggtggg ggtgtccaat 2160

gtgttcggac ctggaacacg cattcccaaa gccgccgtgc aggttctcga cgacattgaa 2220

aagtgcctgg aaaaaaagca gcagtcagtt 2250

<210> 2
<211> 2250
<212> DNA
<213> Artificial Sequence

<220>
<223> Codon optimized sequence that encodes an MCM polypeptide with the I671V mutation

<400> 2
atgctccggg ccaagaatca actgttttta ctatcccccc actatttgag gcaggtgaaa 60

gagagttccg gcagcaggct gatacagcaa cggcttctgc accagcagca accactccac 120

ccagagtggg ctgcactagc aaagaagcag ctgaagggaa agaatcctga ggatctgatt 180

tggcataccc ctgaggggat tagcatcaag cccttataca gtaagagaga cacgatggac 240

ctccccgaag aacttcctgg cgttaaacct tttaccagag ggccttaccc tactatgtat 300

acttttcgac cctggactat cagacagtat gccggtttct ccactgtcga ggagagtaat 360

aaattctata aagacaacat caaagccggg caacagggcc tgtctgtcgc atttgacttg 420

gccacacata ggggctatga ttctgataac ccaagagtgc gcggggatgt gggtatggct 480

ggtgtggcta tcgacaccgt ggaagatact aaaattctct ttgacggaat cccactggaa 540

aaaatgagcg tcagtatgac aatgaacggc gccgtcattc ctgttctcgc taactttatt 600

gtcaccggag aagagcaagg cgtaccaaaa gagaagttga ccgggaccat ccagaacgac 660

attttgaaag aatttatggt gaggaataca tatatttttc ctcccgaacc ttcgatgaaa 720

ataatcgccg acattttcga gtatactgct aagcacatgc ctaaatttaa ttctatatca 780

atttccggat atcacatgca agaagctggg gcagatgcca tcttggaact cgcatatacc 840

ttggcggatg gcttggagta tagcaggaca ggcctccagg ctggactcac aatcgacgag 900

tttgccccac ggctgagttt tttttggggc attggcatga atttctacat ggaaatcgcg 960

aagatgaggg ctggccgccg gctgtgggcg catctgatag aaaaaatgtt ccagccaaag 1020

aattccaagt ctctgctgct gcgcgcacac tgtcagacgt ctgggtggag tcttacagag 1080

caagatccct acaacaacat cgttcgaact gccatcgagg ccatggcagc tgtgttcgga 1140

gggacacaga gcctgcacac aaacagcttc gatgaagctc tgggcctgcc aaccgtcaaa 1200

tccgcaagaa tagcacgaaa cacacaaatt ataatacagg aagaaagtgg aatcccaaag 1260

gtagcagatc cttggggcgg cagttacatg atggagtgtc tcacaaacga cgtctacgac 1320

gctgctctga aactcatcaa cgagatagaa gaaatggggg gaatggcgaa agctgtagct 1380

gaggggatcc cgaagctgcg catagaagaa tgcgccgcta ggcgacaggc tagaatcgat 1440

tccggttctg aagtgatcgt cggcgttaat aaatatcagc tagagaaaga ggatgcagtg 1500

gaggtcctgg ccattgataa taccagtgtg cgcaaccggc agattgagaa gctgaaaaag 1560

atcaaatcca gtagagatca agctttggcc gaaaggtgtc tggctgcctt gaccgaatgt 1620

gccgcaagcg gagatggaaa tattctggct ttagcggtgg acgcgagtcg ggcccgttgt 1680

accgtggggg agataaccga tgcgctgaag aaagtgtttg gagaacataa ggccaacgac 1740

cggatggtgt ctggcgccta ccgccaggaa tttggcgagt cgaaagaaat tacctctgct 1800

attaaacgcg tacacaaatt catggaacgg gaagggcgga gaccgcgcct tctggtcgcc 1860

aagatgggcc aagacgggca cgataggggt gcaaaggtga ttgctactgg cttcgctgat 1920

ttgggctttg atgtggacat cggaccgctg ttccagacgc cgcgagaggt cgcccaacag 1980

gccgtcgacg ctgacgttca cgctgtaggg gtgagcaccc tggccgccgg tcacaaaaca 2040

ctggtgcctg aactgattaa agagctgaat tcccttgggc gccctgacat tcttgtaatg 2100

tgcggcggtg tcataccccc acaggactac gaatttctgt tcgaggtggg tgtgtctaac 2160

gtgttcggcc cgggcacaag aattccgaag gccgccgtgc aggttctgga cgacattgag 2220

aaatgcctgg aaaagaagca acagagcgtt 2250

<210> 3
<211> 2250
<212> DNA
<213> Artificial Sequence

<220>
<223> Codon optimized sequence that encodes an MCM polypeptide with the I671V mutation

<400> 3
atgttacggg caaagaacca attgttcctt ctcagccccc actatctgcg acaggtgaaa 60

gagtcatccg gatcccggct gatccagcag cggctgcttc accagcagca gccactacat 120

ccggaatggg ctgcgctagc taaaaaacag ctaaaaggaa aaaatcccga ggatctaatt 180

tggcatactc ccgagggcat cagtatcaaa cctttgtact ccaagagaga caccatggat 240

ctaccagagg agttaccagg cgttaagcct ttcactaggg gaccatatcc cactatgtac 300

accttcagac cgtggaccat ccgacagtat gccggattta gcaccgtgga ggagagcaac 360

aagttttaca aggacaatat taaggcgggg cagcagggac tttctgtcgc cttcgatttg 420

gcgactcaca gggggtatga cagcgacaat cctagggtgc gcggcgatgt ggggatggcc 480

ggcgtggcca tcgataccgt tgaagacact aagatcctgt tcgacggtat tcctctcgag 540

aagatgagcg taagcatgac catgaatggc gccgtgattc ctgtcttggc caacttcatt 600

gttacaggag aggaacaagg ggtgcctaaa gaaaaactga ccgggactat ccagaatgat 660

atccttaagg agttcatggt gcgcaacact tatatcttcc cgccggagcc gtctatgaaa 720

attatagctg atatcttcga atacacggcc aagcacatgc ccaaatttaa cagcatctca 780

atatctggat atcacatgca agaggccgga gctgacgcga ttttagagtt agcttacaca 840

ttggcagacg ggttggagta tagcagaacc gggttgcagg caggcctcac catcgacgag 900

ttcgctccta ggctttcctt tttttgggga attggtatga atttctatat ggagatcgcc 960

aaaatgcgag ccggccgtag gctttgggca cacctcattg aaaagatgtt ccagccaaaa 1020

aactccaaat cgctcctctt gagggcacac tgccagacat ccgggtggtc tctgactgaa 1080

caggatccct acaataacat cgtccggact gcaatcgagg caatggccgc agtcttcgga 1140

gggacccaat ccctccacac aaactccttt gatgaagctc tgggcctccc gacagtgaag 1200

tccgcccgca tcgcgcggaa cacccaaatt ataattcagg aagagtccgg cattccaaag 1260

gtggccgacc cctggggcgg ctcttacatg atggagtgtc tgacaaatga cgtttacgat 1320

gcagctctga agcttatcaa tgagatagag gagatggggg gcatggcgaa ggccgtggcc 1380

gaaggaattc ccaagctccg catcgaggag tgtgctgcaa gaaggcaggc taggatcgac 1440

tccggctcag aagtgatcgt gggtgtgaac aaataccagc tggagaaaga agacgccgtg 1500

gaagtgctgg ctatcgataa cacgtcagtg cgcaatcgac aaatagaaaa gctgaagaag 1560

attaaatcca gcagggacca agcactcgct gagcggtgcc tcgcagcgtt gaccgagtgc 1620

gccgctagcg gcgacggcaa catccttgca ttagcagttg acgcctcacg agccaggtgt 1680

acagtggggg aaataaccga tgctctcaaa aaagttttcg gtgaacacaa ggctaatgac 1740

cgaatggtca gcggtgcata ccggcaggaa ttcggagagt caaaagagat caccagtgcc 1800

atcaagaggg tacataaatt catggaaagg gagggcaggc ggccccgcct gttggtagcc 1860

aagatgggac aggacgggca cgaccgagga gccaaggtga tagccacggg ttttgccgat 1920

ctgggttttg atgtggacat cggcccactg tttcagaccc cccgtgaggt tgcccagcaa 1980

gctgtggacg ccgatgtgca cgcggtggga gtttccaccc tagcagccgg tcataagaca 2040

cttgttccgg aactgatcaa agagctgaac tccctcggac gtccagacat tttggtcatg 2100

tgtgggggcg tgattcctcc acaggactat gaatttctgt tcgaggtcgg agtcagtaac 2160

gtgttcgggc caggcacccg aatcccaaag gctgcagttc aggtactgga cgatattgaa 2220

aaatgtctcg aaaaaaaaca gcagtctgtg 2250

<210> 4
<211> 2250
<212> DNA
<213> Artificial Sequence

<220>
<223> Codon optimized sequence that encodes an MCM polypeptide with the I671V mutation

<400> 4
atgctgaggg ccaaaaatca gctcttcctg ctttctcctc actacttgcg gcaggttaaa 60

gaatctagcg ggagtcgttt gattcagcag agacttctcc accagcagca gcctctccat 120

ccggagtggg cggcccttgc caagaagcag ttgaagggca agaatccgga ggacttgatc 180

tggcacacgc cggaggggat cagcatcaaa ccgctgtact ccaaaaggga cactatggat 240

ctgcctgagg agctgccagg agtgaagcct ttcacacgcg ggccttatcc taccatgtac 300

accttccgtc cgtggacaat ccgccagtac gcaggtttct ctactgtcga ggagagcaac 360

aaattttaca aggacaatat caaagcaggg caacagggcc tgtctgtagc tttcgacctg 420

gctacacatc gtgggtacga ttccgataac cccagggtgc gaggagatgt tggcatggct 480

ggcgtggcca tcgatactgt tgaagacaca aaaattctat ttgacgggat acctcttgag 540

aagatgagcg tgagcatgac gatgaatgga gccgtcatcc ccgtcctggc gaattttatc 600

gtgactggtg aagaacaagg agtaccaaaa gaaaaactaa ctggcacaat tcagaacgac 660

attctcaagg aattcatggt gcgaaatacc tacatcttcc ctccagaacc atccatgaaa 720

atcatcgctg atattttcga gtacaccgca aagcacatgc ctaaatttaa ctctattagc 780

attagtggat atcacatgca ggaagccggc gcagatgcga tccttgaatt agcctacaca 840

ctagctgatg gcctcgagta ctccagaaca ggcctacaag cgggactgac cattgatgaa 900

tttgctcccc gcctgagctt cttttggggc attgggatga atttctatat ggaaatcgcc 960

aagatgcggg ctggccgtag attatgggcc caccttatcg aaaagatgtt ccagcccaag 1020

aactcgaaaa gtttgctcct tcgagctcac tgtcagacct caggctggtc cctgaccgag 1080

caggacccgt acaataacat cgtcagaacc gccatcgagg ccatggccgc tgtctttgga 1140

ggcacccagt ccttgcacac caatagtttt gacgaggccc tgggtctgcc caccgtcaag 1200

agcgccagaa ttgcaagaaa cacacagatc atcatccagg aagaaagcgg tatcccgaag 1260

gtggcagacc cctggggtgg ctcttacatg atggaatgcc tcacgaatga cgtgtacgac 1320

gcagcgttaa aactcattaa tgagatcgaa gaaatggggg gcatggcaaa ggctgtcgca 1380

gaaggaatcc ctaagctgcg catagaggaa tgcgcggccc ggaggcaggc acgcatcgac 1440

tccggctccg aggtaattgt aggcgtgaat aagtaccagc tggagaaaga agatgctgtt 1500

gaagttctcg ctatagacaa taccagcgtt cggaacaggc agattgagaa gctaaagaaa 1560

atcaagtcat cccgtgacca ggccctggcc gaacggtgtc tcgctgcact caccgaatgt 1620

gccgcttcag gggatggcaa tatcttggcg ctggccgtag acgccagccg cgcaagatgt 1680

actgtcggtg agattacaga cgcactcaag aaggtcttcg gagagcacaa ggccaatgat 1740

cgcatggtca gcggagcata ccgtcaagag ttcggagaga gtaaggagat tacatcagct 1800

atcaagcggg tccacaagtt tatggaaagg gagggaaggc gcccacgact tcttgtcgcc 1860

aagatggggc aggacggcca cgacagaggc gccaaagtca tcgctacggg cttcgcagat 1920

ttgggatttg atgtcgatat tggacctctc tttcagacgc cgcgcgaggt ggctcagcaa 1980

gccgtggatg cagacgtgca cgccgttggg gtatccacgc tcgccgcagg gcacaagact 2040

ctcgtacccg agttgattaa ggagctgaat agtctcgggc ggccagacat cctcgtgatg 2100

tgtggcggcg taattcctcc ccaagattac gagtttctct ttgaggtggg agtttccaat 2160

gtatttggac cgggcacccg gattcctaag gcagccgtgc aagtcttgga cgacattgaa 2220

aagtgtctag agaaaaaaca gcaaagcgtg 2250

<210> 5
<211> 2250
<212> DNA
<213> Artificial Sequence

<220>
<223> Codon optimized sequence that encodes an MCM polypeptide with the I671V mutation

<400> 5
atgcttagag cgaaaaacca gctgttcctg cttagcccac actacctacg gcaggtcaag 60

gaaagttctg gttcacgtct catacagcag agactcttac accagcagca gccactgcac 120

ccagagtggg cagccttggc gaagaagcag ctgaaaggaa agaatcctga agatcttatc 180

tggcacaccc cagaaggcat ctcaatcaag cctctgtact caaagagaga tactatggat 240

ttgcccgaag agctgcccgg cgtcaagcct tttactcgag gcccttatcc gaccatgtac 300

acctttcgtc cgtggaccat ccgtcagtac gctggattct ctacagtcga agaaagcaat 360

aagttctata aggacaacat caaagccggc cagcagggtc tgtccgtggc gtttgacctg 420

gccactcatc ggggctacga tagtgataac ccccgggtca gaggggatgt cggaatggct 480

ggcgtagcca ttgacaccgt ggaggacacc aaaattctat ttgatggcat ccccttggaa 540

aagatgagtg tttccatgac catgaatgga gccgtcatcc ccgtgctggc aaattttatt 600

gtaacagggg aagagcaggg agtgcctaag gagaagttaa cgggtaccat tcaaaacgat 660

atattgaaag agtttatggt tcgaaatacc tatatcttcc cccctgagcc atctatgaaa 720

atcatagcag acatatttga gtacactgcg aaacacatgc ccaaattcaa cagcatctct 780

atcagcggct accacatgca agaggccgga gctgatgcta tcttggaact ggcgtacacc 840

ctggcggacg gtctggagta ctcccgtacc ggactccagg ccggcctgac catcgacgaa 900

tttgccccta ggttatcatt tttttgggga attggcatga acttttatat ggagatcgca 960

aaaatgcggg ccggaagaag gctttgggcc cacctcattg aaaaaatgtt ccaaccgaag 1020

aacagtaaat ctcttctcct gcgggctcac tgccagactt ctgggtggtc ccttactgag 1080

caagatccct acaataacat cgttagaaca gcaatcgaag caatggccgc agtttttggc 1140

ggaacgcagt ccctgcatac caatagcttc gatgaggcgc tcggattacc aactgtgaaa 1200

tccgcaagaa tcgctcgcaa tacccagatc atcattcagg aggagagtgg gattcctaag 1260

gtggcagatc catggggcgg ctcgtacatg atggaatgcc ttaccaacga cgtgtacgat 1320

gctgctctga agctcattaa tgagatcgaa gaaatggggg gaatggccaa agcggtggca 1380

gagggcattc caaagctccg catcgaggaa tgtgctgcaa ggaggcaggc caggatcgat 1440

tccggaagcg aggtcattgt tggggtgaat aagtatcagc tggaaaagga ggatgctgtg 1500

gaagtgctgg caattgataa cactagcgtg aggaaccgtc agatcgagaa gctgaaaaag 1560

ataaagagct cgcgagacca agccttagca gagcggtgcc ttgcggcact aacagaatgt 1620

gctgccagtg gggatggaaa cattcttgca ctggctgtcg acgccagtcg agcaaggtgt 1680

acagtgggag agatcacaga cgctttgaaa aaagtgttcg gagagcacaa ggcgaacgac 1740

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attaagaggg tccacaagtt tatggaacgt gagggcaggc ggcccagatt actcgtggcc 1860

aagatgggtc aagacggcca cgataggggt gcaaaagtga ttgcaaccgg cttcgcagac 1920

cttggatttg atgtggacat tgggccactt tttcagaccc ctagagaagt ggcacagcag 1980

gcagttgatg ccgatgtaca tgccgtggga gttagtaccc tcgcggctgg ccacaagaca 2040

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tgtggcggcg ttatacctcc acaggattac gagttccttt tcgaggttgg tgtttcaaac 2160

gtctttggtc ctggcacgcg tatacctaaa gcagcagtgc aagttttgga tgacattgag 2220

aaatgtctgg aaaagaaaca acagtcagtg 2250

<210> 6
<211> 2250
<212> DNA
<213> Artificial Sequence

<220>
<223> Codon optimized sequence that encodes an MCM polypeptide with the I671V mutation

<400> 6
atgctgcgcg ctaagaatca gctgttcctg ctctctcctc attatctccg ccaggttaaa 60

gaaagctccg ggtctagact cattcagcag aggttgctgc accaacagca gcctctgcac 120

ccagaatggg ctgcactggc caagaagcag cttaaaggga aaaacccgga agacctgatt 180

tggcataccc ccgaggggat tagcattaaa ccattgtatt ccaaacgaga tacgatggat 240

ctgcccgagg agctgcccgg cgtgaagcct tttacaaggg gtccttatcc cactatgtat 300

acatttagac cctggaccat tcgccagtac gccggattta gtacagtcga ggagagcaac 360

aaattttaca aggacaacat aaaagctggg caacagggcc tgagtgtcgc attcgacctc 420

gccactcacc gaggatacga ctccgataat ccgcgggttc gcggtgatgt gggcatggca 480

ggagtcgcaa ttgatacggt ggaggacacc aaaatcctgt tcgacggtat ccccctggag 540

aaaatgagcg tcagtatgac aatgaatgga gccgtgattc cagtcttggc caatttcatt 600

gtaacaggag aggaacaggg cgtccctaag gagaaactaa cagggaccat tcagaacgac 660

atacttaagg agtttatggt gcggaacacc tatatctttc ccccggagcc ttcaatgaag 720

attatcgcgg atatttttga atacacagca aagcatatgc caaaattcaa tagcataagc 780

atcagcggtt atcacatgca ggaagctggg gccgacgcca tcctggagct tgcttatact 840

ctggcggatg gcctcgagta ctcgcgcact ggattgcagg ccggcttgac aattgacgag 900

ttcgccccca gacttagttt cttttgggga atcggtatga acttttatat ggaaattgcc 960

aagatgcgcg ccggcaggcg cctgtgggcg cacctgattg aaaagatgtt tcaacccaag 1020

aacagtaagt cactgctctt gcgggcccat tgccagacta gcggatggag cctgaccgag 1080

caggatccgt acaacaacat tgttcggact gccatcgagg ccatggcggc cgtgtttggg 1140

gggacacaga gcctccatac aaattccttc gacgaggctc tcggactgcc gacagtgaaa 1200

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gagggtattc ccaaacttcg catcgaagag tgtgccgcga ggcgccaggc tcgaattgac 1440

tccggaagtg aggtgatcgt tggagtcaat aagtaccagc ttgagaagga agacgctgtt 1500

gaggtcttag ccattgacaa tacctcagtt agaaatcgcc agattgaaaa actgaaaaaa 1560

atcaagtcct cgcgcgacca ggctctcgct gagcgatgcc tcgcggcact gacagagtgt 1620

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attaaaagag tgcataaatt catggaaagg gaagggagga ggccccgcct acttgtggct 1860

aaaatggggc aggacggcca cgacagaggc gctaaagtaa tcgccacagg cttcgcagac 1920

ttgggctttg acgtcgacat cggccctctc ttccaaaccc ccagggaggt ggcccagcag 1980

gccgttgatg ctgacgtgca tgcagtcgga gtatcaacat tagccgccgg ccacaagaca 2040

ctcgtcccag aattaattaa agaactgaat agtctcgggc ggccagacat tttggtcatg 2100

tgcggagggg tgattccgcc tcaggattat gagtttctat tcgaagtcgg agtgagtaat 2160

gtcttcggcc caggtaccag gatacccaag gctgcggtgc aggtcctcga tgacattgag 2220

aagtgcctgg agaagaaaca gcagagcgtc 2250

<210> 7
<211> 2250
<212> DNA
<213> Artificial Sequence

<220>
<223> Codon optimized sequence that encodes an MCM polypeptide with the I671V mutation

<400> 7
atgctacgcg ccaagaatca gctctttctg ctgtctccgc actacttgcg acaggttaaa 60

gagtcttcgg gctcccggct gattcagcag cgcctgctac accagcaaca acctctgcac 120

ccagaatggg ctgctttggc aaaaaagcaa ttgaaaggta aaaaccccga ggacctcatt 180

tggcataccc ccgagggaat tagtataaag ccattgtaca gtaagagaga tacaatggat 240

ttaccagagg aactccccgg ggtgaaacca ttcacaaggg gtccataccc aaccatgtac 300

accttcagac catggactat ccggcagtac gctgggttct caacagtgga agagtcaaac 360

aagtttata aggacaatat caaagctggc cagcagggtt tgtcagtggc ttttgatcta 420

gccacgcacc gtggctatga tagcgacaac ccaagggtgc gaggggatgt cggcatggcc 480

ggcgtcgcca tagatacagt ggaagacacc aaaatcctgt ttgacggaat acctttggag 540

aaaatgagcg tcagcatgac catgaatggg gctgtcattc ctgtgttggc caactttatc 600

gtcaccggtg aggagcaggg cgttccaaaa gagaagctta ccggaactat tcagaacgat 660

atcctgaaag agtttatggt gcgtaacacc tacatttttc cccccgagcc atctatgaag 720

atcatcgcgg acatattcga atatacggca aagcatatgc ctaagtttaa cagcatctcg 780

atcagcggct atcatatgca ggaagcaggg gccgatgcca tcctcgagct cgcttatacc 840

ctggccgacg gtctggaata ttcccgtaca ggcctacaag ccggtttgac catcgatgag 900

ttcgcaccca gattatcttt tttttggggg attggaatga atttttacat ggaaatagca 960

aagatgcggg ctggacgtag gctgtgggct caccttattg agaaaatgtt tcagccgaag 1020

aactcaaaat cgctcttgct gagagctcat tgccagactt ccgggtggtc tctgactgaa 1080

caggaccctt ataacaatat cgtccgtact gctattgagg caatggccgc agtgtttggc 1140

ggtacccagt cattgcatac aaactcattc gacgaagctc tgggactccc aacggtaaaa 1200

tcagcacgca ttgctaggaa cacacagatc atcattcagg aagaatccgg aattccaaag 1260

gtggccgatc cttggggagg ctcttatatg atggagtgcc tgacgaacga tgtgtatgat 1320

gccgccctca agcttattaa cgaaatcgag gaaatggggg gcatggccaa agctgtagcg 1380

gagggtatac ctaagttgcg cattgaagaa tgcgccgctc gtagacaggc cagaattgat 1440

tctggctcgg aagtgattgt gggcgtaaac aaataccagc tcgagaagga ggacgccgtt 1500

gaggttttgg caatcgacaa tactagcgtg cgcaaccgcc agatagaaaa gctgaaaaag 1560

atcaagtcta gcagagacca agctcttgcc gagcgctgtc tggctgcact cactgagtgt 1620

gccgcaagtg gggacggaaa cattctggcc ctagctgtag acgcttcccg cgcgaggtgt 1680

acggtcggcg aaatcacaga tgccctgaaa aaagtgttcg gggaacataa ggcaaatgat 1740

aggatggtgt cgggggccta ccgtcaagaa tttggagaat ccaaggagat taccagcgcc 1800

ataaaaaggg tgcataagtt catggagaga gaggggagac gccctaggct gctcgttgct 1860

aaaatgggac aggacggcca cgatcgaggc gccaaggtga ttgccaccgg tttcgctgac 1920

ttaggattcg atgtggacat tggtccgttg ttccagacgc cacgcgaggt ggcacagcaa 1980

gccgtggacg ccgatgtgca tgccgtgggc gtgtcgactt tggcagcagg gcacaagacc 2040

ctggttcccg agcttatcaa ggagctaaat agccttggcc ggcccgacat cctggtcatg 2100

tgcgggggag ttattccccc ccaggactac gagtttctat tcgaggtggg agtaagtaat 2160

gtgtttggac cgggtacgag gatccccaag gccgccgtcc aggttcttga cgacatagaa 2220

aaatgtttgg aaaaaaagca gcagagcgtg 2250

<210> 8
<211> 2250
<212> DNA
<213> Artificial Sequence

<220>
<223> Codon optimized sequence that encodes an MCM polypeptide with the I671V mutation

<400> 8
atgctgcggg caaaaaatca gctgtttttg ctttccccac actatctccg acaggtcaaa 60

gagagcagcg gaagtaggct catccagcag aggctgctac accaacagca gcctttgcac 120

cctgaatggg ctgccctggc gaaaaagcaa ctgaagggca aaaaccccga ggacctgatc 180

tggcatactc ccgaaggcat atcgataaag cccctgtatt caaagcgaga caccatggat 240

ctccccgaag aacttcctgg cgtgaaacct ttcacccggg gcccctaccc tactatgtat 300

acattccgcc catggaccat ccggcagtat gcaggcttta gcactgtgga ggagtctaat 360

aagttttaca aagacaacat aaaggcggga cagcaaggac tctctgtcgc attcgacctg 420

gccacccatc gcgggtacga tagcgataat ccaagagtga gaggggacgt cggaatggcc 480

ggtgtggcaa tcgataccgt agaggatacc aaaatccttt tcgacgggat acctctcgaa 540

aaaatgtcag tgtccatgac gatgaatggc gctgtgatac cagtgctggc caacttcata 600

gtgaccggcg aggaacaggg tgtccccaag gagaagctga ctgggaccat ccagaatgac 660

attctcaagg agttcatggt aagaaatacc tacatattcc ctcctgaacc tagtatgaaa 720

ataattgccg atattttcga gtatactgct aagcatatgc cgaagtttaa ttctattagc 780

atttctggct accatatgca ggaggctgga gccgacgcta tcttagaact tgcatacacc 840

ctggccgacg gactcgaata tagtaggaca gggttgcagg ctggcttaac tattgacgag 900

ttcgcaccta gattgtcatt tttttggggt ataggcatga atttctatat ggaaattgcc 960

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ggcacacaga gcctacacac taacagtttt gatgaggcac ttggtctccc cacggtgaaa 1200

tcagcccgaa tcgcccgtaa tacccagatc atcatccaag aggaatccgg aatcccaaag 1260

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gctgcactca agttaattaa cgagatcgag gagatgggag gtatggctaa agccgtagct 1380

gaggggattc caaaattgag gattgaagag tgtgccgccc gacggcaggc aaggattgat 1440

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gaagtacttg ccattgataa caccagtgtg aggaaccggc aaattgaaaa attgaaaaag 1560

atcaagtctt cacgagacca agccctggcg gagcgatgcc tggctgccct gacggaatgt 1620

gccgcatctg gagacggcaa tatactggcg cttgccgtgg atgcatcacg ggccaggtgt 1680

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cggatggtgt ctggcgcgta taggcaggaa ttcggcgagt ccaaggagat aacttccgct 1800

ataaagaggg tccataaatt tatggagaga gaggggagac gcccaaggtt acttgtggca 1860

aagatgggac aggatggaca tgatagaggg gcaaaggtta tcgccacggg gtttgctgac 1920

ctggggttcg atgtggatat cggccccctc ttccagaccc caagagaggt ggcccagcag 1980

gccgtcgacg ccgacgtaca cgccgttggc gtgtccacgc tggcggccgg ccacaagaca 2040

ctagtgcctg agcttatcaa agaattaaac agtctcggga gacctgacat tcttgtgatg 2100

tgcggagggg ttattccacc gcaggattac gaattcctgt tcgaagttgg cgttagcaat 2160

gtcttcgggc ccggcaccag aattcctaaa gctgccgtgc aggtccttga tgacatcgaa 2220

aaatgtctgg agaagaaaca gcaaagcgtg 2250

<210> 9
<211> 2250
<212> DNA
<213> Artificial Sequence

<220>
<223> Codon optimized sequence that encodes an MCM polypeptide with the

I671V mutation

<400> 9

atgcttagag ccaagaatca gttgttcctc ctgagccctc actatctccg ccaggttaaa 60

gagagcagtg gctcacggct gatccaacag cgcctgctgc accagcagca acccctccac 120

cccgaatggg cagccctcgc taaaaaacag cttaaaggga agaatcctga agacctgatc 180

tggcacaccc ctgaaggcat tagtataaaa ccactgtatt ccaagcgcga cactatggac 240

ctgccagagg agctgccagg agtgaaacct tttacaagag ggccgtaccc caccatgtat 300

acttttcggc cctggaccat ccgccagtac gctggattca gtacagtcga agagtctaat 360

aagttctata aagacaacat aaaggctggc cagcaaggac tctctgtagc attcgacctt 420

gcgactcacc gaggctatga tagcgataat cctcgcgtga ggggagatgt tgggatggcc 480

ggagtggcaa tagataccgt cgaagacacc aaaatactct tcgatgggat ccctcttgaa 540

aaaatgtccg tgagcatgac catgaatggt gccgttatcc cggttctcgc gaactttatt 600

gtgaccggtg aagagcaggg agtgcctaag gagaaactga ctggcactat ccagaacgac 660

attctcaaag agttcatggt ccgcaacact tacatcttcc cacccgagcc ttccatgaaa 720

ataatcgctg acatattcga gtacactgct aaacatatgc ccaagtttaa ctcgatcagc 780

attagcggct accatatgca ggaggctggc gccgacgcca tcctcgagct cgcctatact 840

ttggccgacg gcctggaata ctcgaggaca gggcttcagg ccggcttaac aatcgatgaa 900

tttgccccgc gcttgagctt cttttgggga attgggatga atttctacat ggaaatcgca 960

aaaatgcgtg ccggtagacg gctatgggct cacctcattg agaagatgtt tcagcctaag 1020

aacagcaaga gcctgctgct gagagcccac tgtcaaacgt cgggctggtc gcttacagag 1080

caggatccct acaacaacat tgtgcgaacc gccattgagg caatggccgc cgtattcgga 1140

ggcacgcaat ccctgcatac caactctttt gacgaggcgc tgggtctgcc cactgtgaaa 1200

tcggccagga ttgctcgcaa cacacaaatc atcatccaag aagagtccgg gattcccaag 1260

gttgccgatc catgggggg cagctacatg atggagtgcc ttactaacga tgtttatgat 1320

gctgcactta aactgatcaa cgaaatagaa gagatggggg ggatggcaaa ggccgtcgcc 1380

gaagggatac ccaagctgag gatcgaggaa tgcgcggctc gacggcaggc ccggatcgac 1440

tccggaagcg aggtcatcgt cggcgtaaat aaataccaac tggaaaagga ggacgcggtt 1500

gaggtgttgg ccatagacaa cacctcagta cgaaaccgac agatcgagaa attaaaaaag 1560

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atcaagcggg ttcacaagtt catggagcga gaaggcaggc ggccacggtt gttagtggct 1860

aaaatggggc aggatggtca cgacagaggg gctaaggtga ttgccaccgg attcgccgac 1920

ctagggttcg acgtggatat tgggcctttg ttccagacac cacgggaggt ggctcaacaa 1980

gccgtggacg cggatgtgca cgccgtgggg gtgtccaccc ttgccgcagg ccacaaaacc 2040

ctggtgccag aactgattaa ggagctcaat tcattgggca gacctgacat tctggtgatg 2100

tgcgggggcg taattcctcc ccaggactac gagtttctgt tcgaagtggg cgtgagtaac 2160

gtgttcggac ccggtaccag aatccccaag gccgccgtcc aggtgctgga cgacatcgag 2220

aaatgtctgg aaaagaagca acagtctgta 2250

<210> 10
<211> 2250
<212> DNA
<213> Artificial Sequence

<220>
<223> Codon optimized sequence that encodes an MCM polypeptide with the I671V mutation

<400> 10
atgctgcggg ctaagaatca actgttcttg ttgagccccc actatctgag gcaagtgaaa 60

gagagtagtg gaagccggct catccaacaa agacttctgc accagcaaca acctctgcat 120

ccggagtggg cggcgctggc aaagaaacaa ttgaagggta aaaatccaga ggacctgatt 180

tggcacaccc cagaggggat ttcgatcaaa cctctgtaca gcaagaggga cactatggac 240

ttgcctgagg agctgccagg agtcaagcca ttcacaaggg gaccatatcc tacaatgtac 300

acttttaggc cctggacaat tagacaatac gccggttttt caactgtcga ggaaagcaat 360

aaattctaca aggacaacat caaagctggg cagcaaggtc tttcagtggc tttcgacctg 420

gcgactcaca ggggttacga ctctgataac cctcgagtgc gaggggatgt cggaatggcc 480

ggggtggcca tagatacagt ggaggacacc aagattctat tcgacgggat accgctcgag 540

aagatgtcag tttctatgac aatgaacggt gcggtcattc cggtcttggc aaactttatt 600

gttacaggtg aggaacaggg ggttccaaag gaaaaactga ccggaactat acaaaatgac 660

atcttgaagg aattcatggt gcgcaacacc tacattttcc cgccagaacc aagcatgaaa 720

attatcgccg acatattcga gtatactgct aaacacatgc ctaaattcaa cagcattagc 780

atcagcggct atcacatgca agaggccggt gcggacgcca ttcttgaact ggcatacacc 840

ctcgccgatg ggctggagta ctcccgaact gggctccagg ccggactaac aatcgacgag 900

ttcgccccgc gtctctcttt cttctgggga atcggaatga acttctacat ggagattgca 960

aaaatgagag cggggcgcag actatgggca caccttatag aaaaaatgtt ccagcccaaa 1020

aattctaaaa gcctgctact gagagctcat tgtcaaactt ctggctggag tttgaccgaa 1080

caagatccat ataataatat tgtccggaca gcgattgagg ctatggccgc cgtctttggc 1140

ggtactcaga gccttcacac aaattctttt gatgaagcac tggggctgcc gacagttaag 1200

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gaggggattc ctaagctgag aatcgaggag tgcgcagctc ggagacaggc tcgcatcgac 1440

tctgggtccg aagtcatagt tggggtgaac aagtatcagc ttgaaaagga ggatgccgtg 1500

gaggtgctgg ccatagataa tacgtcggtg agaaatagac agattgagaa attaaaaaaa 1560

attaagagta gcagggatca agccctcgct gagcggtgcc tcgcagctct caccgaatgt 1620

gccgcaagcg gcgacggtaa catcctcgct ttagcagtcg acgccagcag ggcccgctgt 1680

actgtgggag agatcaccga tgccctgaaa aaggtcttcg gggaacataa agccaatgat 1740

cgcatggtaa gcggggctta tagacaagaa ttcggtgaga gcaaggagat cacgtccgca 1800

atcaaaaggg tccataaatt catggagaga gagggtagac gcccaagact cctcgtggca 1860

aaaatggggc aggatggaca tgaccggggt gccaaagtga tcgccaccgg attcgcagat 1920

ctgggcttcg atgtcgacat tggcccgctc tttcagacac ctcgtgaagt ggcgcagcag 1980

gccgtcgacg ctgatgtgca cgctgttggg gtgagcactc tcgcagccgg tcacaaaacc 2040

ctggtgccgg aactaatcaa agaactcaac tctctcgggc gtccagacat cctcgtgatg 2100

tgtggcggtg tcatcccacc ccaggattac gagtttttat ttgaagtggg tgtctctaat 2160

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aagtgccttg agaagaagca acagagcgtc 2250

<210> 11
<211> 2250
<212> DNA
<213> Artificial Sequence

<220>
<223> Codon optimized sequence that encodes an MCM polypeptide with the I671V mutation

<400> 11
atgttaaggg caaagaacca gcttttcctc ctgagccctc attacctacg gcaggtgaag 60

gagagctccg gaagccgcct cattcagcaa cgcctcctgc atcagcagca gccccttcac 120

cccgaatggg cggccctggc taagaagcaa ttgaagggta agaacccaga ggacctgatt 180

tggcatactc ccgagggcat ttctatcaaa cccctgtaca gcaagcgcga caccatggac 240

ctaccagaag agttgccagg cgtcaaaccc tttactcggg gcccttatcc taccatgtac 300

accttccgtc cctggacaat ccggcagtat gctggattta gtacagtcga ggagagcaat 360

aaattttata aggacaatat aaaagcaggt cagcagggct tgtccgttgc ctttgaccta 420

gcgacacata ggggatatga ttccgacaat ccccgggtga ggggtgatgt cggcatggct 480

ggagttgcta ttgacaccgt ggaagacact aagatcctat tcgatggaat ccccctggag 540

aaaatgtccg tgagcatgac catgaacggc gctgtgattc ccgtcttagc aaactttatt 600

gtgacaggcg aggagcaggg cgtgccaaaa gagaaattga ctggtaccat tcagaacgac 660

atactgaagg agttcatggt gcggaataca tatatatttc ccccagaacc gtctatgaaa 720

atcattgcgg acatcttcga gtacaccgcg aagcacatgc ccaaatttaa tagcatcagt 780

atcagcgggt atcacatgca ggaggccggc gcagacgcga tccttgaact cgcgtatacc 840

ttggctgatg gactcgaata ttcaaggacc gggttgcaag cagggctgac catcgacgag 900

tttgcacctc gactgagctt tttctggggg atcgggatga acttttatat ggagatcgcc 960

aagatgcgtg cggggcgacg cttatgggcg catcttattg aaaaaatgtt tcaacctaaa 1020

aacagcaagt cgctgctcct ccgggcgcac tgccagacta gcgggtggag cctgaccgaa 1080

caagatccct acaataacat agttaggacc gcaatagaag ccatggcagc ggtgtttggc 1140

gggacgcaga gtctccacac caacagcttc gatgaggccc tgggacttcc cacagtgaag 1200

tctgccagga tcgcccgcaa cacccagatt atcatacaag aagagtctgg aatcccaaag 1260

gtggccgatc cctggggagg gtcttatatg atggagtgtc tgactaacga cgtgtacgac 1320

gcggccctga aactaatcaa tgagatcgag gagatggggg gcatggctaa agcagtggcc 1380

gaagggatac cgaagctaag aattgaggaa tgtgctgcaa ggagacaggc gcgaatcgat 1440

tccggctccg aggtgatcgt gggtgtcaat aagtatcagc tggagaagga ggatgctgtc 1500

gaggtcctgg cgatcgataa cacatcagtc aggaatagac agattgagaa acttaaaaag 1560

attaagagct cccgggatca ggctcttgcc gagcgctgcc ttgctgctct tacagaatgt 1620

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cgaatggtta gcggtgctta tagacaggaa ttcggcgagt ccaaggaaat aacatccgct 1800

atcaagagag ttcataaatt catggagcga gaggggcgta gaccccgcct cctggtcgct 1860

aagatggggc aggacggtca cgacagaggg gcaaaggtca ttgccacagg atttgcagac 1920

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gcagtggacg ccgatgttca tgccgtagga gtgagtaccc tggcagccgg ccacaagacc 2040

ctagtgccag aactgattaa agaactcaac agtttaggaa ggccagatat cctggtgatg 2100

tgcggcggcg taatccctcc acaagactat gaattccttt tcgaagttgg cgtttccaat 2160

gtatttggcc ctggcacaag aatacccaag gccgcagtgc aggtgctcga cgacatcgaa 2220

aaatgcctgg agaagaagca gcaatcagtt 2250

<210> 12
<211> 2250
<212> DNA
<213> Artificial Sequence

<220>
<223> Codon optimized sequence that encodes an MCM polypeptide with the I671V mutation

<400> 12
atgctgcgcg caaaaaacca gttatttctg ctttctcccc attacctgag acaggtgaaa 60

gaatcaagcg gctctcgact gatccagcaa cggctcttac atcagcagca gccgttgcat 120

cctgagtggg cagcactggc caaaaagcag ctgaagggca aaaatcccga ggacctaatc 180

tggcataccc ccgagggaat cagtattaag cctctttatt ctaaacggga caccatggac 240

ctcccagaag aactgcctgg agtaaaacct ttcacccgag gcccttatcc tacaatgtac 300

acgtttagac catggaccat cagacagtac gctgggttct caacagtgga ggaatccaat 360

aagttctata aagacaacat caaagcaggc caacagggac tgagcgttgc ctttgatctg 420

gcaacccacc gcggttacga tagcgacaac cccagggtaa gaggcgacgt cggaatggca 480

ggggtagcga tagacactgt tgaggacacc aaaattctgt tcgatggtat ccctctggaa 540

aagatgagcg tgtccatgac tatgaatgga gcagtgatcc ctgtgctggc aaactttatc 600

gttaccggcg aggagcaggg cgtgccaaag gaaaaactga cggggactat tcaaaacgat 660

atcttaaagg agtttatggt gcgcaacacg tatatatttc caccagaacc tagcatgaaa 720

atcatcgctg atatattcga gtacacagca aaacatatgc ccaaatttaa ctccattagc 780

atatccggat accacatgca ggaagccgga gcggacgcaa tcctcgagct agcgtatact 840

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ggaacacaaa gtctccatac taactcattc gatgaggctc tgggactgcc aactgtaaaa 1200

tctgccagaa ttgctagaaa cacccagatt attattcagg aggagtccgg tatacctaag 1260

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gaagtgctcg caatcgataa tacgtcggtg cgcaataggc agattgagaa gctcaaaaag 1560

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attaagcggg tccataaatt tatggagaga gaggggcgta gaccgcggtt actggttgct 1860

aagatggggc aagacggcca cgatagaggc gccaaagtga tcgccaccgg gttcgcagac 1920

ctcggatttg acgttgacat tggtccactt tttcagaccc cacgcgaggt ggcacagcag 1980

gcagtcgacg ccgacgtaca cgcagtgggc gtatcaactc tggctgctgg gcacaaaacc 2040

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tgtgggggggg tcattcctcc ccaggactac gagttcctct tcgaggtcgg ggtatcaaat 2160

gtgtttggac ccggaacacg aatacccaag gcagccgttc aggtgctgga tgatattgag 2220

aagtgcttag aaaagaaaca gcagtcagtg 2250

<210> 13
<211> 2250
<212> DNA
<213> Artificial Sequence

<220>
<223> Codon optimized sequence that encodes an MCM polypeptide with the I671V mutation

<400> 13
atgctcaggg caaagaacca gttatttctg ttgtcacccc attacctcag gcaggtgaag 60

gaatctagcg ggagccgcct gatacagcag cgtcttttgc accagcaaca gcctttacat 120

ccagagtggg cagctctggc gaagaaacaa cttaagggga agaatcccga ggacttgatt 180

tggcacactc ccgaaggtat tagcattaaa ccgctatact ccaaaagaga tacaatggac 240

ctgcccgaag agcttcccgg agtgaagcca tttacacgcg gcccatatcc aaccatgtat 300

acctttcgac cttggaccat aagacaatat gccgggtttt ctaccgtgga ggaatcaaac 360

aaattctata aggataacat caaggccggg cagcagggcc tcagcgttgc ctttgacctg 420

gccactcaca gaggctatga ttccgacaat ccccgagtga gaggggatgt tgggatggcc 480

ggagtcgcca tagatacagt tgaagatacg aagattctct tcgatggaat ccccctcgag 540

aaaatgagtg taagcatgac catgaacggg gcagtgatac ccgtgctcgc caattttatc 600

gtgactggcg aagaacaagg ggtgcccaaa gaaaagctca caggcaccat tcagaacgac 660

atactgaagg agttcatggt gcgtaacact tacattttcc cccccgaacc ttcaatgaag 720

attatagccg atatattcga atacacagcc aaacacatgc ccaagttcaa cagcattagt 780

attagtgggt accatatgca agaagccggt gccgatgcta tactggagct tgcgtacaca 840

ctcgcagacg ggctagagta tagccgtacc ggcctccagg ccggtctaac tattgacgag 900

ttcgcacccc gtcttagttt tttctgggga attggtatga atttctatat ggagatcgca 960

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caagacccct ataataacat tgttcgcact gctattgagg ctatggcggc ggtgttcggc 1140

gggactcaga gcctgcacac aaacagcttt gatgaagctc ttggacttcc aaccgtcaag 1200

tccgccagaa tagcccgaaa cactcagatt atcatccagg aggagtcagg aattcctaag 1260

gtcgctgatc catggggcgg gtcttacatg atggagtgcc tcaccaatga cgtctacgat 1320

gccgccctca aactgataaa cgaaatagag gagatgggag ggatggccaa ggcagtagcg 1380

gaaggtatcc caaagctccg gatcgaggag tgtgcggcgc gccggcaagc tcggatcgat 1440

tccggaagcg aggtgatcgt cggggtgaac aagtatcagc tagaaaagga agatgctgtg 1500

gaggttctcg caatagataa cacatcagta cgaaacagac agatcgagaa actgaagaag 1560

atcaaatcat caagagatca ggccttggct gagagatgct tggctgcatt gacagagtgc 1620

gccgcaagcg gggatggcaa tatccttgca ttggctgtcg acgcttcccg tgccaggtgc 1680

acagtaggtg aaattaccga cgctttgaaa aaggtgttcg gagagcacaa ggccaatgat 1740

cgcatggttt ccggcgccta ccgacaggag ttcggcgaat caaaagagat cacatccgca 1800

atcaagaggg tgcacaaatt tatggaacgc gaggggagac ggccgcgcct ccttgttgcg 1860

aagatgggac aggatggaca cgacagggga gctaaggtca tagccacggg gttcgcagac 1920

ctaggtttcg acgtggatat cggaccgcta ttccagacac ctcgggaagt agctcaacag 1980

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ctggtgcctg agttgatcaa ggagctcaac tccctggggc gtccagacat attagtgatg 2100

tgcgggggag tcattccacc acaggattat gagtttttat ttgaggtggg cgtatctaat 2160

gtgtttggcc ccggtacacg catcccaaag gcagccgtgc aggttctgga cgacatcgag 2220

aagtgtctcg agaagaagca gcagtctgtg 2250

<210> 14
<211> 2250
<212> DNA
<213> Artificial Sequence

<220>
<223> Codon optimized sequence that encodes an MCM polypeptide with the I671V mutation

<400> 14
atgctgagag cgaaaaacca gctattcctg ttatcaccac actacctgag acaggtaaag 60

gagtcgtcag ggagccggct tattcaacaa cgactgctcc atcaacagca gccactacac 120

ccagaatggg ccgcactggc taaaaaacaa ctgaagggca agaaccctga ggatctgatc 180

tggcacacgc ctgaaggaat ctcaatcaaa cctctgtaca gcaagcgcga cacaatggat 240

ctgccagagg agctgcctgg agttaaaccc ttcaccaggg gcccttaccc aactatgtac 300

acttttagac cttggacgat taggcagtat gctggattct caacagttga ggagtcaaat 360

aaattttaca aggacaacat caaggccgga cagcagggac tctctgtcgc ctttgaccta 420

gccacacata gagggtacga ctcagataat ccccgggtcc gtggcgacgt tggaatggca 480

ggagtggcta ttgataccgt ggaggatacc aagatactct ttgacggcat tcccctggag 540

aagatgagcg tgtctatgac aatgaacggg gcagtgatac ccgtgctagc gaatttcatt 600

gtgacgggcg aggagcaggg cgtgcctaag gaaaaattga ccggtactat tcagaacgac 660

attctgaaag agttcatggt gcgcaacaca tatatctttc ctccagaacc atccatgaaa 720

ataatcgccg acatattcga atacactgcc aagcacatgc ccaaatttaa ctctatatct 780

atttctggtt accatatgca agaagctgga gcagacgcta tccttgaatt ggcctacacc 840

ctggccgatg ggcttgagta ctcccgaact ggattgcagg cgggacttac aatcgacgaa 900

ttcgcccccc ggctcagttt tttctggggt ataggaatga atttctatat ggagatcgcg 960

aaaatgcggg ctgggcggag actctgggcc cacttgatcg agaagatgtt tcagcccaag 1020

aacagcaaat ccctgctcct gagggcccac tgccagacaa gcggctggag cctcacagag 1080

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gccgctctga agctgattaa tgagatagaa gagatgggcg ggatggcaaa ggcagtcgca 1380

gaaggaattc caaaactgcg cattgaggaa tgtgcagccc gcagacaagc ccgaatagac 1440

agcggaagtg aagtcattgt aggagtgaat aaataccaac tggagaaaga ggacgctgtt 1500

gaggtgcttg ctattgataa cacaagcgtc cgcaatcgac agatcgagaa gcttaaaaaa 1560

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aagatgggac aggacggcca cgataggggg gctaaagtga tcgccacagg atttgccgac 1920

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tgtggtggtg taattcctcc ccaggattac gagtttttgt tcgaggtggg ggtctcaaat 2160

gttttcggcc ctggcacacg tatccccaag gccgcagtgc aggtcctcga tgatatagag 2220

aagtgcctgg aaaagaagca gcaaagcgtc 2250

<210> 15
<211> 2250
<212> DNA
<213> Artificial Sequence

<220>
<223> Codon optimized sequence that encodes an MCM polypeptide with the I671V mutation

<400> 15
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gagagttccg gctcacgcct cattcagcag cgtttactac accagcagca gccgctccac 120

cctgagtggg cagctttggc caagaaacag ttgaagggta aaaatcccga agatctcatc 180

tggcacactc ccgaaggaat ctcaattaaa cctctgtaca gtaaaagaga cacaatggac 240

cttccggagg aactcccagg cgtcaagcca tttaccaggg gcccatatcc aaccatgtat 300

accttccgtc cttggacaat aagacagtac gccggcttta gtactgtgga ggaatctaat 360

aagttttaca aagataatat caaagctggc cagcaggggc ttagtgttgc gttcgacctg 420

gccacccatc ggggctacga ctctgacaac cctcgggttc gcggcgatgt gggaatggca 480

ggtgtcgcca ttgataccgt tgaggatacc aagattctgt tcgacggcat ccccttggaa 540

aagatgagcg taagtatgac catgaatggt gctgtcattc cagtgttggc taatttcatt 600

gtaaccggag aagagcaggg agtgccaaaa gagaagctga caggcacaat acagaacgac 660

attctgaagg agttcatggt gcggaatacc tatatcttcc ccccggagcc tagtatgaag 720

atcatcgccg atatttttga gtatacagca aaacacatgc caaaatttaa ctctatttct 780

atttcaggat accatatgca ggaggccgga gccgacgcca ttcttgagct ggcttatact 840

ctggctgacg gcttggagta ctctaggact ggcctgcagg ccggcctcac aatcgacgaa 900

ttcgcacccc gactgtcctt tttttggggg attggcatga atttttacat ggagatcgca 960

aaaatgcggg cgggccgcag actgtgggcc cacctgattg agaagatgtt tcagcccaag 1020

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caggatccct acaacaacat tgtacgaact gccatcgagg ccatggccgc tgtgtttgga 1140

ggcacccagt cactgcatac aaatagtttt gatgaggctc tggggctccc caccgtgaaa 1200

agcgctcgaa tagcccggaa cacgcaaatc atcatccagg aggaatccgg aatacctaaa 1260

gttgccgacc catggggtgg gagctacatg atggaatgtc taaccaacga tgtgtacgat 1320

gcagcattga agcttataaa tgagatcgaa gaaatggggg gaatggcaaa agcagtggcc 1380

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tccggtagcg aggtgattgt gggagtgaat aaatatcaac tggaaaagga agatgccgtg 1500

gaggtgctgg ctattgataa cacctcagta agaaacaggc agattgaaaa attgaaaaag 1560

ataaagtcat cgcgcgatca agccctggcc gaacggtgtc tcgcggccct gactgagtgc 1620

gccgccagtg gtgatggaaa catcttggca ctggctgtcg atgctagccg ggcccgctgc 1680

accgtgggag aaatcactga cgccctgaag aaggttttcg gcgaacataa ggcaaatgac 1740

agaatggttt caggggccta taggcaggaa tttggcgaat ccaaagaaat tactagcgcc 1800

atcaagcgag tgcacaagtt catggagcgg gaaggtcgtc gcccgcgcct gcttgtcgca 1860

aaaatgggcc aggacgggca tgacagaggg gctaaagtca tcgccactgg atttgcggat 1920

ctcggtttcg acgtggatat tggacctctg ttccagacac cacgggaggt ggcccagcag 1980

gcggtggatg cagatgtgca cgcagtcggg gtctcgacac tcgccgcagg acacaaaacc 2040

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tgcggaggcg tgatccctcc acaggattat gaatttttat tcgaagttgg ggtgtctaat 2160

gtttttggcc ccgggacacg gatcccaaag gccgcggtgc aggtcctgga tgatatcgag 2220

aaatgtttgg agaagaagca gcaaagtgtg 2250

<210> 16
<211> 2250
<212> DNA
<213> Artificial Sequence

<220>
<223> Codon optimized sequence that encodes an MCM polypeptide with the I671V mutation

<400> 16

atgctgagag cgaaaaacca gctttttctt ttgtcacctc attacctgag gcaggtcaaa 60

gagagttcgg gttccagact gatacagcag cgccttcttc atcagcagca gcccctacat 120

ccagagtggg cagctctcgc taagaaacag ctgaagggca agaaccccga agatctcatc 180

tggcacactc ctgagggcat ttctattaag cccctgtact ctaaacgaga cactatggat 240

ctccccgagg aattgccagg cgtgaaacca ttcacaaggg gcccataccc caccatgtat 300

actttccggc catggacaat ccggcagtac gccggcttct cgaccgtgga agaatccaat 360

aaattttata aggataacat aaaggcgggg cagcagggac tatccgtggc cttcgatcta 420

gctactcaca gaggctacga cagcgacaac ccaagagtta gaggggatgt tggcatggcc 480

ggggtggcaa tcgacaccgt ggaggatacg aagatcctct tcgatggaat ccccctggag 540

aagatgagtg tgtcgatgac catgaatggc gccgtgatcc ccgttctggc taatttcata 600

gtgacgggcg aagaacaggg ggtgccaaag gaaaaactga ctggaaccat tcagaacgac 660

attttaaagg agttcatggt gaggaatact tacatctttc caccagagcc tagtatgaaa 720

ataatagctg acatttttga gtacaccgct aagcatatgc ctaagtttaa ttcaatctct 780

atttcaggtt atcacatgca agaggcgggt gcagatgcaa tcctagagct ggcctataca 840

ctggctgacg gactggagta ctctcgcacg ggacttcagg ccggactcac tatcgacgaa 900

tttgctcctc ggctgagttt tttctggggg atcgggatga atttttacat ggagatcgcg 960

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aattccaagt ccctgctgct gagggctcat tgccaaacta gcggatggtc tcttaccgag 1080

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gtagctgacc cctgggggg ctcctacatg atggagtgtt tgaccaacga tgtgtacgac 1320

gccgcgctca aactcattaa tgaaattgag gaaatgggtg ggatggctaa agccgtggcc 1380

gagggcattc ctaagctcag aatagaagaa tgcgccgcca gaaggcaggc gcgcattgat 1440

agtggttcag aggttattgt gggagtaaat aagtaccagc tggagaagga agacgccgtt 1500

gaagttctgg ccatcgataa cacaagtgtg cgcaacagac agatcgaaaa acttaaaaag 1560

attaagtcga gtcgggacca ggcattggca gagagatgtt tagccgcact taccgaatgt 1620

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aagatgggcc aggacggaca tgacagaggt gccaaggtga tagcaacagg gtttgccgac 1920

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tgcgggggcg tgatccctcc tcaggactat gaattcctgt ttgaggtggg ggtatcaaac 2160

gtttttggtc cgggcactag gatcccaaag gccgcagtac aggtattgga cgacatagag 2220

aagtgcctcg aaaagaaaca acaatcagta 2250

<210> 17
<211> 2250
<212> DNA
<213> Artificial Sequence

<220>
<223> Codon optimized sequence that encodes an MCM polypeptide with the I671V mutation

<400> 17
atgttgcgcg ccaaaaatca gctttttta ctatcacctc actacctgag acaggtgaaa 60

gagtcctccg ggagccggct cattcaacaa aggctactac atcaacaaca gcccctccac 120

cctgaatggg cagctctcgc aaagaaacag ctcaagggta aaaatcctga ggacttaatc 180

tggcatacac ctgaaggtat ttctataaag cccctgtatt ccaagcgcga tacaatggat 240

ctgccagaag agctccctgg agtgaaacct tttacccggg gtccgtatcc tactatgtat 300

acttttcgcc cttggacgat aaggcaatac gctggattct caactgtgga agaaagtaat 360

aaattttaca aggataacat taaggccggc cagcagggtc ttagtgtggc tttcgatctt 420

gccacacacc ggggttacga ttcagacaat ccacgggtgc gtggcgatgt gggcatggcg 480

ggggtcgcca tcgataccgt ggaggatacc aagatactct tcgatggcat tccattagag 540

aaaatgagtg tatctatgac gatgaacggc gccgtcatcc ccgtcttagc caattttatt 600

gtcacaggcg aggagcaagg agtgcctaaa gagaagctga caggaacaat tcaaaatgac 660

atactgaaag agtttatggt caggaacaca tacatattcc ccccagaacc gtctatgaag 720

attatagcgg atatttttga gtacactgca aagcatatgc cgaaattcaa ctctatctcg 780

atctccggct accacatgca ggaggctggc gccgacgcca tccttgagct ggcctacacc 840

ctcgcagacg ggctggagta ttcccgcact ggcctccaag ccggcttgac gatcgacgaa 900

ttcgcaccca gactgtcatt tttctggggg atcggcatga acttttatat ggagatcgca 960

aaaatgcgcg ccggacggag gctttgggca cacctcatag aaaagatgtt tcagcctaaa 1020

aattccaaat ctctgctgct cagagcccac tgtcagacga gcggatggtc cctgaccgag 1080

caggatccgt acaacaatat tgtgagaacc gccatcgagg ctatggctgc tgtgtttggg 1140

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gctgccctta agctgatcaa tgaaatcgag gaaatgggcg ggatggcgaa agctgtggct 1380

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gaggtcctgg ccatcgacaa tacctccgtg aggaatagac agatcgaaaa gctcaagaag 1560

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aagtgtcttg agaaaaaaca gcagtctgtg 2250

<210> 18
<211> 2250
<212> DNA
<213> Artificial Sequence

<220>
<223> Codon optimized sequence that encodes an MCM polypeptide with the I671V mutation

<400> 18
atgctgagag cgaaaaatca actcttccta ttgtctcctc attatctccg ccaggttaag 60

gagtcttccg gaagccgttt gatccagcag cggctactgc atcagcagca gcccttgcac 120

ccggagtggg cggctctcgc caaaaaacag cttaaaggta aaaatccaga ggatctcatc 180

tggcacacac cagaaggcat cagcattaag cccctgtact caaagaggga taccatggat 240

ctcccggagg agcttccagg ggtgaagcct ttcaccaggg ggccgtaccc cactatgtac 300

acctttagac catggacgat tcgtcagtat gcgggcttta gcaccgtgga agagagtaac 360

aagttttata aggacaacat caaagccgga caacagggtc tgtctgttgc tttcgacctt 420

gccacacacc ggggctatga ttctgacaac ccacgtgtgc gtggcgacgt gggtatggca 480

ggcgttgcca tcgacactgt cgaggacacc aaaattctat tcgatggaat ccccctcgaa 540

aagatgtccg tttctatgac gatgaacgga gccgtgatac ccgtgctggc caattttatt 600

gttacaggcg aggaacaagg tgtcccgaag gaaaagctga ctggaacgat tcaaaatgat 660

atactcaagg agtttatggt acgaaacact tatatttttc cacccgagcc ctctatgaaa 720

atcatcgcag acatattcga gtacacggcc aagcatatgc ccaaatttaa cagcatctca 780

attagcggat accacatgca agaggcgggc gcagacgcga ttctggagct ggcctacaca 840

ttagctgatg gcctcgagta ctcccgcacc ggcctgcagg ccggactgac tatagacgaa 900

tttgcgccta ggctctcctt tttctggggg attggaatga atttctacat ggagatagca 960

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caggacccct acaataacat tgtcaggacc gccattgaag caatggctgc tgtttttggg 1140

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gtggccgacc cctgggggggg tagctatatg atggagtgtc tgaccaacga cgtctatgac 1320

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gaaggtatcc caaagctgcg cattgaggaa tgcgccgcta gacggcaggc gcgaatcgac 1440

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gaggtactgg ctatagacaa cacaagtgtc cgcaaccgac agatcgagaa gctcaaaaag 1560

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gctgccagtg gtgacggaaa catattggcc ctcgccgtgg acgcttcaag ggcacggtgt 1680

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agaatggtat ccggggccta tcggcaggag ttcggagagt caaaggagat tactagcgca 1800

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aaaatgggcc aagacggtca tgatcgcggt gcgaaggtca ttgctacagg tttcgccgac 1920

ttgggctttg acgtcgacat aggcccactc ttccagaccc cccgcgaagt agcccagcag 1980

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aagtgcctgg agaaaaagca gcaatctgtg 2250

<210> 19
<211> 2250
<212> DNA
<213> Artificial Sequence

<220>
<223> Codon optimized sequence that encodes an MCM polypeptide with the I671V mutation

<400> 19
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gagagttcag ggagtcgcct tatccagcag aggctgttac accagcagca gccacttcat 120

cctgagtggg ctgccctggc taagaaacaa ctgaaaggga agaaccccga ggacctgatc 180

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ctgccggaag agttgccagg agtgaaaccc tttacacgag ggccttatcc aaccatgtat 300

acctttaggc cttggaccat aagacagtac gccgggtttt caaccgtgga ggagtctaat 360

aagttttaca aggacaatat caaggctggc cagcagggcc tgagtgtcgc gtttgatctg 420

gccacacatc ggggctatga tagtgacaac ccaagggttc gtggcgacgt gggtatggcc 480

ggtgtggcta tagacacagt ggaggacact aagatcctgt ttgacgggat tcctcttgag 540

aagatgtccg tcagcatgac catgaatggc gccgtgattc ctgttttggc aaacttcatt 600

gtcactgggg aggaacaggg cgttcccaag gaaaagctga cagggactat ccagaatgat 660

atactgaaag agttcatggt tcggaataca tacatattcc ctcctgaacc ttccatgaag 720

atcatcgctg acattttcga atatacagca aagcacatgc caaaatttaa cagcatttcg 780

atttcaggct atcacatgca ggaggctggc gctgatgcca tcctcgaatt agcgtacact 840

ctagctgatg ggctggagta ctcaaggaca ggcctccagg ccggcctgac gattgatgag 900

ttcgctcctc gcctctcttt tttctggggc atcggtatga acttttatat ggagatcgcg 960

aagatgcggg ccggccgcag gctttgggct catctgattg aaaagatgtt tcagccaaag 1020

aatagcaaat cactgctgtt acgcgcccat tgtcagacaa gcggctggag cctgaccgag 1080

caggatcctt ataacaatat cgtacggaca gccattgaag caatggccgc agtcttcggc 1140

ggaacccaga gcctgcatac taatagcttc gatgaggctc ttggtctccc aaccgtcaag 1200

tccgcccgga tcgccaggaa cacccagatc attattcagg aggagagtgg tatccctaaa 1260

gtggctgacc cttggggcgg gagctacatg atggaatgcc tcaccaacga cgtttacgac 1320

gcagccttga aactgatcaa cgagatcgaa gagatgggcg ggatggccaa ggccgtagcc 1380

gaaggaatac ccaaactccg aatcgaagaa tgcgcggcta ggcggcaggc acggattgac 1440

tcaggcagcg aggtgatagt tggggttaac aagtaccagc tagagaagga ggacgctgta 1500

gaagttctgg caatcgacaa caccagtgtg agaaatcgtc aaatagaaaa attgaagaag 1560

ataaagtcat cccgggacca agccctggcc gagagatgtc tcgccgcatt gactgagtgt 1620

gccgcgtccg gcgacggcaa cattctagct ctggctgtcg acgcctctcg agccaggtgt 1680

acagtgggcg aaatcaccga cgctttgaag aaagtcttcg gggagcataa ggctaacgat 1740

aggatggtgt ctggagctta tcgccaggaa ttcggggagt ctaaagagat cacttctgca 1800

attaagcggg ttcacaaatt catggagaga gagggcaggc ggccacgatt attggtagcc 1860

aagatgggcc aggatggaca cgataggggc gccaaagtga ttgctacggg cttcgccgat 1920

ctgggatttg acgtggacat tgggcctttg ttccagaccc ctcgagaagt cgcccagcag 1980

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tgtggcggcg taatcccacc tcaggattat gaattcctat ttgaggttgg ggtctcaaac 2160

gtgttcgggc cagggactag gatcccgaag gccgcagtcc aggttctgga tgacattgaa 2220

aaatgtctgg agaagaagca acagagtgtg 2250

<210> 20
<211> 2250

<212> DNA
<213> Artificial Sequence

<220>
<223> Codon optimized sequence that encodes an MCM polypeptide with the I671V mutation

<400> 20
atgcttaggg ccaagaacca gctgtttctg ctcagccctc actatttacg gcaggtcaag 60

gagagctcag gatccaggct gattcagcag cgtttgctgc accagcagca gcccctccac 120

ccggagtggg ccgcactcgc taagaaacag ctgaaaggga agaatcctga ggacttgatc 180

tggcacacac cagagggaat cagtatcaag cctctgtaca gtaagcggga cacaatggac 240

ctacctgaag aactccccgg agtgaagccg ttcaccagag gaccttaccc aaccatgtat 300

actttcagac cgtggacaat tagacagtat gctggatttt ccactgttga ggaatcaaac 360

aagttttata aggataacat caaagcgggt caacaggggc tgtctgtggc attcgattta 420

gcaacccaca ggggctacga ctcagataat ccacgagtga gaggtgatgt gggcatggca 480

ggcgtggcta ttgatacagt ggaggacaca aagatactct ttgatggaat ccctctggag 540

aagatgtccg ttagcatgac tatgaacggt gccgttattc ccgtgctagc aaacttcatc 600

gtgactgggg aagaacaggg ggttccaaag gagaaattaa ccgggaccat acagaacgac 660

attctcaagg agtttatggt gcgtaacact tacattttcc cgcctgaacc aagcatgaag 720

atcatcgccg atattttcga gtatacagcc aagcacatgc cgaagttcaa cagtatctct 780

atctctggat accatatgca ggaggctggt gcagacgcca ttctagaact agcgtataca 840

ctggccgatg gattggaata cagcagaaca ggcctgcagg ccggactgac tattgacgag 900

ttcgcccctc ggctttcctt tttctggggc atcgggatga acttctatat ggaaatcgcc 960

aaaatgaggg caggccggcg actgtgggct catctgatcg agaagatgtt tcagccaaaa 1020

aacagcaaat ctttgcttct tagggcccac tgccagactt cagggtggag cctcactgag 1080

caagacccat acaacaacat cgtcagaact gcaatcgagg ccatggctgc cgtattcggt 1140

ggcacacagt ctttgcacac taactcattc gatgaggcgc tcggcctgcc aactgtgaag 1200

tctgccagga ttgctcgaaa tacgcagatt atcattcagg aggagagcgg gatccccaag 1260

gtggccgacc catggggtgg gagttatatg atggagtgtc tgacaaatga cgtgtatgat 1320

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gagggtattc ctaagctaag gatcgaagag tgcgctgctc gcaggcaggc cagaattgat 1440

agcgggtctg aagtgatagt gggcgtgaac aagtatcagc tcgagaagga agacgctgta 1500

gaggtgctag ccattgataa cacctccgtg cgaaataggc agatcgagaa attgaagaag 1560

attaagtctt cacgggacca ggcacttgca gagcgatgtt tagcggcact gaccgaatgc 1620

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ataaagagag tccacaagtt tatggaacga gagggtcgtc gcccgcgact gcttgtggcc 1860

aaaatgggtc aggacggaca tgaccgagga gccaaagtaa tagcgacagg cttcgcagat 1920

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gccgtggacg ctgatgtgca tgcagtcgga gtctccacgc tggcagccgg ccacaaaacc 2040

ttagtgcccg aattaattaa ggagctgaac agtttgggga ggccagatat tttggtcatg 2100

tgcggaggcg taattcctcc gcaagattat gaatttttgt ttgaggtagg cgtcagtaac 2160

gtgttcggac ccggaacacg cattccaaaa gcagcagtgc aggtcctcga tgatatcgag 2220

aagtgcctcg agaaaaagca gcaatcggtg 2250

<210> 21
<211> 2250
<212> DNA
<213> Artificial Sequence

<220>
<223> Codon optimized sequence that encodes an MCM polypeptide with the I671V mutation

<400> 21
atgttacgcg cgaaaaatca attatttcta ctgtcacccc attatcttcg ccaggtgaag 60

gaaagctccg ggtcaagact gatccagcaa aggctcctgc accagcagca gcccctccac 120

cccgaatggg ctgcccttgc caagaaacag ttgaagggca aaaacccgga ggacttgata 180

tggcacacac cagaagggat cagcattaag ccactgtact ccaagcgaga caccatggac 240

ctgcctgagg aactgcccgg cgtgaaacct tttacacgtg ggccctaccc tacaatgtac 300

acatttcgcc cctggacaat aagacagtac gccgggttct caaccgtgga ggagtctaac 360

aaattctata aggacaatat aaaggcagga cagcaagggc tctctgtggc attcgatctg 420

gcaacacatc gtgggtatga ctccgacaac ccacgtgtgc ggggggacgt gggtatggcc 480

ggagtcgcaa tcgatacagt cgaggataca aagatcctct tcgatggcat tccactggaa 540

aagatgagcg tgagtatgac aatgaacggg gcagtcattc ctgtgctggc caatttcatt 600

gtgacagggg aagagcaagg tgtccccaag gagaaactga ctggtacgat ccagaacgat 660

atcctgaagg agtttatggt gcggaatact tacatcttcc cccccgaacc atcaatgaag 720

atcatcgccg acattttcga gtataccgcc aagcacatgc ccaagtttaa ctcaattagc 780

attagcgggt atcatatgca ggaggccgga gctgatgcca ttttggagct ggcatatact 840

ctggccgacg gtctggagta ttcaagaaca ggcctgcagg ccggtctgac cattgatgag 900

tttgctcccc gccttagctt tttttgggga attggaatga atttctacat ggaaattgct 960

aagatgaggg ccggcagaag gctctgggca cacctcatcg aaaagatgtt tcagccaaag 1020

aattcgaagt cactcttgtt aagggcgcat tgtcagacgt ctggctggtc tctaaccgaa 1080

caagacccct ataacaacat agtcagaaca gccatcgaag caatggctgc tgtcttcggg 1140

ggcacccaga gcctgcatac caatagtttc gatgaagccc ttggactgcc taccgtgaag 1200

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gcagctctga agctgatcaa cgagatcgaa gagatgggcg gcatggcgaa agccgtggct 1380

gaagggatcc ccaaattacg aatcgaggag tgtgccgctc gccggcaggc ccgaatagat 1440

agcggatctg aagtcatcgt gggagtaaac aaataccagc tggaaaagga agatgccgtc 1500

gaggtgttag cgatagacaa cacttcggta aggaacaggc aaattgaaaa attgaaaaaa 1560

attaagagca gccgcgacca ggcattggct gagagatgtc tcgccgcctt gacagaatgc 1620

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cggatggtct cgggagccta ccgtcaggag ttcggcgaga gtaaggaaat aacaagtgcc 1800

attaagcgag ttcacaaatt tatggagagg gagggacggc ggccccggct cctggtcgct 1860

aaaatgggac aggatggaca cgaccgagga gcaaaagtga ttgctactgg gtttgctgat 1920

ctaggatttg atgtggatat cggccccctg ttccagactc cccgcgaggt ggcgcaacaa 1980

gctgtggatg ccgacgtcca cgcggtgggc gtgtcaactc tggctgccgg acacaagacc 2040

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tgtggcggag tgatccctcc gcaggactat gaattcctct tcgaagttgg ggtcagcaac 2160

gtgttcgggc ctggtacccg catccccaag gcagctgtcc aagtcttgga cgatatcgag 2220

aagtgtctcg agaagaaaca acagtccgtt 2250

<210> 22
<211> 2250
<212> DNA
<213> Artificial Sequence

<220>
<223> Codon optimized sequence that encodes an MCM polypeptide with the I671V mutation

<400> 22
atgttgcgag ccaaaaatca attgtttctg ttatctccac attacctgag acaggtgaag 60

gagagttctg gtagtaggct gattcaacag aggttactcc atcagcagca acccctgcat 120

cctgagtggg cggctctcgc gaagaaacaa ctgaaaggaa aaaaccctga agatttgatt 180

tggcacactc ctgaggggat ttcaatcaag ccgctgtact ccaagcgcga cacaatggat 240

ttgcctgagg agttgcccgg cgttaagccg ttcacccgag ggccctaccc cactatgtac 300

accttccgcc cctggacgat ccggcagtat gcgggattca gtacggtgga agaaagtaac 360

aaattttata aggacaacat taaagcaggc caacagggcc taagcgtggc tttcgacctg 420

gctacccata ggggatacga ctcagacaac ccccgagtac ggggagacgt ggggatggcg 480

ggagttgcca ttgacacagt tgaagacacc aaaatcctgt ttgatggcat ccccctggag 540

aaaatgtctg tttccatgac gatgaatggt gccgtgattc ccgtgctggc aaatttcatc 600

gttacagggg aagagcaggg cgtgccaaaa gagaagctga ccggtaccat acagaatgat 660

attctgaaag agtttatggt gcggaacaca tacatcttcc cccctgagcc tagcatgaag 720

ataatagcag acatttttga gtacaccgcc aagcatatgc ctaaatttaa cagcatcagt 780

atctccggct atcacatgca ggaagccggg gcagatgcta tactggagct ggcttacact 840

ctggcagacg gactggaata ctctcgaaca ggactgcaag cgggactgac catcgatgaa 900

tttgctccac gactgtcgtt cttttgggga atcggcatga acttctatat ggagatcgcc 960

aagatgcggg caggccgtcg tttgtgggct catctgatcg agaagatgtt ccaaccaaag 1020

aattccaaaa gtttgctgct ccgggcacac tgccaaactt cagggtggag cctgacagaa 1080

caagacccct ataataacat tgttagaacg gccatagagg cgatggcagc tgtcttcggg 1140

ggcacacagt ccttgcacac aaacagcttt gacgaagcct tgggccttcc aactgtgaag 1200

tcagccagga ttgccagaaa cacccagatc atcatccaag aggaatctgg catccccaaa 1260

gtggccgacc cctggggcgg cagctatatg atggagtgtc tgaccaatga cgtgtatgac 1320

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gaaggaatac cgaaattgcg gatagaagaa tgtgcggccc ggagacaggc caggatcgac 1440

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gaggttctgg ccattgataa tacgtctgtg cgtaatcgac agattgaaaa actcaaaaaa 1560

atcaaatcca gcagggacca agcgctggcc gagcgatgtc tggcagctct cacagaatgt 1620

gcggcttcag gggatggcaa tatcctagct ctggccgtcg atgcaagccg agcccgatgt 1680

actgtgggcg aaattactga cgcgctgaag aaggtgttcg gagagcataa ggcaaatgat 1740

cggatggtgt ccggcgctta ccgccaagag tttggcgagt caaaagagat tacgagtgcc 1800

attaagcggg tgcacaaatt catggagcgc gagggtcgca ggcccaggtt gcttgtggca 1860

aaaatggggc aagatgggca cgaccgtgga gcaaaagtga tcgccacagg attcgccgat 1920

cttggttttg acgtcgatat tgggccattg tttcagactc ctagggaagt ggcccagcaa 1980

gctgtcgacg ccgatgtgca tgccgttggg gtctccaccc tggctgccgg gcacaagaca 2040

ctggtgccag aactgattaa ggaactgaat tctctgggac gacctgacat tctggttatg 2100

tgtggtggcg ttatcccccc acaggattat gaattcctat tcgaggtagg agtgtctaat 2160

gtgttcgggc ctggtacgag aatcccaaaa gctgcagttc aagtgctgga tgacattgag 2220

aagtgtctgg aaaagaaaca acagtcagtg 2250

<210> 23
<211> 2250
<212> DNA
<213> Artificial Sequence

<220>
<223> Codon optimized sequence that encodes an MCM polypeptide with the I671V mutation

<400> 23
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gagtcgagcg gctctcggct gatccagcaa agactattac accagcagca accgctgcat 120

cctgagtggg ctgcactagc caagaaacag ctaaagggca agaatccaga ggacctgata 180

tggcacactc ccgaaggcat ttctattaaa cccctctata gcaagcgtga caccatggat 240

cttcctgaag aactccccgg cgtaaagccc ttcacgcggg gcccctatcc cactatgtac 300

accttccgcc cctggactat tcgtcagtac gccggtttct ccaccgtgga agaatctaat 360

aagttctaca aagacaatat caaggccggg cagcagggac tcagcgtggc ttttgatctc 420

gctacccatc gcggttacga cagtgacaac cctcgcgtga gaggtgatgt cggtatggcg 480

ggagtggcaa tagataccgt tgaagacact aagatccttt tcgatggcat tcccctggag 540

aagatgtcgg tgtccatgac gatgaatgga gcagtcatcc ctgtgttagc aaatttcata 600

gtaaccggag aggaacaggg tgtccctaag gagaagctga caggaaccat ccagaacgat 660

attctaaagg aattcatggt caggaatacc tatatctttc cgcccgaacc aagtatgaaa 720

atcatcgccg acattttcga atataccgct aaacacatgc cgaaattcaa cagcataagc 780

atttcaggct atcacatgca ggaggccgga gcagacgcaa tcttagaact ggcttacaca 840

ctggcggatg gactagaata ctctaggact ggcctgcagg ccgggctcac aattgacgaa 900

tttgctccac ggctttcttt tttctggggg atcggtatga acttctacat ggaaatagcc 960

aagatgagag ctgggagacg gctgtgggca cacctgatcg aaaaaatgtt ccagccgaaa 1020

aatagtaaaa gcctgctgct gagagctcac tgccagacga gcggctggtc tctgacagag 1080

caggaccctt acaacaacat cgtccgcacc gctattgagg ccatggccgc cgtatttggc 1140

ggaactcagt ccttgcatac caatagtttc gacgaagctc tgggattgcc caccgttaaa 1200

tccgctcgta tcgcccgcaa cacgcagata attattcagg aagagagtgg cattcctaag 1260

gttgctgatc cttggggagg gagttacatg atggaatgtt taaccaacga cgtgtatgat 1320

gccgccctca agctgatcaa tgaaatcgag gaaatgggag ggatggcaaa agcggtggca 1380

gaaggaattc ctaagctcag gatcgaggaa tgtgctgctc ggcgacaggc acgcattgac 1440

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gaagtcctcg ctattgacaa tacctccgtc cgcaacaggc agatagaaaa actcaagaaa 1560

atcaaatcga gtcgcgatca ggctctggcc gaacgttgcc tggccgctct caccgaatgt 1620

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attaagcgcg tgcacaagtt tatggagcgc gaaggccgga gaccccggct gctagtcgcc 1860

aagatgggcc aagacggaca tgaccgaggc gctaaagtaa ttgcgaccgg atttgccgat 1920

cttggatttg atgtcgatat tggacctctg ttccagaccc ctcgcgaagt agctcagcag 1980

gccgttgatg ccgatgtgca cgccgtaggc gtatccacgc tggcagcagg acataagacc 2040

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tgcggcggcg taatcccccc tcaagactac gagttcctgt ttgaggtggg ggtgtcaaat 2160

gtattcggcc ctgggactcg gatccccaaa gcagcagtgc aagtgctgga tgacattgaa 2220

aaatgcctcg aaaagaagca acagagtgtg 2250

<210> 24
<211> 2250
<212> DNA
<213> Artificial Sequence

<220>
<223> Codon optimized sequence that encodes an MCM polypeptide with the I671V mutation

<400> 24
atgcttcggg ctaagaacca gttgtttctc cttagtcccc attacctccg acaggtcaag 60

gaatcttcag gttctcgcct catccaacaa cgcttgctgc atcagcagca gcccctgcac 120

cccgaatggg ctgccctcgc aaagaagcaa ttaaaaggta agaacccgga ggacctgatc 180

tggcatacac ctgagggcat ttccataaag cccctctatt caaaacgcga caccatggac 240

ctacccgaag aactgccggg agtaaagcca tttactcggg ggccttaccc caccatgtat 300

acatttcgcc cctggacaat tcggcaatac gccggattct ccaccgtgga ggaatcaaat 360

aagttttata aggacaacat caaggcagga cagcagggac tttctgtagc attcgacctc 420

gccactcaca gaggctacga ctcagacaac ccacgagtca ggggcgatgt gggtatggcc 480

ggcgtggcta tagacacagt ggaggacact aagatacttt ttgacggcat ccctctggag 540

aaaatgagcg tgagcatgac tatgaatgga gccgtaatcc ctgtcttagc gaacttcatc 600

gtcaccggag aagagcaggg cgtacccaaa gaaaagctta cagggaccat ccaaaacgac 660

atcctcaaag agtttatggt taggaacacc tatatttttc cgccagagcc tagcatgaaa 720

attatcgccg acatctttga atataccgcc aagcatatgc ctaagtttaa ttctattagc 780

attagcggct accatatgca agaggccggg gctgacgcca tcctcgagct ggcctacacc 840

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caagacccct acaacaacat agtcaggaca gctatagagg ctatggcagc agttttcggc 1140

ggaacacaat ccctgcacac taactccttc gatgaagctc tcggactgcc aacagtcaaa 1200

tccgcccgga ttgcccgaaa tacacaaatc atcattcaag aggaatccgg catccctaaa 1260

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gagggaatac ctaaactgcg gattgaagag tgcgcagcta gacgccaagc tcgtatcgat 1440

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gaggtgctgg ctattgataa taccagcgtg cggaacagac aaatcgaaaa gctgaagaaa 1560

ataaaatcaa gccgagacca ggcactcgcc gaacggtgcc ttgctgccct aaccgagtgc 1620

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actgtggggg aaatcacgga cgctcttaaa aaggtctttg gggaacacaa ggcaaatgac 1740

aggatggtat caggcgccta caggcaagag ttcggggagt caaaagagat tacctcagcc 1800

ataaagcgag ttcacaaatt catggaaaga gaggggagac gaccccgact gttggtcgct 1860

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gccgttgatg cggacgtcca tgccgtgggt gtgtccacac tggccgcggg acacaagacc 2040

ctggttcccg aattgatcaa agagctcaac agcctgggac ggcctgacat cctcgttatg 2100

tgtggaggcg taatcccacc ccaggattat gagttcctgt tcgaggtggg agtgtccaac 2160

gtgtttggcc ccggcacgag aattcctaaa gctgctgttc aagtgctgga tgatatcgag 2220

aaatgccttg agaagaagca acaaagcgtc 2250

<210> 25
<211> 2250
<212> DNA
<213> Artificial Sequence

<220>
<223> Codon optimized sequence that encodes an MCM polypeptide with the I671V mutation

<400> 25
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gagtcatccg gttccagact gattcagcag agactcctgc accagcaaca gccactgcat 120

ccagaatggg cagcattagc gaaaaagcag cttaagggaa agaatcccga agatctaatc 180

tggcacacac cggaaggaat cagcatcaaa cctctttaca gcaagcggga tactatggac 240

ctccccgaag agctccccgg tgtgaagcca tttaccagag gaccttatcc aactatgtac 300

acgttccggc cgtggacaat ccgacagtat gctggcttct ctaccgtgga ggagtccaac 360

aagttctaca aggacaatat taaggcgggg cagcagggac tctccgtggc attcgatctg 420

gctacccacc gagggtacga ttccgacaat ccgagggtga ggggcgacgt ggggatggca 480

ggcgttgcca ttgatacagt agaggatact aaaattttgt tcgatggcat ccccttagag 540

aagatgtccg tatccatgac catgaatggt gccgtcattc ctgttctcgc taatttcatt 600

gtaaccggag aggaacaagg tgtccctaag gagaagctga ccggtacaat acaaaatgat 660

atacttaaag agtttatggt gcgcaatacg tacattttcc caccggaacc aagcatgaag 720

atcattgccg atatctttga atataccgcc aagcatatgc cgaagttcaa ttccattagc 780

atttcaggct accatatgca ggaggcaggc gccgatgcca ttctcgaact cgcctacaca 840

ctggcggatg gcctcgagta ttcaaggacc ggtctgcaag caggcctgac aattgacgaa 900

tttgcccccc gactgtcttt tttctggggc atcgggatga atttttatat ggagattgca 960

aagatgcggg caggacgacg cttgtgggct cacctcattg aaaaaatgtt tcaaccaaag 1020

aactctaaaa gcttactgct cagggcacac tgccagactt caggctggag cctgacggag 1080

caagacccct acaataacat tgtgaggacg gctatcgagg ccatggcggc cgtgtttggg 1140

ggtacccaaa gcttgcacac taactctttc gacgaggcgc tgggtttacc gaccgtgaag 1200

agcgctagaa ttgctcggaa cacgcagatt attatccagg aagagtcagg gatcccaaag 1260

gttgccgatc cttgggggg cagttacatg atggaatgcc tgactaacga tgtttatgac 1320

gctgcactaa aattgatcaa tgaaatcgag gaaatgggag ggatggccaa ggcagtagcc 1380

gaaggcattc ccaaactacg catcgaagag tgcgccgcta ggcgacaggc taggatagat 1440

agcggttccg aggttattgt cggtgtcaat aaatatcagc tggagaagga agatgccgtg 1500

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cgaatggtga gtggtgcata tcgtcaggag ttcggagaaa gcaaggagat tacgtcagct 1800

atcaagagag tgcacaaatt tatggagaga gaggggaggc gtccacgctt acttgtggcc 1860

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tgtgggggtg ttatccctcc gcaggattac gaatttctct tcgaggttgg ggtgagcaat 2160

gtgtttggac caggtacgag aatccccaaa gcggccgtcc aagtccttga cgatattgaa 2220

aaatgtttag aaaaaaagca acagtcagtt 2250

<210> 26
<211> 2250
<212> DNA
<213> Artificial Sequence

<220>
<223> Codon optimized sequence that encodes an MCM polypeptide with the I671V mutation

<400> 26
atgctgcgcg ccaagaatca gttgtttttg ttgagtccac actacctgag acaggtaaag 60

gagagctccg gcagcaggtt gatccaacag cgcctgttac accagcagca acccctgcac 120

ccggaatggg ctgcacttgc caagaaacag ctgaaaggga aaaaccccga ggatctgatt 180

tggcacacgc cagaaggtat cagtattaag ccactgtata gtaagcgaga cacaatggac 240

cttccggaag agctcccagg ggtgaaacct tttacgcgtg gaccttaccc tactatgtat 300

acatttcggc cttggaccat ccgccagtat gccggattct ccactgtaga agagagcaat 360

aagttctata aagataatat caaggcagga cagcaaggtt tgagcgtggc ctttgattta 420

gccacccaca gaggatatga tagtgataat ccacgggtta ggggtgacgt tggaatggcc 480

ggagtcgcaa tcgatacagt cgaggataca aagatcctgt tcgacggcat tcctttagaa 540

aaaatgagcg tcagtatgac catgaatggg gccgttattc ctgtcctcgc caacttcatt 600

gtaaccggag aagagcaggg cgttcctaaa gagaaattga cggggacgat tcagaatgac 660

attttaaagg agtttatggt taggaacact tacatattcc ctcccgagcc atccatgaag 720

ataattgcag atatcttcga gtacaccgcc aagcatatgc ccaaattcaa ttctatttcc 780

ataagcggct atcatatgca ggaggcaggg gccgatgcta tcctggagtt agcttatacc 840

ctcgccgacg ggctggaata ttctcgtaca ggcctgcagg cgggtctgac tattgacgag 900

ttcgctcctc gccttagctt tttttggggg attggtatga atttctacat ggaaatagct 960

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aatagcaaat ccttactgtt gagagctcac tgccaaacct caggatggtc cctgacagaa 1080

caggatcctt ataataacat cgttcgcacc gccattgagg ccatggcagc cgtctttggt 1140

ggaactcaga gcctgcatac caacagtttc gacgaggcgc ttgggctgcc gacagtcaag 1200

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gtcgctgatc cctggggagg gtcttacatg atggagtgtc taactaatga cgtttatgat 1320

gccgccttga aactgatcaa tgagatagag gagatgggcg gaatggccaa ggccgttgca 1380

gagggcattc caaaattacg catcgaggag tgcgccgcaa ggcgtcaagc ccgcatcgat 1440

tcaggaagtg aggtcatagt gggtgtcaac aaataccagc ttgaaaagga ggacgccgtg 1500

gaggtgcttg caatcgataa cactagcgtc agaaatcgac aaatagagaa gcttaaaaag 1560

atcaaaagct cacgggatca agctcttgct gagagatgcc tcgcagccct caccgagtgt 1620

gccgcttccg gggatggcaa catactggcg ctcgccgtgg atgcatctag ggctaggtgt 1680

acggtgggtg agattactga tgccctgaag aaggtttttg gagagcataa ggcaaatgac 1740

aggatggtta gtggagcata tcgtcaagag tttggcgaga gcaaggagat tactagcgcc 1800

ataaaacggg tgcacaaatt catggaacga gagggcaggc ggcctaggct tctggtcgct 1860

aaaatgggac aagatggaca tgaccggggt gctaaagtga tcgccacagg ctttgctgac 1920

ttggggttcg acgtcgacat aggaccactg ttccaaaccc cccgggaagt cgcgcagcag 1980

gcggtcgacg ctgatgtcca cgctgttggt gtgagtaccc tcgcagccgg acacaagaca 2040

cttgtgcctg agcttatcaa agagttaaat tccctaggcc ggccggatat actcgtgatg 2100

tgcggggggg ttatcccacc ccaggattat gagtttctgt tcgaggtggg cgtgtctaac 2160

gtattcgggc ctggcaccag aattcccaaa gccgcagttc aggttctaga cgatatcgag 2220

aagtgcctgg agaaaaagca acaatcagtc 2250

<210> 27
<211> 2250
<212> DNA
<213> Artificial Sequence

<220>
<223> Codon optimized sequence that encodes an MCM polypeptide with the I671V mutation

<400> 27
atgcttaggg ccaagaatca actgttcctt cttagcccgc attaccttcg ccaggttaag 60

gagtctagtg gatccaggct aatccagcag cggctgctac accaacaaca gcctctgcac 120

ccagagtggg ctgccctcgc caaaaagcag ctgaagggaa aaaacccaga ggatctcatt 180

tggcataccc ctgagggaat ttctattaag ccgctctata gtaaaaggga cactatggat 240

ctgccggagg agctccctgg agtgaaaccc tttaccaggg gcccataccc gacgatgtat 300

acttttcggc cttggactat tcggcagtat gccggattca gtactgtgga ggagtcaaac 360

aaattctaca aggacaatat taaagccggt cagcagggtc tgtccgttgc tttcgaccta 420

gctactcata gggggtatga tagtgacaat cctcgcgttc gcggagacgt cggtatggcc 480

ggggtggcta ttgacaccgt cgaggatacc aagatcctgt ttgacggcat cccactagaa 540

aagatgagcg tgagtatgac catgaacggc gcggtgatcc ccgttctggc aaactttatt 600

gttacgggag aagagcaagg agtacccaaa gagaaactga caggaaccat tcagaatgac 660

attctgaaag agtttatggt ccgaaatact tacatcttcc cacctgagcc ttctatgaaa 720

ataatcgcag acattttcga atacacagcg aagcacatgc caaagtttaa ctcaattagc 780

attagcgggt accatatgca ggaagccggt gctgatgcca ttctagaact tgcctacact 840

ctggcagatg gcctagagta ctcgcggaca ggtctgcagg caggcctgac aatcgatgaa 900

ttcgcccctc gcctgtcttt cttctgggga attgggatga atttttatat ggaaatcgct 960

aaaatgcgag ccggacggag gctgtgggca catcttatcg aaaagatgtt ccaacccaag 1020

aatagcaaat ctctgctgct gcgggcccat tgccaaacct ctggatggtc cctgaccgag 1080

caggatccct ataataatat tgtacgtacg gccatagaag caatggctgc agtctttggc 1140

ggcacacaga gcctccacac taacagcttc gatgaagcct tgggccttcc gaccgttaag 1200

tcagctagga tcgcgcgtaa tacccaaatt atcatccagg aagaaagcgg gattcccaag 1260

gttgccgatc cctgggggg atcttacatg atggagtgcc ttacaaacga cgtatacgat 1320

gccgcgctga aactcattaa tgaaattgag gagatgggcg ggatggctaa ggccgtagcc 1380

gaaggcatcc ctaagcttag aatcgaagag tgtgctgcaa gacggcaggc taggattgac 1440

tcgggctccg aggtcatcgt cggcgtgaac aagtaccaac tggaaaagga agatgcggtc 1500

gaggtgctgg cgatcgataa tacctcagtc aggaacagac aaattgagaa attaaagaaa 1560

atcaaaagca gtcgcgacca ggccttggct gagcggtgtc tcgctgccct cacagagtgc 1620

gccgcaagcg gcgatggcaa catactagcc ctcgctgttg atgcatccag ggcgcggtgc 1680

accgtgggag agataactga cgccctcaaa aaggtattcg gggaacataa ggctaacgac 1740

agaatggtga gtggagctta ccgccaggag tttggtgaga gtaaggagat aacatcagcc 1800

ataaagagag tgcacaagtt catggagaga gagggccggc gacccagact gctcgtggcc 1860

aagatgggtc aagacggaca tgaccggggc gccaaggtga tcgccaccgg gttcgcagac 1920

ctcgggtttg atgtcgatat cggaccgttg ttccagaccc cacgggaggt cgcccaacag 1980

gccgtggatg cggacgtgca tgcagtagga gtgagtaccc tcgccgccgg gcacaagaca 2040

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tgcggaggcg tgattcctcc acaggactac gaattcttgt ttgaggtcgg ggtgtccaat 2160

gtctttggcc ctggcacgcg tattcctaaa gcggcagttc aggtgctcga cgatatagag 2220

aagtgcctgg agaagaagca gcagtctgtc 2250

<210> 28
<211> 2250
<212> DNA
<213> Artificial Sequence

<220>
<223> Codon optimized sequence that encodes an MCM polypeptide with the I671V mutation

<400> 28
atgctcaggg ctaaaaatca acttttttctg ctctcgcccc actaccttcg ccaggtgaag 60

gagtccagcg gcagtagact tatccagcag cgtctgttgc atcagcaaca gccactgcac 120

cctgagtggg cagcgctggc taagaagcaa ctcaagggca agaaccctga ggatctcatc 180

tggcacacac cggaggggat tagtatcaaa cccttgtact cgaagcggga taccatggat 240

ctgcctgaag aattgccggg agtcaagccc ttcacaagag gcccttatcc caccatgtac 300

acatttaggc cctggaccat ccgccaatat gctggcttca gtactgtgga ggaatcaaat 360

aagttttata aggacaatat caaagccggc caacaaggct tgtctgtggc atttgatctt 420

gctacgcacc ggggctacga ttccgataac ccccgcgtgc gcggagacgt cggcatggca 480

ggcgtggcca tcgacactgt ggaggacact aaaattttat ttgacggtat tccactcgaa 540

aaaatgtccg tgagtatgac catgaacggt gccgtgattc ctgtactggc caatttcata 600

gtgactggtg aggaacaggg agttcctaaa gagaagctga ccggtactat ccaaaatgat 660

attcttaagg agtttatggt aagaaatact tacatctttc ccccagagcc ctctatgaaa 720

atcatagctg acatattcga atacaccgca aaacacatgc caaaattcaa tagcattagt 780

attagtgggt accacatgca ggaagctgga gctgacgcga tcctggaact ggcctacacc 840

ctggcagatg ggctagagta cagcagaacc gggctacagg ctggtctcac aatcgacgag 900

tttgctcccc ggttaagttt tttctggggc atcggtatga acttttacat ggaaattgcc 960

aagatgcggg caggaaggcg tctttgggct catctgatag aaaaaatgtt tcagcccaaa 1020

aacagtaaat cgttgttgct ccgagcacac tgccagacca gcggttggag cctgacggag 1080

caagatcctt acaacaatat tgttcggact gctatagaag ccatggctgc cgtatttggc 1140

gggacacaga gcctccacac taattctttc gacgaggcct tggggttgcc taccgtgaag 1200

agcgctcgta tcgcgaggaa tacacaaata attattcagg aagaatcagg cattccaaaa 1260

gtggcagacc cgtggggagg aagttacatg atggagtgtc tcactaatga tgtgtacgat 1320

gccgccctga agctgattaa tgaaattgaa gagatgggag ggatggctaa ggcagtggcc 1380

gaaggtattc ccaagctccg gattgaagaa tgtgcagcca ggcggcaggc ccgtatagac 1440

tcaggctccg aggtgatagt tggagtaaat aaatatcagc tggagaagga ggatgcggtc 1500

gaagtcttgg ccatcgacaa cacatccgtg aggaatcgcc agattgaaaa gcttaagaag 1560

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gccgctagcg gagacggcaa tatcctagcc ctcgccgtgg atgcctctag agctcgatgc 1680

acagtgggcg aaattacaga tgccctgaaa aaggtctttg gagagcacaa ggcaaatgac 1740

agaatggtct caggcgcgta cagacaggag ttcggggaat caaaggagat cacaagtgca 1800

attaagcggg tccacaagtt catggagcgg gaagggcgga gaccccggct tctggtcgca 1860

aagatgggac aggatgggca tgacagaggt gccaaagtga tcgccacagg atttgccgat 1920

ttgggattcg acgtggatat aggtccctta tttcagaccc cgcgtgaagt agcgcaacag 1980

gcagtggacg cagacgtcca cgccgtcggg gtgagtaccc tggcggcggg acacaaaact 2040

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tgtgggggg ttattccacc ccaggactac gagtttctat ttgaagtggg agtgtccaac 2160

gttttcggcc ctggcacaag aattccaaag gccgccgtgc aagtgctcga tgatatcgag 2220

aagtgcttgg agaagaaaca gcagtctgtt 2250

<210> 29
<211> 2250
<212> DNA
<213> Artificial Sequence

<220>
<223> Codon optimized sequence that encodes an MCM polypeptide with the I671V mutation

<400> 29
atgttgagag ccaaaaacca gctcttcctg ctgagccctc actacctcag gcaggttaaa 60

gaaagctctg gctcacgtct aatccagcaa cgcctgctcc accagcagca acccctgcat 120

ccagagtggg ccgctttagc caagaaacag ctgaaaggta agaatcctga ggatcttatt 180

tggcatactc ctgagggtat cagcatcaaa ccactgtatt caaagcggga taccatggac 240

ctgcccgagg aacttccggg ggtgaagcct ttcacacggg ggccctaccc aaccatgtat 300

acattccgac cttggacaat ccgccagtat gcggggtttt ctactgtgga agaatctaac 360

aagttctaca aggacaacat taaagctgga cagcagggtc tctccgtcgc ctttgacttg 420

gccacacata gggggtacga ctctgacaac cctagggtcc ggggcgatgt gggtatggca 480

ggcgtggcaa ttgacaccgt cgaggacact aaaatcctct ttgacggcat ccccttggaa 540

aagatgtctg tatcgatgac catgaatggc gcagttatcc ctgtgttggc caactttatc 600

gtaactgggg aagagcaggg tgtcccaaaa gaaaagttaa caggcaccat ccagaatgac 660

atcctcaaag agtttatggt ccggaataca tatatctttc caccggagcc gtccatgaag 720

attattgccg atattttcga gtatactgcc aaacatatgc ccaagttcaa tagcatctct 780

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ggcacccagt ctttgcatac caactcgttc gatgaagcgc ttggactacc aaccgtgaag 1200

tctgcccgga tagctcgaaa cactcagatt attatccagg aggagtcggg gatacccaag 1260

gtcgctgatc cttggggcgg tagctatatg atggagtgtt tgacaaatga cgtgtacgac 1320

gcagccctca agcttattaa cgaaattgag gaaatgggtg ggatggcaaa agctgttgcc 1380

gagggaatcc ccaagctgag aatcgaggag tgtgccgcac ggaggcaggc tcgtatagac 1440

agcggtagcg aggttatcgt gggagtgaat aagtaccaac ttgagaagga agatgctgtc 1500

gaggttcttg ctattgacaa caccagtgtg cgcaatcgcc agatagagaa actgaagaaa 1560

atcaagagct caagagacca ggcactagcc gagcggtgcc tggccgcatt gacggagtgc 1620

gccgcatccg gcgatggcaa tatactcgcc ttggctgtag acgcctcacg cgcccgctgt 1680

acagtcggtg agataaccga tgcactcaaa aaggttttcg gcgaacataa ggccaacgac 1740

cgaatggtgt ctggagccta tcggcaggaa tttggggagt ctaaggaaat cacatctgcg 1800

atcaagcggg tgcacaagtt tatggaaaga gaaggacgcc ggccaagact cctggtcgcc 1860

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gtattcggtc cgggaactag gatcccaaag gctgctgtgc aggtcctgga cgatatcgag 2220

aagtgccttg agaagaagca gcagtctgtt 2250

<210> 30
<211> 2250
<212> DNA
<213> Artificial Sequence

<220>
<223> Codon optimized sequence that encodes an MCM polypeptide with the I671V mutation

<400> 30
atgcttcgcg cgaagaatca gttatttctg ctgagccccc actacctgcg gcaggtgaag 60

gagtcctcag gaagtcgcct gattcagcag agactgttgc accagcagca gcccttgcac 120

cccgaatggg ccgcacttgc taagaagcag ttaaagggta aaaaccctga agatttaatt 180

tggcacaccc cagagggcat ttccatcaaa ccattgtatt ctaagcggga tacaatggat 240

ctaccagagg aactccccgg ggtcaagcca tttactaggg gaccataccc tacgatgtac 300

acatttcgac catggactat ccgccagtac gcagggtttt ccaccgttga ggagagcaat 360

aaattttaca aggacaatat aaaagccgga cagcagggac tgagtgtggc atttgatctg 420

gctacccacc ggggctatga ttcagacaac ccaagagtga gaggcgatgt gggcatggcc 480

ggcgtggcca tcgatacggt ggaggacact aagattcttt ttgacgggat tcccctggaa 540

aagatgagtg tgtccatgac catgaacggc gctgtgatac ccgttcttgc taattttatc 600

gtgactggcg aagagcaagg cgtgcctaaa gagaagctca cgggcaccat ccaaaatgac 660

attctcaaag agttcatggt gcggaacaca tatattttcc cacccgagcc ttcaatgaaa 720

atcattgccg acattttcga gtataccgca aagcacatgc ctaagtttaa ctccatatct 780

atttctggct accacatgca agaggccggc gctgacgcga tcttagagct tgcatacaca 840

cttgccgatg gtttggaata cagccgcacg gggttgcagg ccggattaac tatcgatgaa 900

ttcgctccaa ggctgtcatt tttctggggg ataggaatga atttttatat ggaaatagca 960

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gaagtgctgg ctatagacaa cacctctgtt aggaacagac aaattgagaa gctgaaaaaa 1560

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gccgcatccg gggacggcaa tatactggcc ctcgccgtgg acgccagtag agctcgttgc 1680

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atcaaaaggg tccataagtt catggagcgc gaaggcagac ggccaagact cctcgtggct 1860

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gctgtggacg ccgacgttca cgccgtgggc gtgtctacgc tcgcagctgg tcacaagact 2040

ctggtacccg aactgattaa ggagctaaat tcattaggaa ggccagatat tctggtgatg 2100

tgtggcggcg tgatcccacc gcaggactac gaattcctgt tcgaggttgg agtaagtaat 2160

gtattcggac ccggaaccag gataccgaag gccgcagtgc aggtactgga cgacattgag 2220

aagtgcctcg aaaagaagca gcagtcagtg 2250

<210> 31
<211> 2250
<212> DNA
<213> Artificial Sequence

<220>
<223> Codon optimized sequence that encodes an MCM polypeptide with the I671V mutation

<400> 31
atgctgcggg caaaaaatca gctctttttg ctctcacctc actatttgcg ccaggtcaag 60

gagtctagcg gatcaaggct gattcagcag cggctgttgc atcagcagca gcctctacat 120

cccgaatggg ctgccctggc taagaagcag ctcaaaggca agaaccctga ggatttgatt 180

tggcacaccc ccgaggggat atctattaag ccactataca gtaagcggga cacaatggat 240

ctgcccgagg agctccctgg agtcaagcct tttacccgtg gaccgtaccc aactatgtac 300

actttccggc cctggacaat tcgtcaatac gcaggtttct caaccgtcga ggaatcaaat 360

aagttttaca aggataatat aaaggctgga cagcagggat tgtctgtcgc cttcgacctc 420

gccactcata gagggtacga ctccgataac ccacgtgtgc gtggcgacgt cgggatggcc 480

ggtgtggcaa tagatacagt ggaagataca aagatcctgt ttgatggcat tcctctggaa 540

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<210> 32
<211> 2250
<212> DNA
<213> Artificial Sequence

<220>
<223> Codon optimized sequence that encodes an MCM polypeptide with the I671V mutation

<400> 32
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ccagaatggg ccgccctcgc caagaaacag cttaagggaa agaaccctga ggacctgatc 180

tggcacacac ccgagggcat tagtatcaag cccctgtact cgaaaaggga tactatggac 240

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gctacccata gagggtacga tagtgacaat ccacgggtgc gcggcgacgt cggcatggct 480

ggtgttgcca tagacacagt ggaggacaca aaaatcctgt tcgatgggat ccccctggag 540

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ctcggtttcg acgtcgacat tgggccactc ttccagactc cacgggaggt ggcacagcag 1980

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aaatgtcttg agaagaagca gcaaagtgta 2250

<210> 33
<211> 2250
<212> DNA
<213> Artificial Sequence

<220>
<223> Codon optimized sequence that encodes an MCM polypeptide with the I671V mutation

<400> 33
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gagagctctg gatccagatt gattcagcag aggttgctcc atcagcagca gcctctgcac 120

ccagaatggg cagctctcgc aaagaaacaa ctgaagggca aaaaccctga agacctcatc 180

tggcatacac cagaaggcat ttcaatcaag cctctgtata gtaagcgcga tacaatggac 240

ctacccgagg agctacccgg tgtgaaacca ttcacgcggg gtccataccc cacgatgtat 300

actttcaggc cttggaccat ccggcaatac gcaggcttct ctaccgtcga agagagcaat 360

aagttctaca aagataacat taaggcagga cagcagggcc tgtcggtggc cttcgacctg 420

gctacccaca gaggctatga ctccgataac ccgcgggtgc gcggggacgt cggtatggcg 480

ggagtggcca ttgacaccgt ggaggatact aagatcctct tcgacgggat tcccctcgaa 540

aaaatgtcag tgtcaatgac aatgaatgga gcagtcatac cagtcctggc taatttcatt 600

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aagtgcctcg aaaagaagca acagagcgtg 2250

<210> 34
<211> 2250
<212> DNA
<213> Artificial Sequence

<220>
<223> Codon optimized sequence that encodes an MCM polypeptide with the I671V mutation

<400> 34
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cccgaatggg ctgccctggc gaaaaagcaa ctgaaaggca aaaaccctga ggatcttatt 180

tggcatacac ctgagggaat tagcattaag ccattgtact ctaaacgcga cacaatggat 240

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ggcgtggcga tcgatactgt agaggacaca aagattcttt ttgacggcat acctctggag 540

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atccttaagg agtttatggt gcgcaacacg tacatctttc cccctgagcc ttcgatgaag 720

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aaatgtctgg agaagaaaca gcagagcgtg 2250

<210> 35
<211> 2250
<212> DNA
<213> Artificial Sequence

<220>
<223> Codon optimized sequence that encodes an MCM polypeptide with the I671V mutation

<400> 35
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ccagagtggg ctgcattggc caagaagcag ctcaagggta agaaccctga ggatctgatt 180

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<210> 36
<211> 2250
<212> DNA
<213> Artificial Sequence

<220>
<223> Codon optimized sequence that encodes an MCM polypeptide with the I671V mutation

<400> 36
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cccgagtggg cagccctcgc gaagaaacaa ttaaaaggta aaaacccgga ggatctcatc 180

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gccacacaca ggggctatga cagcgacaac ccaagagtga gaggggatgt tggcatggct 480

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<210> 37
<211> 2250
<212> DNA
<213> Artificial Sequence

<220>
<223> Codon optimized sequence that encodes an MCM polypeptide with the I671V mutation

<400> 37
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gaaagtagtg ggagcagact catccagcag cggttgctgc accagcagca gccactgcac 120

cccgagtggg ccgcattggc caaaaagcaa ttgaagggca aaaaccccga ggacttaatt 180

tggcacaccc cagaaggaat aagcatcaaa cctctgtact caaagcgtga caccatggat 240

ttgcctgagg agctacctgg ggtgaagccc ttcacaagag ggccataccc taccatgtat 300

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aagttttaca aagataatat caaggctggt cagcagggtc ttagtgtggc cttcgatttg 420
gctacccacc gggggtacga cagcgacaac ccacgcgtcc gcggagatgt aggtatggct 480
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tgtgggggcg tgatacctcc tcaggattat gagtttctgt tcgaggtagg tgtctccaat 2160
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aagtgtctag agaaaaagca acagtctgtg 2250

<210> 38
<211> 2250
<212> DNA
<213> Artificial Sequence

<220>
<223> Codon optimized sequence that encodes an MCM polypeptide with the I671V mutation

<400> 38
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gagagcagcg gctcccggct gattcaacag cgattactac accagcagca gcccttgcat 120

ccggaatggg cagccttagc aaaaaagcag ttaaaaggga agaaccctga agacctaatc 180

tggcatacac ctgaaggaat ctcgattaag cctctttatt ccaagcggga cactatggat 240

ttgccagaag aactccctgg cgtgaagccg ttcacgcgcg ggccttatcc cacgatgtac 300

accttccggc catggacaat ccgacaatat gccggcttca gcacggtgga agagtccaac 360

aagttctaca aggataacat caaagccggc cagcagggac tgagcgtggc attcgacctg 420

gccactcacc ggggatatga ctctgataac cctagagtaa gaggcgacgt cggcatggca 480

ggcgtcgcca tagatactgt tgaagacact aagatcttgt ttgatgggat accactggag 540

aaaatgtctg tgagtatgac catgaacggc gccgttattc ctgtcctcgc taacttcata 600

gttacaggag aggaacaggg cgtccccaaa gagaagctta ccggaaccat ccagaacgat 660

attcttaaag agtttatggt gcggaatacg tacatttttc cccctgaacc tagcatgaaa 720

atcatcgcag acatctttga gtatacagct aagcacatgc ctaagttcaa ttctatcagt 780

atttcgggct accacatgca ggaggctggg gcagatgcca tcctggagct ggcctatact 840

ttagctgacg gtttagaata ctcgcgcact ggcctccagg cgggcctcac gatcgacgag 900

ttcgccccaa ggctctcatt tttttggggc attggcatga acttctacat ggagatcgcg 960

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aatagcaaaa gcctcctttt gcgggcccac tgccaaacat ccggatggtc gctgacagaa 1080

caggacccat acaacaacat cgtccggaca gctatcgaag ccatggccgc cgtgttcgga 1140

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gaggggattc ccaaactgag gatcgaagaa tgcgcagctc ggcgacaggc tcgaattgac 1440

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attaaacgag tgcacaaatt catggagcgg gaaggcagaa ggccacgctt gctagtcgcc 1860

aagatgggtc aagatggaca tgaccgcggc gccaaggtaa tagctaccgg gtttgccgat 1920

ttgggcttcg atgtggacat cgggcctctg ttccagacac ctagagaggt ggcccagcag 1980

gctgtcgatg ccgatgtcca tgcagtagga gtatcgaccc tcgcggcggg gcataagaca 2040

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tgcggtggag tcattccacc ccaggactac gaatttctgt tcgaggtggg cgtttccaat 2160

gtctttggcc ccggcactcg catccccaaa gctgccgtgc aagtcctgga tgacatagag 2220

aaatgtctgg agaagaaaca gcaatccgtc 2250

<210> 39
<211> 2250
<212> DNA
<213> Artificial Sequence

<220>
<223> Codon optimized sequence that encodes an MCM polypeptide with the I671V mutation

<400> 39
atgcttagag cgaagaacca gcttttcctg ctgtctcccc attatctcag acaagtaaaa 60

gagtcttccg gtagccggct gatccagcaa aggttattac accagcaaca gccacttcac 120

cccgagtggg cggccttagc caagaagcag ctcaaaggca aaaatcctga ggacctaatt 180

tggcacaccc cagagggcat ctccattaag cctttgtact cgaagcgcga cacaatggat 240

ttgcctgagg aattacctgg ggttaagcct tttaccaggg gaccctatcc cacgatgtac 300

acattccgac cttggacaat tcgccaatat gctgggttca gtacagtgga ggaaagcaac 360

aagttttaca aagacaacat aaaagccggt caacagggcc tgtctgtcgc attcgatctt 420

gccactcacc gcggctacga ctctgataac ccgagagtcc gcggggatgt gggcatggca 480

ggagttgcta tcgacacagt cgaagacacc aagattctgt ttgacggtat accactggag 540

aagatgtcag tttcaatgac tatgaatggc gcggtgatcc ctgttctagc aaactttata 600

gtgactgggg aggagcaggg ggtgccgaag gaaaagttaa ctggaactat tcagaacgac 660

atccttaaag aattcatggt gcgaaacacg tacatcttcc ccccggagcc cagcatgaag 720

ataatcgcag acatctttga atacaccgcg aagcacatgc ccaagttcaa ctcaattagc 780

atctcagggt accatatgca ggaagcgggg gccgatgcca tcctcgaact ggcttacacg 840

cttgcggatg gcctagagta tagtagaacc ggattacaag ctggcctcac aatagatgaa 900

tttgcccctc gtctcagttt tttctggggc atcggaatga acttttatat ggagattgct 960

aagatgcggg caggccgccg tctctgggcc cacctgattg agaaaatgtt tcagcccaag 1020

aactccaaat cactgctgtt aagggcccat tgccagacca gcggctggtc cctgaccgaa 1080

caggacccct acaataatat tgtgcgcact gccatcgagg ccatggcagc agtgttcggt 1140

gggacacaga gccttcatac caacagtttt gatgaggccc tggggttacc taccgtcaag 1200

tccgcgcgca tcgcccgcaa cacccaaatc attatccaag aagagtccgg aatacccaag 1260

gtcgcagacc catgggggg gtcctacatg atggagtgcc ttaccaatga cgtgtatgat 1320

gctgccctaa aacttattaa tgagatcgaa gaaatgggag gaatggctaa ggcagtcgcg 1380

gaaggaattc ctaaactcag aattgaagaa tgtgctgcca gacggcaagc acgtatagat 1440

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gaggtcctgg ccattgacaa cacgagtgtg cggaatcgac agattgagaa gctgaagaaa 1560

attaagagct cacgagacca ggctctggcg gagcgctgcc tggcagcact gaccgagtgt 1620

gctgcttcag gtgatggtaa tatccttgcc ctagccgtgg acgccagtcg cgcccgatgc 1680

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atcaaacgag tgcataaatt catggagaga gagggtagac ggcctagact cctggtggcc 1860

aagatgggac aggacggtca cgatcgtggt gctaaggtta tcgccacagg cttcgctgat 1920

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gctgtcgatg ctgatgtcca tgcagttgga gtaagcacac ttgcagctgg acataagaca 2040

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tgcgggggg tcatcccccc ccaggactat gaattcttgt ttgaggtggg agtgtcaaac 2160

gtcttcggtc ccggcacacg gatccccaag gctgcagtgc aggtgcttga tgatatcgag 2220

aagtgcctcg agaagaagca gcaatccgtt 2250

<210> 40
<211> 2250
<212> DNA
<213> Artificial Sequence

<220>
<223> Codon optimized sequence that encodes an MCM polypeptide with the I671V mutation

<400> 40
atgctgaggg ctaaaaacca attgttcctt ctgagccctc actatcttcg gcaggtcaaa 60

gaaagctcag gctcacgcct cattcagcag cggctgctcc accagcagca gccactgcat 120

ccagagtggg ctgcattagc aaagaagcaa ctcaaaggca agaaccctga agacttaatc 180

tggcataccc ccgaggggat cagcatcaaa cccttatatt caaagcggga tactatggac 240

ttgccggaag agttacccgg cgtcaaaccc tttacgcgcg gcccataccc tacaatgtac 300

accttccggc cctggaccat ccgccagtat gccgggttta gcaccgtcga ggaatctaat 360

aagttttata aggataacat taaagctggg caacaaggac tgtcagtcgc ttttgatttg 420

gccacacata gaggatacga ttctgataac ccacgggtga ggggtgacgt ggggatggcc 480

ggagtggcta tcgataccgt tgaggacaca aagatccttt ttgacggcat tcctctcgag 540

aaaatgtctg tcagtatgac catgaatggg gccgtcatcc ccgtgcttgc caacttcata 600

gttacgggag aggagcaggg agtgccgaaa gagaaactga ccgggactat ccagaacgac 660

attctgaagg aattcatggt gcggaatacc tacatattcc cccccgagcc aagcatgaag 720

atcattgccg acatcttcga gtatactgct aaacacatgc ccaagtttaa ttccatcagt 780

atcagtggct atcacatgca ggaggcagga gcggacgcca tcttggaatt ggcatacact 840

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tttgcgccgc gcttatcgtt cttctggggc atcggaatga atttctatat ggaaatcgcc 960

aaaatgaggg ccggtagacg cctgtgggcc catttgattg aaaaaatgtt ccagcccaag 1020

aattccaagt ccctattact aagggctcat tgtcaaacat ctggatggag tttaacggag 1080

caggacccat acaacaatat agtgcgcaca gctattgagg caatggcagc cgtgttcgga 1140

ggcactcaat cactgcatac aaatagtttc gatgaagctc tggggctccc caccgtgaag 1200

agcgccagaa ttgcccgaaa cacccagatc atcatccagg aagagtctgg catcccaaag 1260

gtagctgacc cctggggcgg cagctacatg atggaatgcc tgactaacga tgtctatgac 1320

gctgctctga agctgattaa cgaaattgaa gagatgggcg ggatggccaa agcggtggca 1380

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gaagtactcg caatcgacaa cacctcagtg cggaataggc agatcgagaa gctgaaaaag 1560

atcaaaagct ctagggacca ggccctggct gagcgttgtc tcgcagcttt aacagagtgt 1620

gccgcttcag gtgatggtaa tatccttgcc cttgccgttg acgcatcgag agctagatgc 1680

acagtgggtg agattactga tgccctaaag aaagtatttg gtgagcataa agccaatgat 1740

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aagtgtctgg aaaaaaagca gcagagcgtc 2250

<210> 41
<211> 2250
<212> DNA
<213> Artificial Sequence

<220>
<223> Codon optimized sequence that encodes an MCM polypeptide with the I671V mutation

<400> 41
atgctgcgtg cgaaaaacca gcttttcctg ttgagtccac actacctgag acaagtcaaa 60

gaatcaagcg gttccaggtt gattcagcag cggttgctcc accagcagca gccactccac 120

ccagagtggg cagcactggc aaagaagcag ttgaaaggta aaaaccctga agacctgatt 180

tggcacactc ctgaaggcat ttcaatcaaa cctctgtaca gcaagcgcga cacgatggat 240

cttcccgaag aactccccgg tgtcaaacca tttactagag gcccctaccc tacaatgtat 300

acctttcggc catggactat ccgacagtac gctggatttt ccaccgtcga ggaaagtaac 360

aagttctata aggataacat taaggccggc cagcagggac tgtcggtagc ctttgacctc 420

gcaacccatc ggggctacga tagcgataac ccaagagtga ggggagatgt gggcatggcc 480

ggtgtggcga ttgatactgt ggaagacact aagatactgt tcgatgggat tcctctcgag 540

aaaatgtcag tctccatgac catgaacggg gctgtcatac ccgtgcttgc taactttatt 600

gtgacaggcg aagagcaggg agtgcctaag gagaaactga ccggcacaat tcagaacgac 660

atccttaagg aattcatggt tagaaatacg tacatctttc ctcccgagcc tagtatgaaa 720

attatagcgg acatctttga atatactgcc aaacacatgc caaagtttaa tagcatatcc 780

atatcaggat atcatatgca ggaagcaggt gcggatgcta tccttgagct ggcatacacc 840

ctggctgatg gtctcgaata ttctagaacg ggattacagg ccggtctcac aattgatgaa 900

tttgcaccaa gattaagctt tttttgggga attgggatga atttttacat ggaaatagct 960

aaaatgcgcg cgggacgccg cctctgggcc caccttatcg agaaaatgtt ccagccgaag 1020

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caggacccct acaataacat cgtccggaca gccattgagg ccatggcggc agtcttcggt 1140

ggaactcagt cgctgcacac aaattctttc gatgaagccc tcggcctacc aactgtgaaa 1200

tctgccagaa ttgccaggaa cacccagatc attattcaag aggagagtgg gattcctaag 1260

gtcgccgacc cctggggcgg gtcatatatg atggaatgtc tcaccaatga cgtgtacgac 1320

gccgcactca agttgataaa cgagattgag gagatgggcg gcatggctaa ggctgtggcc 1380

gagggcattc ctaaactcag aatcgaggag tgtgccgccc ggcgacaggc gcgtatagac 1440

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gaggtgctgg ctatcgacaa tacctcagtg cggaatcggc agatcgagaa gctcaagaag 1560

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gtgtttggac ctggaacgcg cattccaaag gctgccgtgc aggtgcttga tgatatcgaa 2220

aagtgcctgg aaaaaaagca gcagtccgtg 2250

<210> 42
<211> 2250
<212> DNA
<213> Artificial Sequence

<220>
<223> Codon optimized sequence that encodes an MCM polypeptide with the I671V mutation

<400> 42
atgcttagag caaagaatca gttattcctg ctgagtcccc attacctgcg acaggtgaag 60

gaaagctcag gcagcagact gatccagcag cgcctgctgc accaacagca gcctctgcat 120

ccagagtggg ccgctctcgc caagaagcag cttaagggaa aaaaccctga agatctgatt 180

tggcacacac ccgaaggtat ctcaataaaa cccttgtatt ctaagcgcga tacaatggac 240

ttgccagaag aactgcctgg agtgaaaccc tttacaaggg ggccctaccc aacaatgtat 300

acatttaggc cttggacaat tagacagtac gcgggtttta gcactgtcga ggagtccaac 360

aaattctaca aggataacat caaagcgggc cagcaaggac tgtcagtggc atttgacttg 420

gccactcata gggggtatga cagtgataac cctcgggtgc gaggtgacgt gggaatggcc 480

ggggtcgcga tcgatacagt ggaagacacc aaaatcctct tcgatgggat acccctggag 540

aagatgtccg tttcgatgac gatgaacggg gccgtgatcc cagttctcgc taacttcatt 600

gtaactggcg aggaacaggg agttcccaaa gagaaactga ccggcactat tcagaacgat 660

atcctaaagg aattcatggt gcggaatacc tacattttcc ctccagagcc ctctatgaag 720

attatagcag atatcttcga gtataccgcc aaacacatgc caaaatttaa ttccatttcc 780

atctctggct accacatgca ggaggccggc gcagacgcca tcctcgagct tgcctacact 840

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ttcgcccctc gcctgtcatt cttttggggg ataggcatga atttctacat ggagatcgcc 960

aagatgcgcg ccggcagaag actgtgggca catctcatcg aaaagatgtt ccagcctaaa 1020

aactccaaga gcctgttatt aagagctcac tgccagacct ccgggtggag tctgactgag 1080

caggatcctt acaacaatat cgtcagaaca gcaatcgagg caatggccgc cgttttggg 1140

gggacgcagt ccttgcatac aaattctttc gatgaagctc tcggactgcc taccgtcaaa 1200

tccgcgagaa tcgcgcggaa cacccaaatc ataattcagg aggaatccgg aattcccaaa 1260

gtggcggacc catggggagg gagttacatg atggaatgcc tcaccaatga tgtgtatgat 1320

gcagcactca agctgattaa tgaaatcgag gaaatgggag gtatggcaaa agctgtcgca 1380

gagggcatcc ccaagctgag aatcgaagaa tgcgccgcca ggaggcaggc cagaattgat 1440

tctgggagtg aggtgatcgt gggggtgaac aagtaccagc ttgagaagga agacgcagtt 1500

gaggttctcg ccattgataa tacctcagtg cgcaaccggc agattgagaa actcaagaag 1560

attaagagct ccagggacca ggcacttgct gagcgttgcc tcgcggcact gacagagtgc 1620

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ctggtccccg agctgattaa agagctgaat tccctgggga gaccagacat cctcgttatg 2100

tgtgggggcg tgattcctcc tcaagactac gagttcctct ttgaggttgg cgtttcaaac 2160

gttttcgggc ccggcacacg gatacctaaa gcagctgtcc aggtgctaga cgatattgag 2220

aagtgtcttg aaaagaagca acagtctgtc 2250

<210> 43
<211> 2250
<212> DNA
<213> Artificial Sequence

<220>
<223> Codon optimized sequence that encodes an MCM polypeptide with the I671V mutation

<400> 43
atgcttcgcg ctaagaatca gttgtttctg ctgtcacctc actatctaag acaagtcaaa 60

gagtcatccg gctctagatt aatccaacaa cggctgttgc accagcagca acctttgcac 120

cctgaatggg ccgccttggc taaaaagcag ctaaagggga aaaatccaga agacctgatt 180

tggcatacac cagagggtat aagtattaag ccactgtatt ctaagcgcga caccatggac 240

ctccccgagg agttaccagg ggtgaagcct ttcaccagag ggccctaccc caccatgtac 300

acctttaggc cttggactat tcgacagtat gcagggttta gcaccgttga agagtctaat 360

aagttctaca aagacaacat caaagccggg cagcaaggcc tttctgtggc tttcgacctg 420

gcaacacatc gcggctacga ttctgataac ccgcgtgtga ggggcgatgt tgggatggct 480

ggcgtcgcta tcgacacggt cgaggacaca aagatcttat ttgatggaat ccctcttgaa 540

aagatgagtg tcagcatgac catgaacggc gctgtgatcc cagtactggc taactttatt 600

gtgacagggg aggaacaagg ggtgccgaaa gagaaactca caggaactat tcagaacgat 660

atcttaaaag agtttatggt gcggaacact tatattttcc cccccgaacc tagcatgaaa 720

ataattgccg acattttcga gtatactgct aagcatatgc ctaaattcaa ctctattagt 780

atcagcgggt atcacatgca ggaggccggg gcggatgcca tactggagct ggcctacacc 840

ctagccgacg gactggaata ttcacgtact ggcctgcagg ctggacttac catcgacgaa 900

tttgcacccc gactgagttt cttctgggga atagggatga atttttatat ggagattgct 960

aagatgagag ctggacgcag gctctgggcc cacctgatcg agaagatgtt tcaacctaaa 1020

aactccaaga gcttgctatt gcgagcccac tgtcaaacct cagggtggag tctgactgaa 1080

caggaccctt ataacaatat tgtgaggacc gccatcgagg caatggcagc tgtattcggc 1140

ggaacccaga gcctgcacac aaactctttc gacgaagctc tgggcctgcc aaccgtcaaa 1200

tccgccagga tagccaggaa cacccagatt attatccaag aagaatctgg tatccccaag 1260

gtcgccgatc cttggggcgg ctcttacatg atggagtgct taaccaacga tgtgtacgat 1320

gcagctttga aactcatcaa cgaaatcgaa gaaatggggg ggatggcaaa agcggtcgca 1380

gagggtattc ccaagctgcg gatcgaagag tgtgcggcaa gacggcaggc acggattgac 1440

agcggttccg aggtgatagt cggcgtgaac aaataccagt tagagaaaga agatgctgtc 1500

gaggttctgg ccatcgacaa cacaagcgtg cgcaacagac aaatcgaaaa actaaaaaag 1560

ataaaatctt ccagagacca ggctctcgcg gagcgctgcc tggccgcgtt gaccgagtgc 1620

gccgcctcgg gcgacggaaa tatcctggcc ctggccgtcg acgccagtag ggcccggtgt 1680

acagtgggag agatcaccga tgcgctgaaa aaagtttttg gggagcacaa agccaacgat 1740

aggatggtgt ccggggcgta tcgtcaggag ttcggcgaga gtaaagaaat tacctctgcc 1800

ataaagcggg ttcacaaatt tatggaaaga gaaggcagga ggcctagact gctcgtggcc 1860

aaaatggggc aggacggcca tgacagggga gccaaagtta ttgccactgg ctttgccgat 1920

ttggggtttg atgtcgacat aggcccccta tttcagaccc ctagggaagt ggctcaacag 1980

gccgtggatg ccgacgtaca cgctgtcggg gtgtccaccc tcgctgcagg ccacaagaca 2040

ttagttcctg aactgatcaa agaactgaat tcactaggcc gccccgacat tctggtgatg 2100

tgcggcggtg tgattccacc tcaggactat gaattcctct ttgaggtggg tgtctctaac 2160

gtgttcggac caggtacccg aattcctaaa gccgcagtgc aggtgctcga cgacattgag 2220

aagtgtcttg agaagaaaca gcagtcagtg 2250

<210> 44
<211> 2250
<212> DNA
<213> Artificial Sequence

<220>
<223> Codon optimized sequence that encodes an MCM polypeptide with the I671V mutation

<400> 44
atgctgagag ctaaaaatca actgtttctt ctgtcgcccc attaccttcg tcaggtaaag 60

gagagcagtg gttcccggct aattcaacag agactgctgc accaacagca acccctgcac 120

cctgagtggg cggccctggc caagaaacaa ttgaagggca agaacccgga ggacctcata 180

tggcatacac cagagggtat ctccatcaag cctctgtaca gtaagcgcga tactatggat 240

ctgccagaag aactcccagg cgtgaaacca ttcacaagag ggccctaccc caccatgtac 300

actttcaggc cgtggacaat aaggcaatat gcagggtttt ccacagtcga ggagagtaat 360

aagttctaca aggataatat taaagctggt cagcaggggc tgtctgtggc cttcgattta 420

gctacgcatc ggggatacga ttctgataac ccccgggtcc ggggcgacgt gggcatggcc 480

ggggtggcta tcgacactgt cgaagatacc aaaatcttgt tcgacgggat tccactagaa 540

aaaatgagcg tcagcatgac gatgaacggc gccgtcatac cagtgctcgc caattttatc 600

gtcactggtg aggaacaggg ggtcccaaag gagaaactta ctgggacaat ccagaatgac 660

attttaaagg aatttatggt gcgtaacacc tatatcttcc caccagagcc atctatgaaa 720

ataatcgctg acatcttcga atataccgcc aagcatatgc ccaagttcaa cagtatttca 780

attagcggct atcacatgca ggaagcaggg gccgatgcca tactggaact cgcttatacc 840

cttgctgacg ggctggaata cagtagaact ggtctgcagg caggcctcac aatcgatgaa 900

ttcgcaccac gtctgtcatt tttctggggc attggcatga atttctacat ggagatcgct 960

aaaatgaggg cagggcggag actgtgggcc catctgatcg agaaaatgtt tcagccaaag 1020

aactccaaaa gtttgctgct gcgcgcgcac tgtcagacga gtggatggtc cttgaccgag 1080

caggacccct ataataacat cgtgcgtacg gctattgaag ccatggcggc cgtgtttggc 1140

ggcacccaaa gcctgcacac taatagtttc gatgaagccc tgggcctgcc caccgtaaaa 1200

agcgcccgaa tcgcccggaa cacacagatt atcatccagg aggaaagtgg aatccctaaa 1260

gtggcagatc catggggcgg cagctacatg atggaatgcc tgacaaacga cgtgtatgac 1320

gctgccttaa agctcatcaa tgagatcgag gagatgggag gcatggctaa agccgtggct 1380

gagggcatcc ctaagctgcg gattgaagag tgtgccgcgc ggcgacaggc caggattgat 1440

agcggaagtg aagttatcgt gggtgtgaac aaatatcagc ttgagaaaga ggacgccgta 1500

gaggtcctgg ccatcgacaa taccagtgtg cgcaataggc aaattgagaa actgaagaag 1560

attaagtcta gcagggatca ggccctggcc gagcggtgcc tggctgccct caccgagtgc 1620

gcagcgagcg gagatggtaa tatactggct ctggcggtgg atgcctcgcg ggcacgatgt 1680

acggtgggcg agatcacaga tgcccttaaa aaggtgtttg gcgaacataa agccaatgat 1740

agaatggtgt ctggagcata tcgtcaggaa ttcggtgaaa gcaaagagat cacaagtgcg 1800

atcaaacgag tgcataaatt tatggaaaga gaagggcgca gaccacgtct gctggtggct 1860

aaaatggggc aggatggcca cgatcgagga gcaaaagtta tcgccacagg ttttgccgac 1920

ctggggtttg atgtagacat aggccccttg tttcagacac ctagggaggt ggcgcagcag 1980

gccgttgacg ccgatgtgca tgctgtggga gtgtccacac tcgcggccgg ccataagacg 2040

ctcgtgcccg aactgattaa agagttgaac agcctgggga ggccagacat tctcgtgatg 2100

tgtggaggcg tgattccccc acaggattat gagtttcttt ttgaggtcgg cgtgtctaat 2160

gtgttcggtc ctggtacccg gattcccaag gcagctgtgc aggtcctaga cgatatcgaa 2220

aagtgcctgg agaagaagca acaaagcgtt 2250

<210> 45
<211> 2250
<212> DNA

<213> Artificial Sequence

<220>
<223> Codon optimized sequence that encodes an MCM polypeptide with the I671V mutation

<400> 45
atgttacgag ccaagaacca gctgtttctg ctttctccgc actacctcag gcaggtgaag 60

gagagtagcg gaagcagact gatacagcag agactcttac accagcaaca gcctctccac 120

cctgaatggg ccgccctcgc aaagaaacag ctgaagggaa aaaatccaga ggacctgatt 180

tggcacactc ctgaagggat cagcattaaa ccgttgtaca gcaaacgtga caccatggat 240

ttgccagagg aactgcctgg agttaaacct tttacacgcg gcccataccc tactatgtat 300

acgttcagac catggacaat cagacagtat gccggtttct caaccgtgga ggagtccaac 360

aagttctata aggataacat aaaggccgga cagcagggtt tgtctgtagc tttcgatctg 420

gctactcaca gaggttatga cagcgacaat ccacgcgttc gcggggacgt gggcatggct 480

ggggtcgcaa tagataccgt cgaggataca aagattctct tcgacgggat ccctctggag 540

aagatgtcag tgtccatgac catgaacggt gctgttatcc ctgttcttgc taatttcatt 600

gtaaccggcg aagaacaggg cgttccaaag gagaaactga ccggaactat ccagaacgat 660

atcctcaaag agttcatggt caggaacact tacatcttcc cgcctgaacc ttctatgaag 720

attattgccg atattttcga gtacactgca aagcatatgc ctaagttcaa cagtatcagc 780

atatccggct accatatgca agaggccggc gccgacgcaa ttctcgaact ggcttacact 840

ttggctgacg gcttagagta cagcaggact ggtctccaag ccgggctgac gattgatgaa 900

tttgcccctc ggcttagttt tttctggggc atcggcatga atttctacat ggagatagcc 960

aagatgaggg ccggcaggcg gttgtgggca catctcatcg agaaaatgtt ccaacccaag 1020

aatagcaagt ccctcctact tcgagcccat tgccaaacga gtggctggtc attaaccgag 1080

caagatcctt ataataatat cgtgaggaca gccattgagg caatggcagc ggtcttcggt 1140

ggaacacaga gtctgcacac gaacagcttt gatgaagccc ttggactgcc tacggtcaaa 1200

agcgccagga tcgctcggaa cacacagatc attatccaag aggaatctgg catccccaag 1260

gtggctgatc cctggggagg ctcttacatg atggaatgcc tcacaaacga cgtctacgac 1320

gccgccctga agttgatcaa cgagatcgag gaaatggggg ggatggctaa ggcagtagcc 1380

gagggaattc ctaagcttag aatagaggaa tgcgctgccc gacgccaggc tcggatagac 1440

agtggttccg aggtcatcgt gggcgtgaac aaataccaac tcgagaagga ggacgccgtc 1500

gaggttctgg ccatcgacaa cacgtcagtt cgtaaccgac aaatcgaaaa attaaaaaaa 1560

ataaaatcta gcagggacca ggctctggcc gagcgttgcc ttgccgcact gactgagtgt 1620

gcagcctcag gcgacggaaa catactggcg cttgcagttg atgccagccg ggctagatgt 1680

accgttgggg agatcacgga cgctctcaaa aaagtgttcg gcgagcacaa ggcgaatgat 1740

cgaatggtgt ccggcgccta tcgtcaggag tttggcgagt ccaaggaaat tacctcagca 1800

atcaagagag ttcacaaatt tatggagcgc gaagggcgcc ggcctcggtt gctcgtcgct 1860

aagatgggac aggacggcca tgaccgtggc gccaaggtga ttgcgactgg ctttgcagat 1920

ctaggcttcg acgtagatat aggcccactg ttccagacgc cccgagaagt ggcgcagcag 1980

gccgtggacg ccgacgtcca cgctgtcgga gtgagtacct tggcagccgg ccacaaaaca 2040

ctggtgccag agcttattaa ggagctaaat tccctggggc ggccagacat cctcgttatg 2100

tgtggagggg tgataccgcc ccaagactat gagttcctgt tcgaggtggg ggtgagtaat 2160

gtcttcggcc ccggcacacg aattcccaaa gcagcagtgc aagtgctgga cgacattgag 2220

aaatgccttg agaagaagca acagagcgtg 2250

<210> 46
<211> 2250
<212> DNA
<213> Artificial Sequence

<220>
<223> Codon optimized sequence that encodes an MCM polypeptide with the I671V mutation

<400> 46
atgctacggg ctaaaaacca gttgtttctc ctatcccccc attatcttcg tcaagtcaaa 60

gagtccagcg ggtccagact gattcagcaa aggctgctgc accaacagca gcctttgcac 120

ccagaatggg ctgcacttgc taagaagcag ttgaagggca aaaatcctga agacctaatt 180

tggcataccc cagaaggaat cagcatcaag ccgctatatt ccaagcgaga taccatggac 240

ctcccagagg agctacccgg tgttaagcct tttacccggg gaccttatcc gacaatgtac 300

acctttcgac cttggacaat caggcagtac gccggatttt ccactgtgga agagagcaat 360

aagttctaca aggacaacat caaagccggc cagcaggggc tgtccgtggc attcgatttg 420

gcaacacacc gcggctacga tagcgataat cctagagtgc gcggcgatgt ggggatggca 480

ggcgtcgcga tagataccgt tgaggatacc aaaatcctgt tcgacggcat ccctctggag 540

aaaatgtcgg tctctatgac aatgaatgga gccgtgatcc ctgtgctcgc gaactttata 600

gtcacgggcg aggaacaggg agttccaaag gaaaaactga cagggactat ccagaacgat 660

atcttaaaag agttcatggt gcggaacacc tatatattcc cacctgagcc ctccatgaag 720

atcattgccg acatctttga gtataccgct aagcacatgc cgaagttcaa ttctatttca 780

atctccggtt accatatgca ggaggccgga gcggatgcta tcctagaact ggcatacaca 840

ttggcggacg gcctagaata ttctagaacc ggtctgcagg cagggctcac catcgatgaa 900

ttcgccccgc ggctgagttt cttctggggc attggaatga atttctacat ggaaattgcc 960

aagatgcgtg caggtcggcg cctgtgggcc catttgatcg aaaaaatgtt tcagccaaag 1020

aacagcaagt ctctgctgct gagagctcac tgccaaactt ccggatggtc cctcaccgag 1080

caggatccct acaacaatat cgtgcggacc gccatcgagg caatggctgc cgtgttcggc 1140

ggcacccaat ctcttcacac caatagtttt gatgaagcct taggactgcc aaccgtcaaa 1200

tccgcacgga tcgctcgaaa tacacaaatc ataattcagg aggagagtgg gatccctaag 1260

gtcgcagatc cctggggcgg tagttacatg atggagtgct tgaccaatga cgtctacgac 1320

gccgcactca aactgatcaa cgagatcgag gagatgggcg ggatggccaa agcagtcgct 1380

gaggggatcc ctaaactccg tattgaagag tgtgcagccc gccggcaagc tcggatcgat 1440

tctggctcag aagtcatcgt tggcgttaac aagtaccagc tagaaaaaga agatgcagta 1500

gaggtgctcg ccatagacaa tacctccgtg cgcaaccgcc aaattgagaa attgaagaag 1560

atcaagtctt ctcgcgacca ggccttggcc gaaaggtgct tagctgcatt aactgaatgt 1620

gctgcatcag gggatggtaa tatactcgct ctggcagtcg acgcgtcccg tgccaggtgc 1680

acagtggggg aaattactga cgcactgaaa aaagtgtttg gtgagcacaa ggccaacgat 1740

aggatggtct ctggtgctta tcggcaggag tttggggagt ctaaagagat aacttctgct 1800

attaagcgcg tgcataagtt catggagcgc gaaggacggc gtccccgact gctggtggcc 1860

aaaatgggac aagacggcca tgacaggggg gccaaagtga tagcaaccgg gttcgcagat 1920

ctgggcttcg acgtcgatat cggaccactt ttccagacac ctagggaggt cgctcaacaa 1980

gcagtcgatg ccgacgtcca tgcggtgggc gtgtccaccc tggctgccgg acacaaaacc 2040

ctggtgccag aattgattaa ggagctaaac tctctgggcc ggccagacat cctggtgatg 2100

tgtggcggag tgattcctcc tcaggattat gagtttctgt tcgaggtcgg ggtatctaat 2160

gtgtttgggc ccgggactcg catcccaaaa gcggctgtcc aggtgttgga cgacatagag 2220

aagtgccttg agaaaaagca gcagagcgtg 2250

<210> 47
<211> 2250
<212> DNA
<213> Artificial Sequence

<220>
<223> Codon optimized sequence that encodes an MCM polypeptide with the I671V mutation

<400> 47
atgctgcggg caaagaacca gctgtttctc ctaagccctc attacctccg ccaggttaag 60

gagtctagtg gctctaggct gattcagcaa cgcctactgc accagcaaca acccctgcac 120

cccgaatggg cggccctggc aaaaaagcag ctcaagggca agaatccaga ggatctgatc 180

tggcacacac ccgaaggcat ctccatcaag ccgctctata gcaaaagaga cactatggac 240

cttccggaag agctacccgg agttaaaccc ttcaccagag gaccttaccc caccatgtac 300

acatttaggc catggaccat ccgtcagtac gccggattct ctaccgtgga ggagtcgaat 360

aagttctaca aggataacat caaggccggg cagcaaggcc tctctgtcgc ttttgatctg 420

gccacacatc gggggtacga cagcgacaac ccacgcgtga ggggagatgt aggaatggct 480

ggcgtggcga ttgacaccgt tgaggacact aaaatcctct tcgatggcat acccctggag 540

aaaatgagcg tgtcgatgac tatgaatggt gccgtcatcc cggtcctggc taatttcatc 600

gtgaccgggg aggaacaggg cgtgcctaag gaaaaattaa ccggcactat ccagaatgat 660

attctgaagg agttcatggt caggaatacc tatatttttc ccccggaacc atcgatgaag 720

atcattgccg acatcttcga gtacacagca aagcacatgc caaagttcaa cagcataagc 780

atctccggat accatatgca ggaggccgga gctgacgcta tccttgagct ggcatacacg 840

ttggcggatg gtctggagta ttccagaaca ggcttgcagg ccggcctgac gatcgacgag 900

tttgcacctc ggctgtcctt cttttggggt attggtatga acttttacat ggagattgca 960

aagatgcgag caggtaggcg cctttgggcc caccttatcg aaaaaatgtt ccagcccaag 1020

aacagcaaga gcctactgct tagagctcac tgtcagacgt ccggatggtc tttgacggaa 1080

caggatcctt acaataacat tgtccggact gctatagagg caatggcagc cgtgttcgga 1140

gggacacaga gcctccacac caactcattc gacgaggcac ttggcctccc cacggtcaaa 1200

tccgcccgta tagccagaaa tacacagatt attattcagg aagaatcagg catccctaaa 1260

gtggccgacc cttgggggg cagttatatg atggagtgcc tgacaaacga cgtgtacgac 1320

gccgcactca agctgattaa tgagattgag gagatgggcg ggatggctaa ggctgttgct 1380

gaaggcatcc ctaagctacg catcgaggaa tgtgccgcga gacggcaagc tagaattgat 1440

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gaggttctgg ctatcgacaa tacctcagtt aggaaccgcc aaatcgaaaa gcttaagaaa 1560

atcaagtcca gccgggacca ggcattagca gaaagatgcc tagccgctct cactgaatgc 1620

gcagcgtctg gagacggtaa catcctagcc ttggcagtcg acgcctcgag agccagatgc 1680

actgttggcg aaataactga cgcgctgaaa aaggtctttg gcgagcataa ggcaaatgat 1740

cgaatggtgt caggagctta cagacaagag ttcggtgaaa gcaaggagat cacttccgca 1800

atcaagagag tgcacaaatt tatggagaga gagggccgtc ggcctcgcct gctggtggct 1860

aaaatgggac aagatggcca cgatcgaggg gccaaggtaa tcgcaaccgg ctttgccgac 1920

ctcggcttcg atgtggatat aggccctctc ttccagacac ctagggaagt ggcccagcaa 1980

gccgtggacg ccgatgttca cgccgtggga gtttccaccc ttgcagctgg acacaaaact 2040

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tgtgggggcg tcatcccccc tcaggactat gagttcctgt ttgaagtcgg agtgtcaaac 2160

gtctttggcc ccggaacaag gatcccgaag gctgctgtgc aggtcttaga cgacatcgag 2220

aagtgcctgg aaaaaaaaca gcaatccgtg 2250

<210> 48
<211> 2250
<212> DNA
<213> Artificial Sequence

<220>
<223> Codon optimized sequence that encodes an MCM polypeptide with the I671V mutation

<400> 48
atgctacgcg ccaaaaacca gctgttcctg ctgtcaccac actacctcag gcaagtgaaa 60

gaaagctccg gctctcggct catccaacag cgtctgctac accagcagca gccactgcac 120

ccagaatggg ctgccctcgc caagaagcag ctgaagggga agaatccaga ggatttgatt 180

tggcacacgc cggaagggat atccatcaag ccccttttaca gcaaacgaga taccatggac 240

ttacctgaag agttgcccgg tgtaaagcct tttactagag gcccctatcc caccatgtac 300

acgttccggc catggacaat aaggcagtac gccggctttt ccacagtgga ggagtctaat 360

aagttctaca aggacaatat taaggccggt cagcaagggc tctcagttgc ctttgatctg 420

gccacccaca gagggtacga cagcgataat ccacgtgtta gaggcgacgt cgggatggcc 480

ggcgtcgcca ttgacaccgt cgaggatacc aaaatcttat tcgacggtat tcccctggaa 540

aaaatgagcg tgtcaatgac gatgaatggg gccgtcattc ctgttttagc aaatttcatt 600

gtgactgggg aggagcaggg ggtgcctaag gagaagctca caggtaccat tcagaacgac 660

atactgaaag agtttatggt gaggaacacc tacatctttc cccccgaacc ttccatgaag 720

atcatcgcgg acattttcga gtacacagca aaacacatgc cgaagttcaa ctccatttct 780

atctctggtt atcatatgca ggaagccggc gctgacgcta tcctggaact ggcatataca 840

ctcgcagacg ggctggagta tagcaggact ggcctgcagg ccggactgac catcgacgaa 900

ttcgcaccca gactgagctt tttttggggt attggaatga acttttacat ggaaattgca 960

aaaatgaggg cagggcgtcg tctgtgggcc catctcatcg agaagatgtt tcagcccaag 1020

aatagcaagt ctctgttgct acgcgcacac tgtcagacat ccggttggtc gctgaccgag 1080

caggatccat acaacaatat tgtcagaacc gccatcgaag caatggcagc cgtatttgga 1140

ggaacacagt ctctccatac caacagcttc gatgaggcat tgggtctgcc cacagtgaag 1200

tctgccagaa ttgctcgtaa cacacagatt attatacaag aggagtccgg tattccaaaa 1260

gtggccgacc catgggggg gagctatatg atggagtgct tgaccaatga tgtgtacgac 1320

gccgcgctga aactaatcaa cgagattgaa gagatgggcg gtatggctaa agccgtcgca 1380

gaagggatac ctaaacttcg aatcgaagaa tgtgccgccc gtagacaagc tcgcatcgac 1440

agtgggagcg aggtgattgt cggcgttaac aagtaccagc ttgagaagga ggacgcagtt 1500

gaggtccttg caatcgacaa cactagcgta agaaatcgtc agatcgaaaa attaaaaaaa 1560

atcaaatcaa gccgcgacca ggcactggcg gaacgctgcc tggccgctct gactgaatgc 1620

gcagcatccg gcgacggtaa tattttagca ctcgccgtgg acgcgtctcg tgcacgctgc 1680

actgtcggag agattacaga cgccctgaag aaagtttttg gagagcacaa ggctaacgac 1740

cgaatggttt caggggccta ccgccaggaa tttggggagt caaaagagat aacctctgcc 1800

ataaagagag tccataaatt catggaaaga gagggccgtc gacccagact tctcgtcgct 1860

aaaatgggtc aggacggaca tgacagggga gccaaggtca tcgcaaccgg attcgccgat 1920

ctcggctttg acgtcgacat tggcccgctc tttcagacac cccgagaggt ggcacagcag 1980

gcggttgatg cagacgtaca cgccgtcggg gtctccacac tagccgccgg acataaaact 2040

ctggttcctg aacttatcaa ggagcttaat agtctcggga ggccggacat cttggttatg 2100

tgtgggggcg tgatacccc acaagactat gagttcctct ttgaggttgg ggtatcaaat 2160

gtgtttgggc caggcaccag aattccaaag gccgcagttc aggtactcga tgacatcgag 2220

aagtgcttgg agaaaaagca gcagtccgtc 2250

<210> 49
<211> 2250
<212> DNA
<213> Artificial Sequence

<220>
<223> Codon optimized sequence that encodes an MCM polypeptide with the I671V mutation

<400> 49
atgctgcgcg ccaagaacca gctttttctg ctgtcgcccc actatcttag gcaagtgaag 60

gaatctagcg gcagcaggct catccaacag cggcttctgc accaacagca accgctgcat 120

cctgaatggg ctgccctggc taagaaacaa cttaaaggaa agaatcccga ggatttgatt 180

tggcatacgc ccgagggcat ttctatcaag cctctgtatt ccaaacgaga cactatggac 240

ctaccagagg agcttcctgg cgttaagccc tttacccgag gaccctaccc gaccatgtat 300

actttcaggc catggaccat tcggcagtac gccgggttct ccacagttga ggagtctaac 360

aagttctata aagataatat taaagctggc cagcaagggc tcagcgtcgc ttttgatctg 420

gctacacaca gagggtatga ttcagacaat cctcgggttc ggggagatgt cgggatggcc 480

ggggtggcta tcgacacagt agaagataca aaaatcctct ttgatggcat tcctctcgaa 540

aaaatgtccg tatctatgac tatgaacggg gccgtgatcc ccgtgctggc aaatttcatc 600

gttacaggcg aagaacaggg cgtgcctaag gagaagttga caggcacgat tcagaatgat 660

atattgaagg aattcatggt gagaaacaca tacatcttcc cacccgaacc cagtatgaag 720

attatcgctg atatttttga atacaccgct aaacacatgc ccaaattcaa tagcatttct 780

atatccggct accatatgca ggaggccggg gctgatgcca ttctagagct ggcatacacc 840

ctggctgatg gactggaata cagccggaca ggactccaag caggtctgac aatagacgag 900

ttcgctcccc gcttgagttt cttctgggga ataggaatga acttctatat ggagatcgct 960

aaaatgcgtg caggaagaag actttgggcc catctaatcg aaaaaatgtt tcagccgaag 1020

aatagcaagt ccctcctgct gcgcgcacac tgccagactt ctggttggag cctgacagag 1080

caagatcctt acaacaatat cgtgagaacc gctattgagg ctatggcagc ggttttcgga 1140

ggcactcaat cactacacac aaactctttc gacgaggccc tgggtctccc gaccgtgaag 1200

tcagcccgca ttgccaggaa cacacagatc attattcagg aagagagtgg catcccaaag 1260

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gctgcgttga aacttattaa tgaaatcgag gagatgggag gcatggctaa ggccgtcgcc 1380

gaggggattc ccaagctgcg aatcgaggaa tgcgctgctc gacgccaagc ccggatcgac 1440

agcgggagcg aagtgatcgt gggagtgaac aagtatcaac tggagaagga ggatgctgtg 1500

gaagtcttag cgatcgacaa tactagcgtg aggaatcggc aaatcgaaaa actgaaaaag 1560

attaagtctt ctcgcgacca ggccctcgct gaaaggtgtc tggcagctct gactgagtgt 1620

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cgaatggtta gcggtgctta tcgccaagaa ttcggggaga gtaaggaaat aacctccgct 1800

attaagcggg tgcacaagtt catggaacgg gagggcaggc ggcctcggct cttggtggca 1860

aaaatgggac aagatggtca cgacaggggc gccaaagtaa tagcaactgg atttgctgat 1920

ctcggctttg atgtcgacat cggtccactg ttccagaccc cacgggaggt ggctcagcag 1980

gccgtggacg ctgacgttca cgccgtggga gtgtctaccc tcgccgcagg acacaagaca 2040

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tgtggcggcg tgattccccc gcaggattac gaattcttgt tcgaagttgg agtgtccaat 2160

gtcttcggcc ccggcactcg gattccgaag gcggctgtgc aggttctcga cgacatcgaa 2220

aaatgtctcg aaaagaaaca gcagtcagtc 2250

<210> 50
<211> 2250
<212> DNA
<213> Artificial Sequence

<220>
<223> Codon optimized sequence that encodes an MCM polypeptide with the I671V mutation

<400> 50
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gagagcagcg gcagcaggct gatacagcag aggttactgc atcagcagca gcccttgcac 120

cctgaatggg cagccttagc caagaaacag ctgaagggca aaaatcccga agatttgata 180

tggcatactc ccgagggaat ctccattaag ccactgtaca gcaagagaga tacaatggac 240

ctgcccgagg agctcccagg cgtgaagcct tttacgaggg ggccataccc gaccatgtat 300

acgtttcgac cctggactat tcggcagtat gcaggatttt ccaccgttga ggaatccaat 360

aaattctaca aagataacat caaagctgga cagcagggcc tcagcgtggc ttttgatctg 420

gcaacccaca gaggatacga ctcagataat cccagagtga ggggcgacgt gggcatggct 480

ggagtcgcaa tagacacagt ggaagataca aagatcctgt ttgacggtat tccactagag 540

aagatgtccg tgtcaatgac aatgaatggt gccgtgatcc ctgtcctggc taactttatc 600

gtgacgggag aagaacaggg ggtccccaaa gaaaagctta ccgggacaat ccagaacgat 660

atcctcaagg aatttatggt tcggaacaca tacatcttcc ccccagagcc ttcaatgaaa 720

attatcgccg atatttttga gtacactgct aagcatatgc caaaattcaa ttccataagc 780

atttccgggt accacatgca ggaagccggc gccgacgcca tcttggagct ggcatatact 840

ctggcagatg ggctcgaata ctccagaacc ggactgcagg ccggcctcac catcgacgag 900

ttcgccccta ggctctcttt cttttggggc atcggaatga atttctacat ggagatcgcc 960

aagatgcggg ccgggcggcg cctctgggcg catcttatcg agaagatgtt tcagcccaag 1020

aattccaagt ctctgctcct tagagcccat tgccaaacta gcggctggtc cctcacagag 1080

caggacccat ataacaatat tgtgagaaca gcaatcgaag ctatggcggc tgttttcggc 1140

ggaacccaga gcctgcatac gaattcgttc gacgaagccc taggcctccc aacagtcaag 1200

agcgctagga ttgccaggaa cacccagatt ataatccaag aggagtccgg cattccaaaa 1260

gtcgctgatc cttggggtgg atcatatatg atggaatgcc ttacgaacga cgtgtatgac 1320

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gaaggcatcc ccaagttacg gatcgaggag tgcgcagccc gtagacaagc cagaatcgac 1440

tctggctccg aagtcattgt cggggtaaac aagtatcagc tggaaaagga agatgcggtt 1500

gaggtcctgg ccatagacaa cacctccgtg cgaaacagac aaatcgaaaa gcttaagaaa 1560

atcaagagca gtcgcgatca ggccctggcc gaaaggtgcc tggcagccct taccgagtgt 1620

gcagcctccg gggacggcaa tatactggca ctggcagtgg atgccagtcg cgcacggtgc 1680

acagtcggag agatcactga cgcgttgaaa aaagtgttcg gggagcataa agctaacgac 1740

aggatggtct ccggtgctta taggcaggaa tttggtgaga gtaaagaaat aacatccgcc 1800

attaaaagag ttcacaagtt catggaacgg gagggaaggc gcccacgact cctagtggcc 1860

aaaatgggtc aggacgggca tgatcggggc gccaaggtca tcgcaacagg cttcgcagac 1920

ctgggcttcg atgtggatat tggaccgctt ttccagaccc ccagagaggt agcacagcaa 1980

gcggtggatg ccgacgtgca cgctgttgga gtatccaccc tagccgcggg tcataagacc 2040

ctggttcctg aactgattaa ggagttgaac agcctcgggc gccctgacat tctagtgatg 2100

tgcggaggcg tgatccctcc acaggactat gagttcctgt ttgaggtggg ggtctccaat 2160

gtgttcggtc ctggaacccg gattcctaaa gcagcagtgc aggtgctcga tgatattgaa 2220

aagtgtttgg agaaaaagca gcagagcgtt 2250

<210> 51
<211> 2250
<212> DNA
<213> Artificial Sequence

<220>
<223> Codon optimized sequence that encodes an MCM polypeptide with the I671V mutation

<400> 51
atgctgagag caaagaacca gcttttcttg ctctctcctc attacctgcg ccaggtgaag 60

gaaagctccg gcagcaggct gatccagcag cgtctactgc atcagcagca acccctgcat 120

cctgaatggg ctgctctggc aaaaaagcag ctgaagggta agaatcccga agaccttatc 180

tggcacaccc ccgaagggat cagcatcaag ccgttgtaca gcaagcgcga cactatggat 240

ctgcccgagg aactgcctgg cgtgaagcct tttacccggg gcccataccc taccatgtac 300

accttccgcc cctggactat tagacagtac gcaggttttt ccacggtgga ggagagtaac 360

aagttctaca aagataacat taaggcaggg cagcagggac tgagcgtggc cttcgatctc 420

gcaacccatc ggggatatga ctccgataac ccaagggttc ggggtgatgt gggtatggcc 480

ggcgtagcta tcgatacagt ggaagacaca aaaatactgt ttgatgggat cccgctggag 540

aagatgtcag tctcaatgac aatgaacggt gccgtgatcc ctgtgctcgc caacttcatc 600

gtgactggcg aggagcaagg tgtccctaag gaaaagctca ccggcaccat ccagaatgac 660

attcttaaag aattcatggt gagaaataca tacatcttcc cccctgaacc atccatgaag 720

attatcgctg atatctttga atacaccgcg aagcacatgc ccaagttcaa ttctattagt 780

atttctggat atcacatgca ggaggctggg gctgatgcca tattggagct ggcatacact 840

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tttgccccaa gactcagttt tttctggggg atcggcatga acttttacat ggaaatcgcc 960

aagatgcgtg cagggaggcg tctatgggcg catctgatcg aaaaaatgtt tcagccgaaa 1020

aatagtaaat ccctgctgct cagagcccac tgccaaacaa gcggctggtc tcttacagag 1080

caggatcctt acaataatat tgtgagaacg gctattgagg ctatggccgc tgtgttcggg 1140

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gcagccctca agctgatcaa tgagatagaa gaaatgggag ggatggctaa agctgtggcg 1380

gagggaatac ctaaattaag aatcgaagag tgcgcagccc gtagacaggc acgtatcgac 1440

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gaagtgttgg ctatagacaa tacgtccgtg cgaaaccgcc agatagagaa attaaagaag 1560

attaagtcat ccagagacca ggcccttgcc gagcggtgcc tagctgctct gactgagtgc 1620

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aagatgggtc aggatggcca tgacaggggt gcaaaagtga ttgccacggg gtttgcagac 1920

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tgcggaggcg tgatccctcc acaggactac gaattcctgt tcgaagtggg agtaagtaat 2160

gtctttggcc ccggaactcg aatcccgaaa gccgccgtgc aggtgctgga tgacattgaa 2220

aagtgcctgg agaagaagca gcagtctgtc 2250

<210> 52
<211> 2250
<212> DNA
<213> Artificial Sequence

<220>

<223> Codon optimized sequence that encodes an MCM polypeptide with the I671V mutation

<400> 52

atgctgagag ctaaaaacca gctcttcctc ctgtcacccc attacttgcg tcaggtgaaa 60

gagtccagcg ggtcccgact gatccagcag cggttactgc accagcaaca gccactgcac 120

ccagagtggg ctgcccttgc aaaaaagcag cttaagggca agaaccccga agaccttata 180

tggcacacac ctgaggggat ttctatcaag cctttgtata gcaaaagaga tactatggac 240

ctgccagaag agcttccagg cgtgaagccc ttcacccggg gcccctatcc cacaatgtac 300

accttccggc catggacaat tcgacagtat gccgggttta gcaccgtcga ggaatccaac 360

aaattctata aagataatat caaagctggc cagcaaggcc tgtctgtcgc cttcgacctt 420

gccactcaca gagggtatga ttctgataac cctcgtgtgc gtggggacgt gggcatggcc 480

ggagtcgcaa tcgacactgt agaagatacc aagattctct tcgatggtat cccattggag 540

aagatgagcg tctctatgac catgaatggc gcagtgatac cggttttagc aaacttcatc 600

gtgacaggcg aggagcaggg cgttcccaag gaaaagctca ccggtactat ccagaacgac 660

atccttaagg aatttatggt gcgaaacacc tacatctttc ctcctgaacc atccatgaaa 720

atcatcgcag atatcttcga atacactgca aaacacatgc ccaaattcaa tagcatctct 780

atatctggct atcacatgca ggaagccggg gccgacgcca tactggagtt ggcctatacc 840

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aattcaaaaa gcctcctact acgggctcac tgtcagacca gcgggtggtc tctgacggag 1080

caggatcctt ataacaatat agttagaacg gccatcgaag caatggccgc tgtcttcgga 1140

gggacacaat ctttgcatac taatagcttc gacgaggccc tcggactgcc cacagtgaag 1200

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attaaacggg tacataagtt tatggagaga gaaggaagac gtccgagatt gctggtagcc 1860

aagatggggc aggatggtca tgatcggggc gctaaagtca ttgctactgg ctttgccgat 1920

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gccgttgatg cagatgtgca cgccgtgggc gtgtctactc tggccgccgg gcataagact 2040

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gtgttcgggc ctggcactcg aatcccaaag gctgcggtcc aggtcttgga cgacatcgaa 2220

aagtgcctgg agaaaaagca acagtccgta 2250

<210> 53
<211> 2250
<212> DNA
<213> Artificial Sequence

<220>
<223> Codon optimized sequence that encodes an MCM polypeptide with the I671V mutation

<400> 53
atgttgaggg caaagaacca actgttcctg ctgtcgcccc actacctcag acaggtcaag 60

gagtcatctg ggtccaggct gatacagcag aggctgctcc accagcagca gcctttacac 120

cctgagtggg ctgcacttgc taaaaagcaa ctgaagggta agaatccgga agatctgatt 180

tggcacactc cagagggcat atctatcaaa ccactctatt ccaaacggga cacgatggac 240

ctgccggaag agctgcccgg cgtcaaaccc ttcacccgag gaccataccc gacaatgtac 300

acatttaggc cctggacaat ccgccaatac gctggattta gcactgtgga ggagagcaac 360

aaattttaca aagacaacat taaagcgggc caacaaggtc tttctgtggc atttgatctc 420

gctactcata ggggctatga ctcagataac ccacgagtaa ggggggacgt tggaatggcc 480

ggcgtggcaa tcgataccgt tgaagatact aaaatactgt ttgatggtat tccactggag 540

aaaatgagcg tgtccatgac gatgaacggt gccgtgatcc ccgtgctagc caactttatc 600

gttacgggcg aagaacaggg agttcccaag gagaaattaa ctggtactat ccaaaacgac 660

attctgaagg agtttatggt ccgcaatact tacatctttc ctcctgagcc aagcatgaag 720

ataatagccg acatcttcga gtatactgca aagcatatgc caaagttcaa ttccattagt 780

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gtgttcggtc ctggaacaag aattccaaag gcagctgtgc aagtcctaga cgatattgaa 2220

aaatgccttg agaaaaagca acaatcggtg 2250

<210> 54
<211> 2250
<212> DNA
<213> Artificial Sequence

<220>
<223> Codon optimized sequence that encodes an MCM polypeptide with the I671V mutation

<400> 54
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gagagctcag gctcccggct aattcagcag cgactcctgc atcagcagca gccactgcat 120

ccagagtggg ctgctctggc taagaagcag ctgaagggaa agaaccccga agacctgatt 180

tggcacaccc ctgaggggat tagtatcaag cctctctact cgaagagaga tactatggac 240

cttcctgagg agctgcccgg ggtcaaacca ttcaccaggg gaccatatcc taccatgtac 300

accttccggc cttggacaat taggcagtat gctggatttt ctaccgtgga ggagagtaat 360

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gccacccata gggggtatga cagcgacaat cccagggttc gcggagatgt cgggatggca 480

ggcgtggcca ttgatactgt cgaggatacc aagattttgt ttgacggaat cccacttgag 540

aagatgtccg tatctatgac aatgaatggc gctgttatcc ccgttcttgc caatttcatc 600

gtcaccggcg aggaacaggg agtgcctaag gagaaactta cggggactat ccagaacgat 660

atcctgaagg agttcatggt tagaaacact tatatattcc ctccagaacc gtcgatgaag 720

atcattgccg atatttttga atacactgcc aagcatatgc cgaaattcaa ctcaatcagc 780

atctcagggt atcacatgca ggaagcaggc gcagatgcga ttctggaatt agcatatact 840

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tttgccccca gactttcctt tttttgggga attggtatga atttttatat ggagattgct 960

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gccgccctga aattaatcaa cgaaatcgag gagatgggag gcatggctaa ggcagtggct 1380

gaaggaatac ccaagctccg aatcgaggag tgcgccgcgc ggcgacaggc gcgcattgac 1440

tctgggagcg aagtcatagt cggtgtgaat aagtaccagc tagagaagga ggacgcagtc 1500

gaggttttgg ccatcgataa cacatccgtg cgcaacagac agatagagaa attgaagaag 1560

atcaagtcct caagggatca ggctcttgcg gagcggtgcc tcgccgccct gactgagtgc 1620

gcagcatctg gcgacggcaa catcctcgcc ttggcagtgg atgcaagccg ggctcgatgt 1680

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cgcatggtga gtggcgctta cagacaggag ttcggcgagt ccaaagaaat cactagcgcc 1800

atcaaacggg tccacaagtt catggaaagg gaaggcagaa ggcctcgtct cctcgtcgcc 1860

aagatgggcc aggatgggca cgaccgcgga gccaaggtga ttgctactgg ctttgcggat 1920

cttgggtttg acgttgatat tgggccgctt tttcagactc caagagaggt tgcccagcag 1980

gctgtcgatg ctgatgtcca cgccgtgggc gttagcaccc tggctgccgg tcataagacc 2040

ctggtaccag aattaataaa ggaacttaac agccttgggc gcccggatat tctagttatg 2100

tgcggtggtg ttatccctcc ccaagactat gaattcctgt ttgaagttgg agttagcaac 2160

gtgtttggtc ctgggacaag aattcctaag gccgcggtac aggtcctcga cgatatcgaa 2220

aagtgtctcg aaaagaagca acagagcgta 2250

<210> 55
<211> 2250
<212> DNA
<213> Artificial Sequence

<220>
<223> Codon optimized sequence that encodes an MCM polypeptide with the I671V mutation

<400> 55
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ccggagtggg ccgcccttgc caaaaaacag ctcaaaggta agaacccaga ggatctgatc 180

tggcacaccc ccgaaggcat cagtatcaag cccctgtata gtaaacggga cacaatggac 240

ctgccggagg agctgccggg agtcaagccc tttactcggg gtccataccc cacaatgtac 300

acttttcggc cttggactat ccgccagtat gccgggttca gcaccgtaga agaaagtaac 360

aaattttaca aggacaatat taaagcaggg caacagggtc tgtcagtggc atttgacctg 420

gccactcaca gagggtatga ctctgataac ccccgcgtga gaggcgatgt aggcatggca 480

ggtgttgcca ttgacacggt cgaagatacg aaaatcttgt tcgatggaat ccccctcgaa 540

aaaatgtcag tgagcatgac tatgaacgga gccgtaatcc ccgtgctggc taatttcatc 600

gtaaccggcg aggagcaggg cgtccccaag gagaaactga ccggcacgat acagaatgac 660

atcctgaagg agtttatggt ccgtaacacc tacatattcc cacccgaacc gtcgatgaaa 720

attatcgctg atatatttga atacacggcc aagcacatgc ctaagttcaa ctccattagc 780

atctctggct accacatgca agaagcaggg gctgacgcca tcctggaact cgcctacaca 840

ctggctgatg gacttgaata ctctagaacc ggtctgcaag ctgggttgac gatagatgag 900

tttgctccca ggctctcatt cttctggggc ataggtatga atttctatat ggagatagct 960

aaaatgaggg ccggtaggag gctgtgggcc caccttatcg aaaaaatgtt ccaaccgaag 1020

aatagcaagt ctcttttgct gcgcgcccac tgccagacca gtggctggtc acttacagaa 1080

caggatccat acaacaacat tgtcaggact gccatcgaag ccatggccgc ggtttttgga 1140

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gaagggatcc caaagctcag aattgaggag tgtgccgctc gtcggcaagc aaggattgac 1440

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gaggtgctcg ctattgacaa taccagcgtg cggaaccgtc agatagagaa attgaagaaa 1560

ataaagtcca gccgagacca ggcgctggca gaaaggtgtc tggctgccct aacagagtgt 1620

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gccgtggacg ctgatgtgca tgcagtggga gtgtcaactt tggccgccgg acacaagacc 2040

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tgcggcgggg tgattcctcc gcaggactat gagttcctgt ttgaggtggg ggtgagcaac 2160

gtcttcggac ccggtaccag aatcccaaag gcagctgtgc aggttttgga tgatattgag 2220

aagtgtctcg agaagaaaca gcagtcggtg 2250

<210> 56
<211> 2250
<212> DNA
<213> Artificial Sequence

<220>
<223> Codon optimized sequence that encodes an MCM polypeptide with the I671V mutation

<400> 56
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gaatctagtg gaagcaggct gatccagcag cggctgctcc atcaacagca gccccttcac 120

cctgagtggg cagccctggc caagaaacag ctgaaaggaa aaaaccccga agatctgatc 180

tggcatacac cagaggggat atcaatcaag ccattgtata gcaaaagaga tacgatggat 240

cttccagaag agctgcccgg tgtcaagccc tttaccagag gcccctaccc taccatgtat 300

acttttcgtc cttggactat ccggcagtat gctggcttta gcactgtgga ggagtcaaac 360

aagttctaca aagacaatat aaaagcagga cagcaaggcc tttctgtcgc ctttgacctc 420

gccactcaca ggggctatga tagcgacaac ccaagagtaa gaggtgatgt aggcatggcc 480

ggagtggcta ttgacactgt ggaggataca aaaatcctct ttgatggcat ccctctggag 540

aaaatgtctg tgtccatgac catgaacgga gccgtgatcc ccgtcctggc aaacttcatc 600

gtcacggggg aagaacaagg cgtgccaaaa gagaagctga ccgggaccat tcagaacgac 660

attctgaaag agtttatggt tcggaatacc tacattttcc ccccagaacc atccatgaag 720

atcattgccg atatcttcga gtatactgca aaacacatgc caaaatttaa ctccattagc 780

atctccgggt accatatgca ggaagctgga gcggacgcta ttctcgagct tgcatacacc 840

cttgcggatg gactcgagta ctctcgcaca ggcctccagg ctggcctgac aatcgatgag 900

ttcgctccac ggctgagctt cttctggggg atcggaatga atttttatat ggagatagct 960

aaaatgcggg cggggcggcg tttatgggca cacctgatcg aaaagatgtt ccaacctaag 1020

aactccaagt ccttgctgct tcgagcccac tgtcagacct caggatggtc tttgaccgag 1080

caagaccctt acaataatat tgtccgtacc gctatcgagg ccatggccgc cgttttcgga 1140

ggcacgcagt cactccatac taatagcttt gatgaggctc tgggactgcc aacggtgaaa 1200

tccgcccgga tagcccgtaa tactcaaatc ataatacagg aggagtcagg aattcccaaa 1260

gtggccgacc cttggggagg aagctacatg atggaatgcc ttaccaatga cgtgtacgac 1320

gctgccctga aactgattaa tgagattgaa gagatggggg ggatggcaaa agctgttgcc 1380

gagggtatcc cgaaactgag gattgaggag tgcgctgcaa ggcgtcaggc cagaattgat 1440

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gaggtcctgg cgatcgacaa tacaagcgtt cgcaatcggc agatcgaaaa attgaagaag 1560

ataaagtctt caagggatca ggctctggca gagcggtgtc tggccgccct cactgagtgt 1620

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attaagaggg tgcataaatt tatggagagg gaggggcgcc gccctcggct gctcgtcgcc 1860

aaaatgggcc aggatggaca tgatagggga gccaaagtga tcgctactgg atttgccgat 1920

ttagggtttg acgttgatat agggccactc ttccagaccc ctagggaagt cgctcagcag 1980

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tgtggtggag tgatacccca tcaggactac gagtttttgt ttgaggttgg cgtttcgaat 2160

gtgttcgggc ccggtacacg cattcccaaa gcagctgttc aggtgctgga cgacattgag 2220

aaatgtcttg agaagaagca acaatccgtg 2250

<210> 57
<211> 2250
<212> DNA
<213> Artificial Sequence

<220>
<223> Codon optimized sequence that encodes an MCM polypeptide with the I671V mutation

<400> 57
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gaatcctccg gatccaggct tatccagcaa aggctcttgc accagcagca gccgctgcat 120

cccgaatggg cggccctcgc aaagaagcag ttaaagggca aaaaccccga agatctcata 180

tggcacaccc cggagggtat ctccataaag cccttgtatt caaagcgcga tacgatggac 240

ctgccagagg aactgccggg ggtgaagcca tttactagag ggccatatcc caccatgtat 300

accttcaggc cctggaccat ccgacagtac gctggcttct ccaccgtgga ggagagcaat 360

aaattttata aagacaacat aaaagccggc cagcaaggac tctcagttgc gtttgacctt 420

gccactcacc gtgggtacga ttccgataat cctagagtaa ggggggacgt gggcatggcg 480

ggggtggcaa ttgataccgt tgaagacact aagattttgt ttgatggcat ccctctggag 540

aagatgtccg tttccatgac tatgaacggt gctgtcatcc cagtgctggc caatttcatt 600

gtgactggcg aagagcaagg ggtacccaag gaaaagctga cgggaaccat ccagaacgac 660

atcctcaagg agttcatggt gcgcaacacc tacatctttc caccggagcc ctcgatgaaa 720

ataatcgccg acattttcga gtatactgcc aagcatatgc ctaaatttaa ttccattagc 780

atcagcggct accacatgca ggaagccggt gcagacgcca ttctggagct cgcctacact 840

ctcgctgacg gactggagta tagcaggacc ggcctccagg cgggcctgac gatagacgag 900

ttcgcaccca ggctatcatt cttctggggt atcggcatga atttctacat ggaaattgcc 960

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aattcaaaga gtctgctatt gcgggcccat tgtcagacct ctggctggtc gctgacagaa 1080

caggatccat ataacaacat tgtgcgcacc gccatcgaag ctatggcagc cgtttttgga 1140

ggaacccagt ccctgcacac aaattctttt gatgaggctc tgggcctgcc gactgtcaaa 1200

agtgcgagga tcgccaggaa cactcagatt attattcagg aggaatcggg tatcccgaaa 1260

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gaagggattc ccaaactcag gattgaggag tgcgccgccc ggagacaggc acgcatcgat 1440

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gaggtcctcg ccattgacaa tacgagcgtg cgcaacaggc agatagagaa gttgaagaag 1560

attaaatcta gccgtgacca ggcactcgcc gagcgatgcc tagcagctct tacggagtgt 1620

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tgcggcggcg tcatacctcc tcaagactac gaattcctgt tcgaagtagg agtcagcaac 2160

gtttttgggc cagggacaag gatcccaaag gcggctgttc aagttttaga tgacatcgag 2220

aaatgcctcg agaaaaaaca acagtcagtt 2250

<210> 58
<211> 2250
<212> DNA
<213> Artificial Sequence

<220>
<223> Codon optimized sequence that encodes an MCM polypeptide with the I671V mutation

<400> 58
atgctgaggg caaaaaatca actctttctt ctgtccccac actacctgcg tcaggtaaag 60

gagagttccg gtagcagatt gatccagcag agactgctcc atcagcagca gcctctgcat 120

cccgagtggg ccgctctggc taaaaaacag ctgaagggga agaatcccga ggacttgatc 180

tggcataccc ctgagggaat ctccatcaag cctctataca gcaagcggga cacgatggat 240

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gctacccatc gggggtatga cagcgataac ccccgcgtga gaggagatgt tggaatggcc 480

ggtgtggcca tagatacagt ggaagatacg aagattctct tcgatggtat cccactggaa 540

aaaatgtctg tgagcatgac catgaatgga gctgttattc cggtgcttgc taattttatt 600

gtgactggag aggagcaggg agtgccaaaa gaaaagctca cgggcacaat tcagaacgac 660

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aagtgccttg aaaagaagca acagtctgtt 2250

<210> 59
<211> 2250
<212> DNA
<213> Artificial Sequence

<220>
<223> Codon optimized sequence that encodes an MCM polypeptide with the I671V mutation

<400> 59
atgctcagag ccaaaaatca gctcttcctg ctgagcccac actacttacg tcaagtgaaa 60

gagagctctg gcagcagact gattcaacag cggcttctcc atcagcaaca gccactccac 120

cccgaatggg cagccctggc caagaaacag cttaagggga aaaatccaga ggatcttatt 180

tggcacactc cagagggcat tagtatcaag cccttatatt caaagagaga taccatggat 240

ctccccgaag agcttccggg tgttaagcct ttcacgaggg gcccataccc tacaatgtac 300

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gctacccatc ggggctatga ttcagacaac ccaagggtgc ggggcgacgt cggaatggcc 480

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aaaatgagcg taagtatgac catgaacggc gccgtgattc cggttctcgc taacttcatt 600

gtgacaggtg aggagcaagg tgtccctaaa gaaaagctca ccggaacaat tcagaacgac 660

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tgcggaggag tcattcctcc gcaagattat gaatttctgt tcgaggttgg ggtgtccaac 2160

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aaatgtttag aaaaaaaaca acagtctgta 2250

<210> 60
<211> 2250
<212> DNA
<213> Artificial Sequence

<220>
<223> Codon optimized sequence that encodes an MCM polypeptide with the I671V mutation

<400> 60
atgctaaggg ccaaaaatca acttttcctg ctgagcccgc actatttaag gcaggttaag 60

gaatcctcag gttccaggct gatacagcag cggttgctcc atcagcagca acctttgcat 120

cccgagtggg ctgctctggc gaaaaagcag ttaaaaggca aaaatccaga ggacctcatc 180

tggcatactc ctgagggcat ctctattaag cccctgtatt ccaaacgcga tacaatggat 240

cttcccgaag aattgccagg tgttaagcca ttcactaggg ggccttaccc taccatgtac 300

acgtttcggc cttggacgat ccgccagtat gcaggattta gcaccgtgga ggagtctaat 360

aaattctaca aagataacat taaagcgggc cagcaaggtc tgtccgtagc cttcgatttg 420

gccacccatc gagggtacga ttccgacaat cctcgggtgc gaggtgacgt agggatggcc 480

ggggttgcca ttgatactgt tgaggatact aaaatactct tcgatgggat ccccccttgaa 540

aaaatgagcg tgtcgatgac aatgaatggg gctgtgatcc ctgtcctggc taactttata 600

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<210> 61
<211> 2250
<212> DNA
<213> Artificial Sequence

<220>
<223> Codon optimized sequence that encodes an MCM polypeptide with the I671V mutation

<400> 61
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<210> 62
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<213> Artificial Sequence

<220>
<223> Codon optimized sequence that encodes an MCM polypeptide with the I671V mutation

<400> 62
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<210> 63

<211> 2250
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<213> Artificial Sequence

<220>
<223> Codon optimized sequence that encodes an MCM polypeptide with the I671V mutation

<400> 63
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ctgccagagg agcttcctgg tgtgaagccc ttcacacgcg gcccgtatcc tactatgtat 300

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<211> 2250
<212> DNA
<213> Artificial Sequence

<220>
<223> Codon optimized sequence that encodes an MCM polypeptide with the I671V mutation

<400> 64
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<211> 2250
<212> DNA
<213> Artificial Sequence

<220>
<223> Codon optimized sequence that encodes an MCM polypeptide with the I671V mutation

<400> 65
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ccagagtggg cggctcttgc caagaagcag ctgaagggta agaaccctga agacctaata 180

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<223> Codon optimized sequence that encodes an MCM polypeptide with the I671V mutation

<400> 66
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atcagtggct accatatgca ggaagccgga gctgacgcca tactcgaact ggcttataca 840

ctcgccgacg gtctcgaata ctccaggact ggcctacaag ccggactgac aatcgatgaa 900

tttgctccac ggttatcttt tttctggggg attggcatga acttttacat ggaaatagcc 960

aaaatgaggg ccggccggag gctttgggcc catctgatcg agaagatgtt ccagcccaag 1020

aatagtaaaa gccttcttct aagagcccac tgccagactt ctgggtggtc tctcactgag 1080

caggatccct acaataacat cgtcagaacc gctattgaag ccatggccgc cgtgtttggc 1140

ggcacccaaa gcttgcacac gaacagcttt gacgaagcac tcgggctacc gacagtgaag 1200

tccgcccgca ttgctcggaa cacccagatt attatccaag aagaaagcgg aattcctaag 1260

gttgccgatc cctggggcgg ctcatatatg atggaatgtc tgacgaatga cgtctacgat 1320

gcagcgctga agctgattaa cgagatcgaa gaaatgggag gcatggccaa ggctgtagct 1380

gagggcatac caaagctgcg cattgaggag tgcgccgccc ggcggcaggc ccgaatcgac 1440

tccggtagcg aagtcatcgt tggagttaat aagtatcagt tagaaaagga ggatgctgtg 1500

gaggtgctgg caatcgacaa taccagcgtg cggaatcgcc agattgaaaa actcaagaag 1560

atcaaatcct cccgagacca ggccttggcc gagcggtgct tggcggcctt aacagagtgc 1620

gcggccagtg gcgatgggaa cattctagca ctcgccgttg acgctagccg tgcaaggtgt 1680

acagtcggcg agatcacaga cgctttgaag aaggtgttcg gcgagcataa agcaaatgac 1740

cgcatggtgt ctggcgcata tcgccaagag ttcggagagt ctaaggaaat cacctccgcc 1800

atcaaaagag tgcataaatt catggagagg gaagggcgcc gcccacgtct gttagtggcc 1860

aaaatggggc aagacggtca tgaccgaggg gctaaagtga tagccacagg ctttgctgat 1920

ctgggatttg acgtggacat aggccccctg ttccagacgc caagggaagt cgcacagcag 1980

gctgtggatg cagacgtgca tgccgtgggg gtgtctacac tggctgccgg acataagact 2040

cttgtgccag aactgattaa ggagttaaat agtctgggac gcccagacat tctggtaatg 2100

tgtggagggg tgatccctcc tcaggactac gagtttctgt ttgaagtggg cgtgagcaac 2160

gtgttcggac ccggtacccg cattcccaag gcggcagtgc aggtgcttga tgatatcgaa 2220

aaatgccttg agaagaaaca gcagagtgtg 2250

<210> 67
<211> 2250
<212> DNA
<213> Artificial Sequence

<220>
<223> Codon optimized sequence that encodes an MCM polypeptide with the I671V mutation

<400> 67
atgttacggg ctaagaatca gctgttcctc ctctcgcccc attatctgcg ccaggtcaaa 60

gaaagctccg ggtctagatt gattcagcag agactcctgc atcagcagca gcctctgcac 120

cccgagtggg cagccctagc gaagaaacag ctaaagggca agaaccccga ggatctgata 180

tggcacactc ccgaagggat ctcgatcaag cccctctatt cgaagcggga cacaatggac 240

ctcccagagg agctccccgg agtaaagcct ttcactaggg gcccataccc aaccatgtac 300

actttccgcc cttggactat acggcagtac gccggctttt ccacagttga ggaaagcaac 360

aagttctaca aggataatat caaagccggc caacaagggt tgtccgtggc atttgacctg 420

gcgactcaca gggggtacga ctctgataat cctagggtgc ggggcgacgt tgggatggcc 480

ggggttgcga tcgataccgt ggaggacact aaaatattgt tcgacggcat cccattggag 540

aagatgagcg tgtcaatgac aatgaacgga gcagtgatac ctgttcttgc caacttcatt 600

gtgaccggtg aagagcaggg agtaccgaag gagaaactga caggcaccat ccagaatgac 660

atccttaaag agtttatggt cagaaacacc tatatattcc cacctgagcc tagtatgaaa 720

atcatagcag acatttttga atacacggcc aaacatatgc cgaagtttaa ctcaatcagc 780

atctctgggt accacatgca agaggcaggt gccgacgcta tcctggaact ggcatacacg 840

cttgcagatg gtttagaata ctccagaaca ggattgcagg ccggactcac aatcgacgaa 900

ttcgccccta gactctcctt cttctgggga attgggatga atttctacat ggaaattgcc 960

aaaatgcggg ccggccgacg cctttgggcg cacttgattg agaagatgtt ccagcctaag 1020

aactcgaagt cgttactgct cagagcgcac tgccagacat cggggtggtc tttaactgaa 1080

caggaccctt acaataatat tgtgcgcact gccattgagg ccatggcggc cgtattcggc 1140

gggacgcaat cgcttcacac caatagtttt gatgaagctc ttgggttacc taccgtgaag 1200

tccgcaagaa tcgcccgcaa tacccagatt attatccagg aggagagcgg cattccgaaa 1260

gtggccgatc catggggcgg cagctatatg atggaatgcc tcaccaatga cgtctatgat 1320

gctgctctca aacttataaa tgagatcgaa gagatgggtg gcatggctaa agccgtggcc 1380

gaaggcattc cgaaattgcg gatcgaggaa tgtgcagcga gacgccaggc tagaattgat 1440

agcggcagtg aagtaattgt cggggtgaac aagtaccagt tagaaaaaga ggatgccgtg 1500

gaggtgctgg ccatcgacaa cacttctgtt cggaacaggc aaatcgaaaa gctcaagaaa 1560

attaagtcaa gccgagatca agctctggcc gagagatgtt tggctgcctt gacagaatgt 1620

gctgcttcgg gggatggaaa catcttggct ctggctgtgg acgcaagccg ggcacgttgt 1680

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aggatggtga gcggggcgta tcgtcaagaa tttggcgagt ccaaggagat cacttcagct 1800

attaaaagag tccacaaatt tatggaaagg gaagggagga gaccgaggct actggtggcc 1860

aaaatgggcc aggatggaca tgaccggggg gctaaggtta tcgccacagg attcgctgat 1920

ttgggattcg acgtggatat cggaccactt tttcagacac ctcgcgaggt agcgcaacag 1980

gcagtggatg cagatgttca cgctgttggt gtgtctacac tggctgccgg tcataaaacg 2040

ttggttcctg agttaataaa agaactgaac tcattgggac gacccgacat cctggtgatg 2100

tgtggcggtg tcatcccccc ccaggattac gagttcctgt ttgaggtcgg ggtgtccaat 2160

gtctttgggc ccgggaccag aattcccaaa gctgccgttc aggtgttgga cgatattgaa 2220

aagtgcttag aaaaaaagca gcagtcagtg 2250

<210> 68
<211> 2250
<212> DNA
<213> Artificial Sequence

<220>
<223> Codon optimized sequence that encodes an MCM polypeptide with the I671V mutation

<400> 68
atgcttagag ccaagaatca actgttctta ctctcaccac actatctcag acaggtgaag 60

gaatcaagcg gaagtagact gattcagcaa cgactattgc accagcaaca gccactgcac 120

cccgagtggg cagcactcgc caagaagcag ctgaagggga aaaaccctga agacctcatt 180

tggcatactc cagagggcat ctcaatcaaa ccactgtatt caaaacggga cacgatggac 240

ctacccgaag agttaccagg agtgaagccg ttcaccaggg gaccatatcc cacgatgtac 300

accttccggc catggacaat tcgccagtat gccggtttct ctaccgtcga agaatcaaat 360

aagttttata aggataacat caaggccggc cagcagggac tgtctgtggc ctttgatctt 420

gcaactcacc gcggctacga ttcagataat ccccgcgtgc ggggtgacgt tggtatggct 480

ggcgtggcga tcgatacagt tgaggacacc aagatcctgt tcgacggaat ccctctggaa 540

aaaatgagcg tctcaatgac gatgaatggt gccgtgatcc cagtgctggc caacttcatt 600

gtcacaggcg aggaacaggg tgttccgaaa gagaagctga caggcaccat ccagaatgat 660

atcctgaaag agtttatggt gagaaatact tatatcttcc ctccagaacc cagcatgaag 720

attattgccg atattttcga atacacagcc aaacacatgc caaaattcaa ttcgatctct 780

atctcaggtt atcacatgca ggaggcgggg gctgatgcca tcctggaact ggcatacact 840

ttagccgacg gattggagta ctccaggact ggcctgcaag caggactaac tattgatgag 900

tttgccccaa ggttgagctt tttttggggc attgggatga acttttacat ggagatcgca 960

aagatgagag ctggcagaag actatgggcc catctgatcg agaaaatgtt tcagccgaaa 1020

aactcaaaga gcttactgtt gcgagcgcat tgccagacat ccggctggtc attgacagaa 1080

caagacccct ataacaacat cgtgcggacg gccattgagg ccatggcggc cgtgtttgga 1140

gggacacaaa gcttgcacac caacagtttc gacgaggccc tgggcctccc cacagtgaaa 1200

tcagcgcgaa tagccaggaa tacccaaatc atcatccagg aagaatctgg tatcccgaag 1260

gtggcggacc cctggggcgg atcctacatg atggagtgtc ttaccaacga tgtgtacgat 1320

gcagccctga aactcatcaa tgaaatcgaa gagatgggag gcatggccaa ggccgtggcc 1380

gaagggatcc cgaaattgag gatcgaggag tgcgccgcta gacgccaggc gcgcatcgac 1440

tccgggtccg aagtcatagt tggcgtcaat aaataccagc tggaaaaaga agatgccgta 1500

gaggttttag caattgacaa taccagtgtg aggaaccgcc agattgagaa gttgaaaaag 1560

atcaaaagct cgcgagatca ggcccttgcc gagcgctgcc tagctgccct cactgagtgc 1620

gccgcttcag gcgacggcaa cattctggct ctcgctgtcg acgccagtcg agctagatgc 1680

accgtcggtg agatcactga cgccttgaag aaggtgttcg gggaacacaa ggcaaatgac 1740

cgcatggttt caggggctta cagacaggag tttggggagt ctaaagaaat taccagtgcc 1800

ataaaacgcg tccacaaatt catggaaaga gagggaagac ggcctcggct gttagtggcg 1860

aaaatgggcc aggacgggca tgaccggggc gccaaagtga ttgctaccgg ttttgcggac 1920

ctgggctttg atgttgacat aggacctctg ttccagactc cccgcgaggt cgcacagcag 1980

gccgtagacg ccgacgtaca cgcagtcggt gtgagcacat tggctgccgg ccacaagacc 2040

ctggttcccg agttgatcaa agagctgaac agtttgggtc gacctgatat cctcgttatg 2100

tgtgggggg tgatacccc ccaggactac gaatttttgt tcgaggttgg ggtcagcaat 2160

gtgttcgggc cgggcacaag gatccccaag gcagccgtac aggttctcga cgatatcgaa 2220

aaatgtctcg aaaagaaaca acagtctgtg 2250

<210> 69
<211> 2250
<212> DNA
<213> Artificial Sequence

<220>
<223> Codon optimized sequence that encodes an MCM polypeptide with the I671V mutation

<400> 69
atgctgagag ccaaaaacca actgtttctg ctctctcctc attatctgcg ccaggtcaaa 60

gagtcatctg gaagcaggtt aattcagcag aggctgctgc accagcagca gccccttcat 120

ccagagtggg ctgctctggc taagaaacag ctgaagggta agaatccgga agacttgatc 180

tggcacaccc cagagggcat aagcattaag cctctttata gtaagcgtga tacaatggac 240

ttacctgaag aactacccgg tgtgaagcca tttacaagag gcccgtatcc tacaatgtat 300

acatttcgcc cgtggaccat caggcagtac gcgggcttca gcaccgtaga agagtcaaac 360

aaattttata aggataatat taaagccgga cagcaagggt tgtccgtggc gtttgacttg 420

gcaacacacc gcggctacga ctcagacaac cctagggtca gaggcgacgt aggcatggcc 480

ggggtggcca tcgacacggt cgaggacaca aagatcctgt tcgatggcat tcccctggag 540

aagatgagtg tctctatgac aatgaacggg gccgtgattc ccgtgctcgc aaactttatc 600

gtgacagggg aggagcaggg agtacccaaa gagaagctca ccggtaccat acaaaacgat 660

attctgaagg agtttatggt aaggaacacg tatatctttc caccagaacc atccatgaag 720

attattgctg atatttttga atacactgca aaacacatgc ccaagttcaa tagcatctca 780

ataagtggct atcatatgca agaggctggc gcagacgcca ttctggaact cgcctatacc 840

ttggccgacg gtttggagta ctcccgcacc gggctccagg ctggcctgac cattgacgag 900

tttgcgccca ggcttagttt tttctggggt attggaatga atttttacat ggagatcgcc 960

aagatgaggg caggcaggag actctgggcg catctgatag agaagatgtt ccagcctaaa 1020

aattccaagt ccctgctgct gagagcccat tgccaaacca gcggttggtc tctgactgaa 1080

caggacccgt ataataatat cgtgagaaca gctatcgaag ctatggcagc cgtcttcgga 1140

ggaacacaat ctttgcacac gaatagcttc gacgaggcac tgggattgcc cactgtgaag 1200

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gttgccgacc cttggggcgg gtcctacatg atggagtgcc tgacgaacga tgtgtatgat 1320

gctgccctca agttaataaa cgagatcgag gagatgggtg gcatggccaa agccgtggct 1380

gagggaattc ctaaactgcg gattgaagag tgcgcagcac ggagacaggc ccgaattgac 1440

tctggatctg aagtgatcgt cggagtcaat aagtaccagc tggagaaaga agatgctgtg 1500

gaagtcctgg ccatagacaa caccagcgtc cggaatagac agatcgagaa actgaaaaaa 1560

ataaagagta gcagagatca ggctcttgct gagcggtgtt tagccgctct gaccgagtgc 1620

gcagcgagcg gcgatggaaa tattctggct ctcgctgtag atgcttcaag agcaaggtgc 1680

actgtgggcg agatcactga cgcgttaaag aaggtcttcg gcgagcacaa agcgaatgac 1740

agaatggtgt ccggcgcata tcggcaagag tttggagagt ctaaggagat aacgagcgca 1800

ataaaacggg ttcacaaatt tatggaaaga gaaggccgcc gcccacgtct gctggtagca 1860

aagatgggcc aggatggcca tgaccgcggc gcaaaagtga ttgcaaccgg gttcgctgat 1920

cttggcttcg atgtggacat tgggccactg ttccagacac ctcgggaagt ggctcagcaa 1980

gcagttgatg cagacgttca cgcagtcggt gtgtccacgc tcgccgccgg acataagact 2040

ctcgtgcccg aactgatcaa agaactaaat tccttgggca ggccagacat cctggtgatg 2100

tgtggcggcg taattcctcc ccaggattac gagtttctct tcgaggtggg cgtgtccaat 2160

gtcttcggcc cagggacgcg tatccctaag gctgccgttc aggttctcga tgacatcgaa 2220

aagtgcctcg agaaaaagca gcagtcagtt 2250

<210> 70
<211> 2250
<212> DNA
<213> Artificial Sequence

<220>
<223> Codon optimized sequence that encodes an MCM polypeptide with the I671V mutation

<400> 70
atgctgcggg ctaagaatca actgtttctg ctgtcaccac attacttgag gcaggttaag 60

gaatctagcg gaagcaggtt aatacagcag aggttattgc accagcaaca acccttgcat 120

cccgagtggg ccgcgttagc caaaaagcag cttaagggca aaaatcccga ggacctgatc 180

tggcatacac cagagggcat tagtataaag ccactctatt ctaaaagaga tacaatggac 240

ctcccagagg agctgcctgg agtcaagccc tttactcggg gcccgtatcc caccatgtat 300

acattccggc cctggaccat ccggcaatat gccggattca gtactgtgga agaatcgaac 360

aaattctata aggataacat caaggccggg caacagggac tgagcgtggc attcgactta 420

gctacccaca gaggctacga cagcgataat ccaagagtcc ggggcgatgt gggtatggca 480

ggcgtggcca tcgacactgt cgaggacact aaaatcctct tcgatggaat acccctcgag 540

aagatgtcag tgtccatgac tatgaacggc gcggtgatcc cggtgctggc taactttatc 600

gtgacggggg aggagcaggg cgtgcctaag gagaaattga ccgggaccat ccaaaatgac 660

attctaaaag agttcatggt tagaaatacc tacattttcc cccctgagcc cagcatgaag 720

ataattgccg atatttttga gtatactgcc aaacacatgc caaaatttaa ctcaatcagc 780

atttcagggt atcatatgca ggaggccggc gctgatgcaa tcttagaact tgcttatact 840

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tttgctccac gcctgagctt cttttggggc attggcatga acttctacat ggagattgcc 960

aaaatgagag caggacggcg actgtgggca caccttatag agaaaatgtt ccagcccaag 1020

aattccaaat cgctactgct tagagcgcac tgtcagacct ccggatggtc gctgaccgaa 1080

caggacccgt acaataatat tgtgaggact gccatcgagg ccatggcggc tgtctttggg 1140

gggacgcaat cgctacatac gaattctttc gacgaagctc tcggcctgcc aacagttaaa 1200

tcagctcgca tcgccagaaa cacccagatc atcattcagg aggaaagcgg gattcccaag 1260

gtggctgacc cttggggagg atcatatatg atggagtgtc tgaccaatga cgtatacgac 1320

gctgcactta agctcatcaa tgagattgag gagatgggcg gcatggctaa agctgtagcc 1380

gaagggattc caaaactgag gatcgaagag tgcgccgcaa ggcgacaagc acgtatagat 1440

tctggtagtg aggttatcgt gggcgtgaat aagtaccagc tggagaagga ggatgccgtt 1500

gaggttctgg ccattgacaa cacgtctgta cgcaatagac agattgagaa acttaagaaa 1560

atcaagagca gtagagatca ggctctggct gagcgctgtc tggcggcact cactgagtgt 1620

gcggcctccg gtgacggcaa tatactggca ctggcggtgg atgcgagcag ggcacggtgc 1680

accgttggag aaattacgga cgccctcaaa aaggtgttcg gcgaacataa ggcgaatgat 1740

cggatggtga gcggtgccta ccggcaggag ttcggcgaga gcaaggagat cacgtccgcc 1800

attaagagag tccataaatt catggaacga gagggccgcc ggccaagact gctggtggct 1860

aagatgggac aggacggaca cgaccgtggg gctaaggtca ttgccacagg gtttgccgat 1920

cttggcttcg atgtggatat cggcccttta ttccaaacac ctcgggaggt ggcccagcaa 1980

gcagtggatg ctgatgtaca tgccgtgggt gtgtctacgc ttgccgccgg ccataagacc 2040

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tgcgggggag tgataccgcc tcaggactac gaatttctgt tcgaggtcgg cgtcagtaat 2160

gttttcgggc ctggcacacg cattccaaaa gccgccgtac aggtcttgga tgatattgaa 2220

aagtgcctgg agaagaagca gcagagcgta 2250

<210> 71
<211> 2250
<212> DNA
<213> Artificial Sequence

<220>
<223> Codon optimized sequence that encodes an MCM polypeptide with the I671V mutation

<400> 71
atgctgcgtg ccaagaacca attgtttctt ctgagccccc actatctcag acaggtgaaa 60

gagagctcgg ggtcacggct gatccagcag agactactgc accagcagca gcccctacac 120

cccgagtggg ctgctctggc caagaaacag ctgaagggca agaaccctga agacctgatc 180

tggcacaccc ctgaaggcat ttcaatcaaa cccttgtaca gcaagcgaga tactatggac 240

ctgccagagg agctccctgg cgttaagcct tttacacggg ggccctatcc caccatgtac 300

acattccgtc cctggaccat caggcaatat gcaggcttca gcacagttga ggagagcaat 360

aagttctaca aagacaacat caaagccggg cagcagggcc ttagcgtggc atttgatctg 420

gccacccata ggggttatga cagcgacaat ccccgtgttc gcggcgacgt gggtatggcc 480

ggcgtagcga ttgacacagt cgaggacact aagatcctat tcgacggaat cccgctggaa 540

aagatgtctg tgtctatgac catgaatggg gcagtgatcc ctgtgctcgc taacttcatc 600

gtcaccgggg aagaacaggg cgtgcccaaa gagaagctga ccggaacaat tcagaacgat 660

atcctcaaag agttcatggt gcgcaatacc tatatttttc cccctgaacc tagtatgaaa 720

attatagccg atatctttga atataccgca aaacatatgc ctaagtttaa ctccatctca 780

attagcgggt accacatgca agaagccggg gccgacgcta tcttggagct ggcatatacc 840

ttggccgacg gactggaata ttctcggacc gggcttcagg ccggtcttac cattgacgag 900

tttgcaccaa gactctcatt tttctggggc atagggatga acttctacat ggagatagct 960

aaaatgagag ccgggcgacg cctatgggcc caccttattg aaaaaatgtt tcagcctaag 1020

aattctaaat ccttgctgtt gcgggcccac tgccagacga gcgggtggag cctgacggag 1080

caggacccct ataacaacat cgtgaggaca gcaatagagg ccatggccgc agtgttcggg 1140

ggcacccaaa gcctgcacac aaactccttt gatgaggcac tcggtctccc cacagtcaaa 1200

agcgcgcgga tcgccagaaa tacccagata attattcagg aagagtcggg tattccaaaa 1260

gtggcagacc cgtggggagg gtcttatatg atggaatgcc tgactaacga tgtgtatgac 1320

gcagccttga agctgataaa tgaaatagag gagatgggtg gaatggcaaa agccgtcgca 1380

gagggtattc ccaagctccg gattgaagag tgtgccgcac gcaggcaggc tagaatagac 1440

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gaagtgctag ctatcgacaa tacaagcgtt agaaatagac agatcgaaaa gctgaaaaag 1560

attaagtcca gccgtgacca ggcactggct gagcggtgcc tggccgcact gacagagtgc 1620

gccgccagcg gagatggcaa tattctggct ctggcagtgg atgcatccag ggcacggtgc 1680

accgtgggag aaatcaccga cgccctcaag aaggtgttcg gagagcataa ggccaacgac 1740

aggatggtga gtggtgcgta tagacaggaa ttcggggaga gtaaggagat cacctcagcc 1800

ataaagaggg tccacaagtt tatggagaga gaagggagac ggccccgact gctcgtcgcg 1860

aagatggggc aggacgggca cgatcggggg gcaaaggtta ttgccactgg ctttgcagac 1920

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tgtggtggtg ttattcctcc gcaggactac gaatttttgt tcgaagtcgg cgtgagcaac 2160

gttttcgggc caggtaccag aatccccaaa gctgcagtac aggtactgga tgatattgag 2220

aagtgcctgg agaagaaaca gcagagcgtg 2250

<210> 72
<211> 2250
<212> DNA
<213> Artificial Sequence

<220>
<223> Codon optimized sequence that encodes an MCM polypeptide with the I671V mutation

<400> 72
atgctgcgag ccaaaaacca actcttcctg ctgagccctc actatcttcg gcaagttaag 60

gagagctctg gctcccgact gatccagcag agactgctcc accagcaaca accacttcat 120

ccggaatggg ccgcgctggc caagaagcag ctaaagggga agaaccccga ggacctgatc 180

tggcacactc cggaagggat tagtatcaaa cccttatata gtaagaggga tacaatggat 240

cttccggagg agttaccagg agtgaaacct tttacccgcg gcccctatcc cactatgtac 300

actttcaggc cttggacgat taggcaatat gctggatttt ccacagtgga agaatctaac 360

aagttctata aagataatat taaagcgggg cagcagggcc tgtcagtggc tttcgattta 420

gcgacacacc gcggctacga ttcagacaac ccgagagttc gaggggatgt tggaatggcc 480

ggagtggcca tagacactgt cgaggacact aagattctgt ttgatgggat ccctcttgag 540

aaaatgtctg tgagtatgac aatgaatgga gctgtgatcc ctgtgctggc gaacttcatc 600

gtcactggcg aagaacaggg tgtacctaaa gagaagctga cgggcactat ccagaacgat 660

atactgaagg agtttatggt gcgcaacact tacatcttcc caccagagcc ctctatgaag 720

atcatcgccg atatctttga gtatacagct aagcatatgc ctaaattcaa cagtatcagt 780

atatctggat atcacatgca ggaagccggt gccgacgcga ttcttgagct ggcctacacc 840

ctggccgacg ggctcgagta cagcagaacg ggtctgcaag caggactgac tatagacgaa 900

ttcgcccccc gattatcatt cttctggggt attgggatga atttttacat ggaaatagct 960

aagatgagag ctggtcggag gctgtgggcg cacttgatcg agaagatgtt tcagccaaaa 1020

aattctaagt ctctcttgtt gcgcgcgcac tgtcagactt caggatggag cctgaccgag 1080

caggatcctt acaataatat cgttcgcaca gcaatcgagg cgatggctgc tgtgttcggg 1140

ggcacccaat ccttgcacac caattccttc gatgaagctc ttgggctgcc aaccgtcaaa 1200

agcgctcgga ttgctaggaa cacacagatt atcatacaag aagagtcggg catccctaaa 1260

gttgccgatc cgtggggtgg gtcttacatg atggagtgtc tgaccaatga cgtctacgat 1320

gccgcactga aactgatcaa cgaaatcgag gaaatggggg ggatggcaaa agcggtagct 1380

gagggcatcc ccaaattgcg tatcgaggag tgcgccgcaa ggagacaggc cagaattgat 1440

tcaggaagcg aagtaatagt aggcgtcaat aagtaccaat tggaaaagga ggacgcggtc 1500

gaagtgctgg ctattgacaa cacctccgtg aggaatcgcc aaatagagaa actcaaaaag 1560

atcaaatctt ccagggatca ggccctggcc gagcgctgtc tcgccgcttt gaccgaatgc 1620

gccgcttccg gcgacggtaa catcttagcg cttgccgtgg acgcatctcg cgctcgatgc 1680

acggtgggcg aaataaccga tgcattgaag aaggtctttg gcgagcacaa ggcaaacgat 1740

cggatggtgt ctggtgccta tcgtcaggag tttggcgaat ccaaggaaat tacctctgct 1800

ataaagcgag tacacaagtt tatggagcgg gagggccgcc ggccccgact gctggttgcg 1860

aagatgggac aagatgggca tgatcgcggc gctaaagtga ttgcaactgg cttcgcagac 1920

ctgggcttcg atgttgatat aggtccactc ttccagacac cacgcgaagt tgctcagcag 1980

gcagtggacg ctgatgtcca tgccgtgggg gttagtacat tagctgctgg gcataagacc 2040

cttgtcccgg aattaattaa ggaactgaac agcctgggga ggcctgacat cctggtcatg 2100

tgcggcgggg tgatcccccc ccaggactac gagtttctgt tcgaagtggg agttagtaat 2160

gttttcggac ccgggacccg cattcctaaa gcagcagtcc aggttctgga tgatattgag 2220

aagtgtctgg agaaaaaaca gcagtccgtc 2250

<210> 73
<211> 2250
<212> DNA
<213> Artificial Sequence

<220>
<223> Codon optimized sequence that encodes an MCM polypeptide with the I671V mutation

<400> 73
atgctgagag caaaaaacca gctcttcctg ctgtcgcccc attatctgcg acaggtcaag 60

gagtcgagcg gcagtaggct catccaacag cgcctgctgc atcaacagca acccccttcac 120

cctgagtggg cagccctggc caagaagcag ctcaaaggca agaaccctga ggatctgatt 180

tggcatacac ctgagggtat ttctattaaa ccactgtact caaaaagaga cacaatggat 240

ctccccgaag agcttcccgg agtgaagcct tttactaggg gaccttaccc aacgatgtat 300

acgttcagac cctggacaat tcgtcaatat gcaggattct ccacggtgga agaatcgaac 360

aaattttaca aagataacat caaagcggga cagcaggggc tcagcgtggc gttcgatcta 420

gcgacccatc gcggatacga ctcggacaac cccagggttc gggggggacgt gggcatggcc 480

ggcgtggcca tagatacagt cgaggacacc aaaattctgt ttgacggcat ccccctggaa 540

aaaatgagtg tttcaatgac gatgaacggg gccgtcatcc ccgtactggc aaacttcata 600

gtgacagggg aagagcaggg cgtgccaaag gagaagctca cagggaccat ccaaaatgac 660

attctaaaag agttcatggt tcgaaacacc tacatcttcc cccccgagcc ttctatgaag 720

attatagctg atatctttga gtacactgcg aagcacatgc caaaattcaa ctctatctct 780

atcagtggat accatatgca ggaggcaggt gctgatgcca tcttagaatt agcctacacc 840

ttggctgacg ggctcgagta cagccgaacc ggcctgcagg ctggactcac aattgatgaa 900

ttcgctccta gactcagctt cttctgggga attggcatga atttctatat ggagatcgcg 960

aagatgcgag ctggccgcag gctctgggcc catctcatag aaaagatgtt tcaacctaaa 1020

aatagcaagt cactgttatt gcgcgcccac tgtcagacgt ccggctggag cctgacggag 1080

caggacccat acaacaatat tgtcagaaca gcaatcgaag ctatggcagc tgtgttcggt 1140

gggacacaat ctctgcatac taatagtttt gacgaggcgc tcgggttgcc cacggtcaaa 1200

tctgccagaa tagcgcgcaa cacccagatc attatccagg aagagagcgg tattcctaaa 1260

gtagccgacc cttgggggggg cagctacatg atggagtgtc tgaccaacga cgtttacgat 1320

gctgctctga aattgatcaa tgaaatcgaa gagatgggcg gaatggctaa ggctgtcgct 1380

gaagggattc ctaaattgag aattgaggag tgtgcagcca ggcgtcaggc ccggatcgac 1440

tctgggtctg aggtcattgt gggcgtcaat aaatatcagt tggagaagga ggacgccgta 1500

gaagttctgg caatcgataa caccagtgtt agaaacaggc agatcgaaaa attgaaaaag 1560

attaagtcat cacgagatca ggccttggca gaacgttgcc ttgctgcttt aaccgaatgt 1620

gccgcctcgg gggatgggaa tatcctggcc ctcgcggtag acgcatccag agcacgctgc 1680

accgttggtg aaatcacaga tgcgctgaag aaagtgtttg gcgaacataa ggcgaacgac 1740

agaatggtga gcggagccta ccgccaagag ttcggcgaat ccaaagagat tactagcgcg 1800

atcaagcgag ttcacaagtt tatggaacgg gagggcagaa ggccaagact gctggtcgct 1860

aaaatgggcc aggatgggca tgaccgtggc gctaaggtga tagctaccgg ctttgcagac 1920

cttggattcg atgtggacat aggtcctctg tttcagactc ccagagaggt ggctcaacag 1980

gcagttgatg ctgacgttca cgccgtgggc gtatcaacct tagccgccgg gcacaaaaca 2040

ctcgtccccg aattgatcaa ggaattgaat tccctaggca gaccggacat cttggtgatg 2100

tgtggcggcg tgattccccc acaggactat gaattcctct tcgaagttgg agtttccaac 2160

gtgttcggac caggaacccg tattcctaag gcagctgtac aggtcctgga tgacattgag 2220

aaatgcctgg aaaagaaaca gcaaagcgtc 2250

<210> 74
<211> 2250
<212> DNA
<213> Artificial Sequence

<220>
<223> Codon optimized sequence that encodes an MCM polypeptide with the I671V mutation

<400> 74
atgttgcggg cgaagaacca gctcttctta ttgtccccgc actacctccg acaagtaaaa 60

gaatcctctg gctcaaggct gattcaacag cgattgctcc accagcagca acctttacat 120

cccgaatggg ctgctctggc caagaagcag ctgaagggaa aaaaccctga agacctgatc 180

tggcatacac cggaggggat ttccattaag ccgctctatt cgaaacgaga cacgatggat 240

ctgcctgagg agctgcctgg ggtcaaacca tttaccaggg ggccgtaccc cacgatgtat 300

actttccggc cctggaccat aagacaatac gccggcttct ccaccgtgga agagtccaac 360

aaattttata aggataacat taaggcggga caacagggtc tgtccgtggc atttgacctc 420

gccacacatc gcggctacga ttctgacaat ccacgcgttc gcggggacgt gggcatggca 480

ggcgtcgcaa tcgacaccgt ggaagatacc aaaatcttgt ttgacggcat tccgttggag 540

aagatgtctg tcagcatgac catgaacgga gcggtgattc ccgtcctcgc caacttcatc 600

gttacaggcg aggaacaggg tgtccccaag gaaaaactga ctggcaccat ccagaatgac 660

attctaaagg aatttatggt ccgcaatacc tacatcttcc cacctgaacc gtccatgaag 720

atcatcgccg atattttcga gtataccgcc aaacatatgc ctaaattcaa cagcataagt 780

atttcaggat accatatgca agaggctggt gccgacgcga ttctggaact tgcttacact 840

ctggcggacg gcttggagta ttctcgcacc ggtctccagg cgggcctgac aattgatgag 900

tttgccccaa ggctgtcgtt tttctggggt atcggtatga acttctatat ggagatcgcg 960

aagatgaggg ccgggcggcg cctatgggca cacctgatcg aaaaaatgtt tcagcccaag 1020

aatagcaaat cactgctgct acgggcccat tgtcagacgt ctggatggtc cctcaccgaa 1080

caggacccct acaataacat agtgcgtacc gccattgaag cgatggctgc cgttttcgga 1140

ggcacccagt cccttcacac aaactccttc gatgaagccc tgggcctccc tacagtcaag 1200

tctgcccgca ttgcacgcaa tactcagatc attattcagg aagagtcagg aatccccaag 1260

gttgcagacc catggggtgg cagttatatg atggagtgtc ttacaaatga cgtctacgat 1320

gctgctctga agctaatcaa tgagattgag gagatgggag ggatggccaa ggcagtcgcc 1380

gaggggattc ccaaactcag aatcgaagag tgcgcagcaa ggagacaggc ccggattgat 1440

tccgggtccg aagtgatcgt tggtgtgaat aagtatcaac tcgaaaaaga ggatgctgtg 1500

gaggtcctgg ccatcgacaa cacctccgtc aggaatagac agatcgaaaa attgaagaag 1560

atcaagtcat ctcgcgacca agccctggca gagagatgct tagcagccct aaccgagtgt 1620

gcagcctctg gggacgggaa catcttggct cttgctgtgg atgctagcag ggcacgatgc 1680

accgtggggg agatcacaga tgccttgaag aaagtgttcg gcgagcacaa agccaatgac 1740

cgaatggtaa gcggggctta tagacaagaa tttggggaat ctaaagagat aacctcggcc 1800

atcaagcgcg tccataagtt catggagcgg gagggacgca ggccccggct gctcgtagcc 1860

aaaatgggtc aggacgggca cgatagggga gctaaggtga tcgcgaccgg ctttgctgat 1920

cttggcttcg acgtcgacat cggaccactg tttcagactc ctagagaagt tgctcaacag 1980

gccgtagacg ccgatgttca cgccgtgggg gtgagcacac tggctgccgg gcataaaaca 2040

ctcgtgccgg agctcatcaa agaacttaac tcgcttggaa gacccgatat cctagtgatg 2100

tgcgggggtg taattccccc gcaggactac gagtttcttt tcgaggttgg agttagcaat 2160

gtgtttggac ccggtacccg gatccctaaa gctgcggtgc aggttctgga cgacattgag 2220

aagtgtctcg agaagaaaca gcaaagcgta 2250

<210> 75
<211> 2250
<212> DNA
<213> Artificial Sequence

<220>
<223> Codon optimized sequence that encodes an MCM polypeptide with the I671V mutation

<400> 75
atgctgcgcg ccaagaacca gttgttcctg ctttctccac actacctgag acaggtcaag 60

gagagcagcg gatctagact catccaacag agactgcttc accagcagca gccgcttcat 120

cctgagtggg ccgcccttgc caagaagcaa ttaaaaggaa agaaccccga ggatcttatc 180

tggcatacgc ctgaaggtat ttcaatcaag cctctctata gcaaaagaga cacaatggat 240

ctccccgagg agctgccagg ggtgaaacct tttacgagag ggccctatcc aacaatgtat 300

acattcaggc catggaccat tcggcagtat gcaggctttt ccactgtgga agagagcaat 360

aaattttaca aagacaacat taaggcgggc cagcagggtt taagtgtggc cttcgattta 420

gccactcatc gcgggtacga ttcagacaat cccagagtgc ggggggacgt aggcatggcg 480

ggtgtcgcaa ttgacaccgt agaggacaca aaaattcttt tcgacgggat tccccttgag 540

aaaatgagtg ttagcatgac tatgaacggg gctgtcattc cagtgctggc gaattttatt 600

gtgaccggcg aggagcaggg ggtacccaag gagaaactga caggtaccat acagaacgac 660

attttgaaag agttcatggt gcgcaacaca tatatattcc ctcctgaacc atctatgaag 720

attatcgcgg acattttcga gtacaccgca aagcatatgc ccaagttcaa ctcaatctct 780

atttctggct atcacatgca ggaagcaggg gctgatgcga tactggagct ggcctacaca 840

ctggccgacg ggcttgaata ctcccggacc gggttgcaag caggactaac gattgatgaa 900

tttgcgccga gactatcttt cttttgggga attggtatga atttctacat ggagatcgcc 960

aagatgcgcg cgggcagacg cctctgggcc cacctgatag agaaaatgtt ccaaccaaag 1020

aatagtaagt ccctgctgtt gagggcccac tgtcagacct ccggatggag tctgaccgag 1080

caggacccat ataacaacat tgtgagaacc gcaatagaag ccatggccgc agtcttcggt 1140

ggcacacaat ccctgcatac caactctttt gacgaagctt taggtctacc aaccgtcaag 1200

tctgctcgca tcgccaggaa cactcaaata atcatccagg aagagtcggg aattcctaaa 1260

gtggccgacc cgtggggtgg gtcatacatg atggaatgcc tcaccaatga tgtgtatgac 1320

gctgctctta aactgataaa cgagatcgag gaaatgggcg gaatggctaa agccgtggcg 1380

gaaggtatac cgaaactcag gatcgaagaa tgtgcagctc ggcggcaggc taggatcgac 1440

tctggctcag aggtgatcgt tggagtgaac aagtatcagc tagagaagga agatgctgtc 1500

gaagtgctcg caattgacaa cacaagcgta cgtaatagac agatcgaaaa actcaaaaaa 1560

atcaaaagct ctcgagacca ggctctcgcc gaaagatgcc tcgctgcact caccgaatgc 1620

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agaatggtaa gtggcgcgta tcggcaggaa tttggagaat ctaaggagat tacatcagca 1800

attaaacgcg tccataagtt catggaaagg gagggaaggc gcccaagact cctggtggca 1860

aaaatgggcc aagacgggca cgatcgaggc gctaaagtga ttgccaccgg gtttgctgat 1920

cttggctttg atgttgacat aggccctctg tttcaaaccc cgcgcgaggt tgctcagcag 1980

gctgtcgacg cagacgttca cgctgtcggc gtatccactc tcgctgccgg tcacaaaact 2040

ctggtccccg agttgataaa ggaactgaac tccctcggaa gaccagacat actggtgatg 2100

tgtgggggcg tcattccacc acaggattat gagtttctgt ttgaagtggg tgtgtctaac 2160

gttttcggac ccggaaccag gataccgaag gccgccgttc aagtattgga cgacattgag 2220

aaatgtctgg aaaaaaagca acaaagcgtt 2250

<210> 76
<211> 2250
<212> DNA
<213> Artificial Sequence

<220>
<223> Codon optimized sequence that encodes an MCM polypeptide with the I671V mutation

<400> 76
atgctgaggg caaaaaatca actgttcctg ttgagccccc actatttgcg tcaagtgaaa 60

gaaagctccg gctcccgctt aatccaacag cggttgcttc atcaacagca acccttgcac 120

cccgaatggg ccgcccttgc taagaaacag ctgaagggga aaaacccaga agacctgatt 180

tggcacaccc ccgaagggat tagtattaaa cctctttaca gcaagaggga cacaatggat 240

ttacctgaag agcttcctgg ggtcaagcct tttaccaggg gaccatatcc aacaatgtac 300

acttttaggc catggacaat tcgacaatat gctgggttca gcactgtgga ggagtctaat 360

aagttctaca aagataacat taaagcagga cagcaaggac tcagtgtcgc attcgattta 420

gctacccatc gaggctacga ctccgacaat ccaagagttc gcggcgacgt aggcatggcc 480

ggtgtcgcga tcgacactgt agaagatacc aagatactgt tcgacgggat tccattggaa 540

aaaatgtcag tcagcatgac aatgaacggc gccgtgattc ccgtgcttgc aaactttatt 600

gttacgggtg aggaacaggg agttcccaaa gagaaactga cgggcacaat tcagaatgat 660

atcttgaaag agttcatggt aagaaataca tatatctttc caccagaacc ctctatgaaa 720

attatagcgg acatttttga gtacaccgct aagcatatgc ctaagtttaa ttctatctcc 780

atcagcgggt accacatgca ggaggccgga gccgacgcca tcctcgaatt ggcctacacg 840

ctggcagacg gattggaata ttcccgaacc ggactccaag ctggcctcac aatagatgag 900

ttcgctcccc gcctttcatt tttttggggt atcggaatga atttttacat ggagatcgcc 960

aaaatgaggg ccggtagacg gctgtgggct catctgatcg aaaagatgtt ccagcctaag 1020

aatagcaagt ctctcctttt acgggcacac tgtcagacga gtggatggag tttgacagag 1080

caggatccct acaacaacat cgtgcgaacc gccattgagg ccatggccgc cgtgttcggg 1140

ggaacccaga gcttgcatac caactccttt gacgaagctc tgggcctgcc cacagtgaag 1200

agcgcccgca tagcacgcaa cacacagatt ataatccagg aagagtcagg cattcctaag 1260

gtcgcagatc cctggggtgg ttcttatatg atggaatgtc tgacaaacga cgtctacgac 1320

gctgccctaa agttgatcaa cgagatcgag gagatggggg gcatggcaaa ggcagtcgcc 1380

gaggggatcc ctaagctgag aatcgaagag tgcgccgcac ggaggcaggc ccgaattgac 1440

tcagggtctg aagtgattgt gggcgtaaac aaataccaat tggagaagga agacgctgta 1500

gaagtgcttg ctatcgataa taccagcgtg cgcaaccggc agatcgaaaa gctgaaaaaa 1560

attaaatctt cgcgtgacca ggctctggca gagcgatgtc tcgctgcgct tacagaatgc 1620

gccgccagcg gagatggaaa tatcctggca ctggccgtcg acgccagtag ggcccggtgc 1680

acggtgggag aaatcacaga cgctctgaag aaggtttttg gagagcacaa ggcgaatgat 1740

agaatggtct caggcgctta ccgtcaagag ttcggtgagt ccaaggagat cacctccgcc 1800

attaaacgag tccacaagtt catggaacga gaaggccgtc gtccccgact gctggtcgcc 1860

aagatggggc aggacggaca cgaccgcggt gccaaggtta tcgccacagg cttcgccgac 1920

ctggggtttg atgtggatat cggacccctg ttccagactc cgagggaagt tgctcaacaa 1980

gcagtggatg ctgacgttca tgccgttggt gtgtcgactc tcgcagcggg gcacaaaacg 2040

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tgcggcggcg tgattccccc tcaggattac gagtttctct tcgaggtggg tgtcagtaac 2160

gtgtttgggc cgggaactag aattcccaaa gcagctgtgc aggtgctgga tgatatcgag 2220

aaatgccttg aaaaaaagca gcagagcgtg 2250

<210> 77
<211> 2250
<212> DNA
<213> Artificial Sequence

<220>
<223> Codon optimized sequence that encodes an MCM polypeptide with the

I671V mutation

<400> 77

atgcttaggg caaagaacca gctgttcctt ctgtcccccc actatcttag acaggtaaag 60

gagagctcgg ggtcacggct gatccagcag aggctcctgc accaacagca gcctctgcac 120

ccagaatggg ccgccctggc caaaaagcaa ctgaagggca aaaatccgga agacctgatt 180

tggcacaccc ccgagggtat tagcataaaa cccttgtaca gcaaaagaga taccatggac 240

ttaccagaag agttaccggg cgtgaaaccg ttcacccggg gaccctatcc cacaatgtac 300

accttccgtc catggacaat ccgccagtat gccggattca gcaccgtaga ggagagcaac 360

aagttttata aagacaatat caaggccggc caacagggac tctctgttgc gttcgacctt 420

gccacccacc ggggctacga ctcggacaac cctagggtcc gaggtgatgt tggcatggct 480

ggtgtggcca tcgacacggt tgaagatacc aagatcctgt tcgatggaat acctctcgag 540

aagatgtctg tttcaatgac gatgaacggc gcggttatcc cggtgttggc caatttcatt 600

gtgaccggtg aggaacaagg ggtccccaag gaaaagttaa caggcacaat ccaaaatgat 660

atcctcaaag aattcatggt gcgcaatacc tacatctttc cgccagaacc ttcaatgaaa 720

attatcgcag acatctttga atacaccgcc aagcacatgc ctaagttcaa ttctatatca 780

attagtgggt atcacatgca ggaagccggt gcagacgcta tattagagct tgcctacacc 840

ctcgccgatg gcctggagta ttctcgcacg ggtttgcagg ccggcctgac aattgacgag 900

tttgccccta gactaagctt tttctgggga atcgggatga atttctacat ggagatagcg 960

aaaatgcggg ctggaagacg gctctgggcc cacctcatcg aaaagatgtt ccagccaaaa 1020

aattcgaagt ctcttttact gagagcacat tgtcagacta gtgggtggag tctgaccgag 1080

caggatccgt acaacaacat cgtgagaact gccattgaag ctatggccgc agtgtttggg 1140

ggtacccagt cccttcacac caattccttt gacgaggctc tcggcctgcc aactgtgaag 1200

tctgccagga tcgctcgaaa tactcaaatt atcattcagg aggagagcgg aattcccaag 1260

gtggccgatc catggggagg ttcgtacatg atggaatgtc tgactaacga cgtctacgat 1320

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gaaggcatac ctaagcttag gattgaagag tgcgcagcaa gacggcaggc tagaatagat 1440

agcggaagtg aagtgatcgt tggggtgaac aaataccagc tcgaaaaaga agatgccgtt 1500

gaagtgctgg caattgacaa taccagtgtc cgaaataggc aaattgagaa acttaaaaag 1560

atcaagtcct ctcgggatca ggccctggcc gagcgatgtc tggcggctct cacagagtgt 1620

gccgcatccg gagacgggaa catccttgct ctggctgttg atgccagcag ggccagatgt 1680

actgtagggg agatcactga cgcccttaag aaggtcttcg gggaacataa ggctaatgac 1740

aggatggtct caggagccta tcgacaagag tttggagagt ctaaggagat aaccagtgct 1800

atcaagagag ttcacaaatt tatggagagg gaaggtcgcc gccctaggct tctggtggcc 1860

aaaatgggac aggatgggca cgatcggggc gctaaggtga ttgctaccgg gtttgccgat 1920

ctgggttttg atgtcgatat cgggcccctc ttccaaacac caagggaggt tgcccagcaa 1980

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tgtgggggag tgattccgcc tcaggactac gagttcctgt ttgaagtggg tgtctccaat 2160

gtctttggac ccggaacccg gatacctaag gccgcagtgc aagtgctaga cgacatagaa 2220

aagtgtttag aaaagaagca gcagtctgtc 2250

<210> 78
<211> 2250
<212> DNA
<213> Artificial Sequence

<220>
<223> Codon optimized sequence that encodes an MCM polypeptide with the I671V mutation

<400> 78
atgctaagag caaaaaatca gctcttccta ctgtccccac actacctgag gcaggttaag 60

gagtcttcag gctctagact cattcaacag cgcctcctcc atcaacaaca gccccttcat 120

cctgagtggg ccgcattggc gaaaaagcag ctcaaaggaa aaaatccaga ggacctgatc 180

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aagatgagtg tctctatgac catgaacgga gccgttatcc ctgtgctcgc caatttcatc 600

gtcaccggag aagaacaggg cgttcccaaa gagaagctga ccggaactat ccaaaatgat 660

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<210> 79
<211> 2250
<212> DNA
<213> Artificial Sequence

<220>
<223> Codon optimized sequence that encodes an MCM polypeptide with the I671V mutation

<400> 79
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cctgagtggg ccgccctcgc taagaagcag cttaaaggaa agaatcctga ggacctgatt 180

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aaattctaca aggacaatat caaggcgggt cagcagggcc tgtcagtggc atttgacctg 420

gcgacacaca ggggatacga ttcggataac ccccgggtta gaggtgacgt tgggatggcg 480

ggggtggcca tcgacacagt cgaagataca aaaatcctgt ttgacggtat accattagaa 540

aaaatgagcg tgagtatgac tatgaacgga gctgtaatcc ccgtgctcgc aaacttcatc 600

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caagacccct ataacaacat tgtacggacc gcaatcgaag cgatggcagc cgtgtttggc 1140

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aaatgtctgg agaagaagca acaatcagtt 2250

<210> 80
<211> 2250
<212> DNA
<213> Artificial Sequence

<220>
<223> Codon optimized sequence that encodes an MCM polypeptide with the I671V mutation

<400> 80
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cctgagtggg ctgcgcttgc aaagaagcag ctaaagggca agaatcccga agacctcatc 180

tggcataccc ctgaagggat atctatcaaa cccctctata gtaaaagaga tacaatggat 240

ctccccgaag agttgcccgg cgtcaagcct ttcactagag gcccctatcc gaccatgtac 300

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gccacacacc ggggctacga cagtgataat ccccgggtaa gaggcgacgt gggtatggcc 480

ggcgtagcca ttgacaccgt ggaggacacc aagattcttt ttgatggaat tcctctagag 540

aagatgagcg tgagtatgac catgaatggg gccgtgattc cagttctggc aaatttcatt 600

gtgaccggag aggaacaggg ggtgcctaag gaaaagctca cggggacgat ccaaaatgac 660

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aagtgcttgg agaagaaaca gcagtccgtg 2250

<210> 81
<211> 2250
<212> DNA
<213> Artificial Sequence

<220>
<223> Codon optimized sequence that encodes an MCM polypeptide with the I671V mutation

<400> 81
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gaaagctcag gaagtaggct gattcagcag cgcctcctgc atcagcagca acccctgcac 120

ccagaatggg ccgcactggc taagaagcaa cttaaaggaa agaatcccga ggacctgatc 180

tggcacaccc ccgaaggaat tagtatcaaa ccactgtatt ccaagcggga caccatggac 240

ttgccggagg agctgcctgg agttaagcca ttcacgagag gcccttaccc tactatgtat 300

acgttcagac cttggaccat ccgacagtac gctggctttt ctaccgtgga agagtccaac 360

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gcgacacacc ggggctacga ttctgataat ccgcgggtcc gtggcgatgt cggaatggcc 480

ggggtggcta ttgacacagt tgaggacact aagattcttt ttgacggcat cccacttgaa 540

aaaatgtccg tttctatgac tatgaacggg gccgtcatac cagtcctggc aaatttcatc 600

gtgaccggcg aggaacaggg cgtgcctaaa gagaagctca ctggtacgat ccaaaatgac 660

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aaatgcctag agaaaaagca acagtccgtg 2250

<210> 82
<211> 2250
<212> DNA
<213> Artificial Sequence

<220>
<223> Codon optimized sequence that encodes an MCM polypeptide with the I671V mutation

<400> 82
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gagtctagcg gaagtcggct tatccagcaa aggttgctgc accagcagca gcctctgcac 120

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<210> 83
<211> 2250
<212> DNA
<213> Artificial Sequence

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<223> Codon optimized sequence that encodes an MCM polypeptide with the I671V mutation

<400> 83
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cctgaatggg ctgcactggc aaagaagcaa ttgaagggga aaaatcctga ggatttgatc 180

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tgcggcgggg ttattccacc tcaggactac gagtttttat tcgaagtggg ggtatctaac 2160

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aagtgcctgg agaagaagca acagtctgtt 2250

<210> 84
<211> 2250
<212> DNA
<213> Artificial Sequence

<220>
<223> Codon optimized sequence that encodes an MCM polypeptide with the I671V mutation

<400> 84

atgctcagag cgaaaaacca gcttttcctc ctttctccgc actatctgcg acaggtcaaa 60

gaaagttctg ggtctcgtct gattcagcaa cgcctactgc accagcagca gccactgcac 120

cccgagtggg cagcgcttgc caagaagcag cttaagggaa aaaacccaga ggatctgatc 180

tggcacaccc ccgagggaat tagcataaag cctctgtatt ccaagcggga tacaatggac 240

ctccctgagg agcttcccgg cgtgaagcca ttcacccgtg ggccctatcc gaccatgtac 300

actttcagac cctggaccat tcgacagtat gctgggttca gtaccgtaga agagagtaac 360

aagttttata aggacaatat caaggccggc cagcagggcc tatccgttgc ctttgatctg 420

gcgacgcacc ggggctatga cagcgacaac ccaagggtcc gcggggacgt gggaatggcc 480

ggtgtcgcca tcgatacagt cgaagacacc aaaattctgt ttgatggcat tcctctggaa 540

aaaatgtctg tgagtatgac tatgaacggg gccgtgatcc ccgttcttgc taactttatt 600

gtaacggggg aggagcaggg cgtaccaaaa gaaaagctca cagggactat tcagaacgac 660

atccttaaag agtttatggt aagaaatact tatatctttc ctcctgagcc ttcgatgaag 720

ataatcgccg acatttttga gtatactgca aagcacatgc ctaagtttaa ttccatcagt 780

atcagcggtt atcatatgca ggaggctgga gctgacgcca ttctagaact tgcctacacc 840

ctggccgatg ggttggagta cagtaggaca ggtttgcagg ctggcttaac aatcgatgaa 900

tttgccccta ggctgtcctt cttctggggc ataggcatga acttttacat ggagatagct 960

aaaatgcgcg ctggcagaag gctgtgggcc catctgattg agaagatgtt tcaaccaaag 1020

aacagtaaga gcctactctt gcgggcccac tgccagactt cgggctggag cctgacagag 1080

caggacccct acaacaacat cgtccgcact gccatcgaag ctatggccgc tgtattcggc 1140

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gttgctgacc cgtggggagg ctcctacatg atggaatgcc tgaccaacga cgtttatgat 1320

gctgcactca agttgatcaa cgaaatcgaa gagatgggcg gaatggctaa agctgtggcc 1380

gagggcattc cgaagcttag aatagaggaa tgcgccgcca gacggcaggc ccgtatcgac 1440

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gaagtcctgg caatagacaa tacaagcgtt cggaacagac agattgagaa actaaaaaag 1560

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cgtatggtga gcggggccta ccggcaagag ttcggggaga gcaaagagat aacgagcgca 1800

attaaaaggg tgcataagtt tatggagagg gaaggtcgcc ggccgagact gctggtagcc 1860

aaaatggggc aggacggcca tgatcgaggc gctaaagtga ttgctaccgg cttcgctgat 1920

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gctgttgatg cggacgtgca cgctgtaggc gtgtcaacat tagctgctgg acacaagact 2040

ctcgtgcccg aactgatcaa ggagcttaat tcattgggaa ggcccgatat ccttgtcatg 2100

tgcggaggag tgattccccc ccaagattac gaatttctct tcgaggtagg agtcagtaac 2160

gttttcggac cagggacgag aatccccaag gctgccgtgc aggtgttgga tgatattgag 2220

aagtgcctcg aaaagaagca gcagagcgta 2250

<210> 85
<211> 2250
<212> DNA
<213> Artificial Sequence

<220>
<223> Codon optimized sequence that encodes an MCM polypeptide with the I671V mutation

<400> 85
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gaatcctccg ggagcagact gatccagcag agactgcttc accagcaaca acctctgcac 120

ccagagtggg cggcgctcgc taagaagcag ctgaaaggta agaaccccga agatctgatc 180

tggcacaccc cggaggggat ctccattaag cctctttatt ccaaacggga caccatggat 240

ttgcctgaag aactgcccgg tgtcaagcca ttcactcggg ggccctaccc taccatgtac 300

acattccggc cttggactat ccgacagtac gcagggtttt ccaccgttga ggaaagcaat 360

aaattctata aggataacat caaagccggt cagcaaggcc tctccgtcgc ttttgatctc 420

gccacacatc gcgggtatga ttcagataat ccacgagtca ggggggatgt cgggatggca 480

ggagtcgcta tagatacagt cgaagatacc aagatattgt ttgacggtat tcctcttgaa 540

aagatgtcag tttctatgac gatgaatggt gccgtcatac cagtactggc aaatttcatt 600

gtaactgggg aggaacaggg agtgcccaag gaaaagctta ctggcacaat tcagaatgac 660

atccttaaag aatttatggt gcggaacacc tatatctttc cacctgaacc cagtatgaaa 720

attatcgctg atatctttga atatactgcc aaacacatgc caaagttcaa ctctatatct 780

atcagcggtt atcatatgca ggaagccgga gccgatgcga ttctggaact ggcctacacc 840

ttggctgatg gcctggaata ctctcgcact ggtctgcaag ctggcttgac aattgacgag 900

ttcgccccac ggttgtcctt tttttggggc attggaatga atttttacat ggaaatcgcg 960

aaaatgcgcg ctggcaggcg gctctgggcc caccttattg agaagatgtt ccagccaaaa 1020

aattcgaagt ccctgctgtt gcgagcccac tgccaaacaa gtggatggag tctcactgag 1080

caagaccctt acaataacat cgtccggaca gctatcgagg cgatggctgc cgtgttcgga 1140

gggacccagt ctcttcatac aaactctttt gacgaggccc tgggactccc cactgttaag 1200

agtgctcgca ttgctcggaa cactcaaatc atcatccaag aggaatccgg tatccccaaa 1260

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gagggaattc cgaagctgcg catcgaggag tgtgcggcca ggagacaggc ccggatcgac 1440

agcggaagtg aagtgatagt gggcgtcaat aagtatcagc tagagaaaga agacgccgtg 1500

gaggttctag ctatcgacaa cacgtccgtg cgtaacaggc agattgagaa actcaagaaa 1560

attaagagct cccgcgatca ggccttggct gagagatgct tagccgccct gactgaatgt 1620

gctgcctccg gggacggtaa tatcctcgcc ctcgctgttg atgcttcaag ggcgcgttgc 1680

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aaaatggggc aggatggaca cgacagggga gccaaggtga ttgctacagg tttcgccgac 1920

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gccgtcgacg ccgatgtgca cgcagtgggg gtgtccaccc tcgccgcagg gcacaagacc 2040

ctcgtacccg aattgattaa ggagcttaac tccctgggca gacctgacat tttggttatg 2100

tgtggtggtg tgataccgcc acaggattac gaattcctgt ttgaggtggg agtgagcaac 2160

gtattcggcc ccggcaccag gatcccgaag gctgccgtac aagtgttgga tgacatcgag 2220

aagtgcctcg agaagaaaca gcagtctgtc 2250

<210> 86
<211> 2250
<212> DNA
<213> Artificial Sequence

<220>
<223> Codon optimized sequence that encodes an MCM polypeptide with the I671V mutation

<400> 86
atgcttaggg caaaaaacca gttattcttg ctgagcccgc actatttgcg tcaagtcaag 60

gagtctagcg ggtccagact gattcagcag cgactgctgc atcagcagca acctctccac 120

cccgagtggg ccgctttagc caaaaaacag ttaaaaggca aaaatcccga agacctgatc 180

tggcacactc cagagggcat tagcatcaaa cccctgtatt ctaaacgcga taccatggac 240

cttccagagg aactgccagg cgtgaagccg ttcacacgtg gaccttatcc cactatgtac 300

accttccgcc catggactat tcggcagtac gccggttttt ctacggttga agaaagcaat 360

aagttctata aagataatat caaagccgga cagcagggac tgtctgttgc attcgacctg 420

gccactcaca gagggtatga ctcagataat cccagagtca gaggtgacgt tggcatggcc 480

ggggtggcta ttgatacagt cgaagacaca aaaatactgt ttgacggaat ccccctcgaa 540

aaaatgagcg tctcaatgac gatgaacggt gccgtgatac ccgtccttgc gaatttcatt 600

gtcacaggag aagagcaggg ggtcccaaaa gaaaaactaa caggtacaat tcagaatgac 660

atcctgaagg aattcatggt tcgcaacact tacatctttc cccctgaacc ctcgatgaag 720

atcatcgccg acattttcga atataccgca aaacacatgc ctaagttcaa ctccatctcc 780

atcagcgggt accacatgca ggaagccggg gctgacgcga tcctggagct ggcatacact 840

ctcgccgatg gcttagagta ttccagaacc ggcttgcagg caggcctgac aatagacgag 900

tttgcgccac ggctgtcttt cttctgggga atcggcatga acttttacat ggagatagca 960

aagatgagag cagggcggcg cttgtgggct catctgatcg agaaaatgtt ccagccgaag 1020

aacagcaagt ccctgctgct gcgggcccac tgtcaaacct ctggttggag cctgacagag 1080

caggatcctt acaataatat agtgcgaaca gcgattgagg caatggctgc tgtgttcggc 1140

ggaacacaga gtctgcatac aaactctttt gacgaggccc ttggcctgcc aacagtgaaa 1200

agcgctagaa tcgcccggaa tactcagatc ataatccagg aagagagtgg aatccccaaa 1260

gtggcagatc cttggggtgg gagttatatg atggaatgtc tgaccaatga tgtctacgat 1320

gccgctctca agctgattaa tgaaatcgag gagatgggtg ggatggccaa ggctgtcgcc 1380

gagggtatcc ccaaactcag gattgaggag tgcgctgccc ggagacaggc gcgaatcgat 1440

tcgggctctg aggtgatcgt gggcgtgaac aagtaccagc tagagaagga ggacgctgtg 1500

gaagtcctgg ccattgataa taccagtgtg cggaacaggc agatcgaaaa attaaaaaaa 1560

attaaaagta gtcgcgacca agcactggca gagcgctgct tggcggccct gacggagtgc 1620

gcagcctctg gagatggcaa tatcctggca ctggccgtcg acgcctcaag agctcgatgc 1680

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ttggggtttg acgtcgatat cggacccctg tttcagacgc cacgggaagt agctcagcaa 1980

gccgtggacg cggatgtgca cgccgtaggc gtgtctacct tggcagcagg ccataaaacc 2040

ctagtgcccg agctcataaa agagctgaac agcctgggac ggcctgacat cctagtgatg 2100

tgcgggggcg tcatcccacc tcaggattat gagttcctct tcgaggtggg agtttccaat 2160

gtgtttggac ccggcacacg aatccccaaa gcagccgtgc aggtgttgga tgacatcgag 2220

aaatgcttag aaaagaaaca acagtccgtc 2250

<210> 87
<211> 2250
<212> DNA
<213> Artificial Sequence

<220>
<223> Codon optimized sequence that encodes an MCM polypeptide with the I671V mutation

<400> 87
atgctgcgcg caaaaaacca actgttcctc ctgagcccac actatttgcg acaggtcaaa 60

gagtcctctg gatcaaggtt aatccagcaa cggctcctgc atcagcagca gccactccac 120

cccgagtggg ccgcccttgc aaagaagcag ttaaaaggca aaaatcccga agatctgatc 180

tggcacacac cagagggaat cagcatcaag ccgctttaca gtaaaaggga cactatggat 240

cttcctgagg aactcccagg cgtgaaaccc ttcacgaggg gcccttatcc cactatgtat 300

acctttagac cctggaccat taggcaatac gccggattct cgaccgtgga agagtctaat 360

aagttttaca aggacaatat taaggcaggg cagcaggggt tgagtgtcgc ctttgatctc 420

gcaacacata gggggtacga cagtgacaat ccaagggtcc gaggtgacgt ggggatggcg 480

ggcgtggcca tcgacactgt ggaggatact aagattctgt tcgatggaat ccccctggag 540

aaaatgtcag tctccatgac aatgaatggt gctgtaattc ctgttctggc taactttatt 600

gtgaccgggg aagagcaggg agttcccaag gaaaagctaa ctggcactat tcaaaatgat 660

atccttaaag aattcatggt ccgaaatacc tatatatttc cacctgagcc atctatgaaa 720

ataattgcag atatctttga gtatactgct aagcatatgc caaagttcaa cagtattagc 780

attagtgggt accacatgca ggaagctggg gctgatgcaa ttctggaact tgcgtatacc 840

ttggccgatg gactcgaata cagccggacc ggcctgcagg ccggactgac aatagatgag 900

ttcgctccac gcctttcttt cttttggggc attggaatga acttctacat ggaaattgca 960

aagatgcggg ctgggagaag gctatgggct cacctcatcg aaaagatgtt tcaacccaaa 1020

aatagcaagt ctctcctcct gcgggctcac tgccagacca gcgggtggtc tctcaccgag 1080

caagaccctt acaataacat cgtgagaact gccattgagg cgatggctgc tgtgtttggt 1140

ggtacccaat cacttcacac gaactctttt gacgaggccc ttgggctgcc aaccgtgaag 1200

agcgctcgga ttgctcgcaa cactcagatt ataattcagg aggagtcagg catccccaag 1260

gtggcggacc cttggggagg aagctacatg atggagtgcc tgaccaacga cgtgtacgat 1320

gcagctctga agctgatcaa cgaaatcgaa gaaatggggg gtatggccaa ggccgtggcc 1380

gaagggattc ctaaactgag aattgaagaa tgtgctgctc gccggcaggc cagaattgat 1440

agcgggtcag aggtgatcgt gggggtgaac aagtatcaat tggagaagga agacgccgtc 1500

gaggtgttag caatagataa tacttctgtc agaaatcgtc agatcgaaaa gctcaaaaag 1560

atcaaatcct ctcgggatca ggctcttgct gagaggtgcc tcgctgccct gactgaatgc 1620

gccgcttcgg gcgacggtaa tatcctggca ttagctgtgg acgcctcacg ggcgcgttgc 1680

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cgaatggtga gcggggctta caggcaggag ttcggagagt caaaagagat tacatctgcc 1800

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tgtgggggtg tgatcccacc ccaggactat gaattcctgt tcgaggtcgg agtgtccaat 2160

gtgttcgggc ccgggacccg aatacctaag gccgcagtgc aagtgttgga tgatattgaa 2220

aagtgtctag aaaaaaaaca gcagtctgtt 2250

<210> 88
<211> 2250

<212> DNA
<213> Artificial Sequence

<220>
<223> Codon optimized sequence that encodes an MCM polypeptide with the I671V mutation

<400> 88
atgctgcgcg caaagaacca gctgttttta ctgtcacctc attacctgcg ccaggtcaaa 60

gaatctagtg gatccagact gatacaacag cgtctgctgc accagcaaca gcctttacac 120

cctgagtggg ctgccctcgc taaaaagcag ctgaagggaa agaatccaga ggatcttatt 180

tggcacacac ctgagggcat atcaatcaag cctctttata gcaagaggga tacgatggac 240

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acgttcagac cctggactat tcggcagtac gccggattct ccaccgtgga agaatcaaat 360

aagttctaca aagataacat caaagcaggc cagcagggcc tgagtgtcgc tttcgatctc 420

gctacacatc gcggctacga ttcagacaac cccagagtga ggggagatgt gggcatggca 480

ggggttgcta ttgatacagt ggaggatact aagatcctgt tcgacggcat ccctcttgaa 540

aagatgtcag tgagcatgac aatgaacggc gccgtgatac cagtcctggc aaattttatc 600

gtgacagggg aagagcaggg tgtgcctaag gagaaactga ccggtactat ccagaacgac 660

atccttaaag aatttatggt gcggaatacc tatatttttc ccccagaacc aagtatgaaa 720

attatagcag acatcttcga gtacacggcg aaacatatgc ccaagttcaa ttcaatcagc 780

atctctggtt accacatgca agaagctggg gccgacgcta tcctggaact cgcttacact 840

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agcgctcgta tcgcgagaaa tacccagatt attatccaag aggaatccgg catccccaag 1260

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gaggttttgg ccatcgacaa cacttccgtt cgtaaccggc agattgagaa gcttaagaag 1560

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gctgttgacg cggatgtcca cgctgtcggt gtctccactc tagcagccgg ccacaaaacg 2040

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tgcggagggg tgattccacc ccaggactat gagttcctgt ttgaagtggg cgtttcaaac 2160

gtattcggac cagggacccg gattcccaag gctgccgtgc aggtgctcga cgatatagag 2220

aaatgcctgg agaagaagca gcagagtgtg 2250

<210> 89
<211> 2250
<212> DNA
<213> Artificial Sequence

<220>
<223> Codon optimized sequence that encodes an MCM polypeptide with the I671V mutation

<400> 89
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gaatctagcg gctcaagact gattcagcag cgccttctgc accagcaaca acccctgcat 120

ccagagtggg ccgcgctcgc aaaaaaacag ttaaagggga agaacccaga ggatctcatc 180

tggcatacgc ccgagggtat ttcgattaag cccttgtatt ctaagagaga taccatggac 240

ttgccagaag agcttcctgg agttaaacca tttacacgag ggccctaccc cactatgtat 300

acgttcaggc cctggactat tagacagtac gcaggtttca gtactgtgga agagtcaaat 360

aagttctata aagataatat caaagccggt caacaggggt tgtcagtggc tttcgatctg 420

gctacccatc ggggttacga cagtgataac cctagggtaa gaggggatgt cggaatggcc 480

ggcgtggcca tagacactgt ggaggataca aaaatcctgt tcgacgggat tcctctcgag 540

aaaatgagtg ttagtatgac gatgaatggc gccgtcatac cagtcctcgc caattttata 600

gtgactgggg aagaacaggg ggtgccaaaa gagaagttga ccggaaccat ccagaacgat 660

atattaaaag agttcatggt tcgaaatact tacatttttc ctccggagcc ttcaatgaaa 720

attatcgccg atatctttga gtacacagca aaacacatgc caaaattcaa cagcatctca 780

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ttcgctccaa ggctgtcttt tttctggggc atcggaatga atttctacat ggagattgct 960

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caagatccct acaacaacat agtgcgaacc gccattgaag ccatggcggc cgtctttggg 1140

ggcacgcaga gcctgcacac caattccttt gatgaagctt tgggcctgcc aacagtcaag 1200

tctgcacgga ttgcacggaa cacccagatc atcatacagg aggagagcgg gataccaaaa 1260

gttgccgatc cctggggagg atcctacatg atggagtgtt taacaaacga cgtgtacgac 1320

gcagccctga aattgataaa cgagattgag gagatgggag gcatggccaa agccgtcgct 1380

gagggcattc caaaacttcg catcgaagaa tgtgctgccc gtcggcaggc ccgaatcgac 1440

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attaagagtt cccgagacca ggcgctggcc gaacggtgtc tagctgcctt gacagagtgt 1620

gctgcgtccg gggacggtaa tatactggcc ttagcagttg acgcttcgag agccaggtgt 1680

acagtggggg agatcactga tgccttaaaa aaggtcttcg gtgagcataa ggctaacgat 1740

cggatggtat cgggggccta cagacaagag ttcggcgagt cgaaggagat tactagcgca 1800

attaagaggg tccacaaatt catggagcga gagggtagga ggcctcggct cttagtcgca 1860

aaaatggggc aagatggcca cgatcgagga gccaaggtga ttgctaccgg atttgctgat 1920

ctaggcttcg atgttgacat tgggccgttg ttccaaacgc cccgggaggt ggcacagcaa 1980

gccgttgacg cagacgtgca tgccgtcggt gtgagtaccc ttgctgcagg acataaaact 2040

cttgttcctg agcttataaa agagttgaat tctctgggtc gccctgacat cctggtcatg 2100

tgcggaggtg tcattccgcc ccaagattac gaattcttgt ttgaggtcgg ggtaagtaat 2160

gtgttcggcc caggtacgcg gattcctaaa gctgctgttc aggttctgga tgatatcgag 2220

aaatgcctcg agaaaaaaca gcagagtgtc 2250

<210> 90
<211> 2250
<212> DNA
<213> Artificial Sequence

<220>
<223> Codon optimized sequence that encodes an MCM polypeptide with the I671V mutation

<400> 90
atgctgcggg caaaaaatca attatttctt ctgtcccccc actaccttag acaagtcaaa 60

gaatcctcag gtagccgtct tattcagcag agattgttac accaacagca gcccctgcac 120

cctgagtggg cagcacttgc caagaagcag ctcaagggga aaaatccaga ggatctgatt 180

tggcatacac ctgaaggaat ctccatcaag cccctatatt ctaaacggga cactatggac 240

ctgcctgagg aactcccagg ggtgaaaccg tttaccaggg gaccctaccc aaccatgtat 300

accttccggc cctggacaat ccgtcagtac gccggttttt ctaccgtcga ggaatccaat 360

aagttttata aagataacat caaggctggc cagcaaggcc ttagcgtggc ctttgatctg 420

gctacccatc gggggtacga ctccgataac ccccgtgtga gaggagacgt aggcatggca 480

ggggtggcta tcgacaccgt cgaggacacg aagatactgt ttgacggaat tcccctggaa 540

aagatgtcag tgtccatgac catgaatggc gcggtgatcc cagttctggc caacttcatc 600

gttacaggag aagaacaggg cgtgcccaag gagaagctga ccgggactat tcaaaatgat 660

attctcaaag aatttatggt gcgcaatacc tatatctttc cccccgaacc aagtatgaaa 720

attatagccg atatcttcga atataccgct aagcacatgc ctaagttcaa cagcattagc 780

atcagtggtt atcatatgca ggaagcaggc gcagacgcca tcttagaact ggcatacaca 840

ctggccgacg gactggagta ttcccggact ggcctccagg ctgggctgac tatcgatgag 900

ttcgcccccc gactctcttt tttctgggga attggaatga atttctatat ggagatcgcc 960

aagatgcggg ctggccgaag gctgtgggcc catctgatcg aaaaaatgtt ccagcccaag 1020

aactcaaagt cgctgctcct tcgggcccac tgccaaacct ccggttggtc cctgaccgag 1080

caggatccct acaacaatat cgtgcgaact gccattgagg ctatggccgc tgtgtttggt 1140

ggcacccagt ccctacatac aaacagcttt gacgaagctc tgggactccc aaccgtgaaa 1200

tctgccagga tcgcgagaaa cactcagatt attatccagg aggaaagtgg catccccaag 1260

gtggccgacc catggggcgg ctcatatatg atggaatgcc tgactaatga cgtgtatgac 1320

gctgccctga aactgatcaa cgagatcgag gagatgggag gcatggccaa agctgttgct 1380

gagggcatac caaagctgcg tatcgaagag tgcgctgcac ggagacaggc gagaattgac 1440

tccgggtccg aggtaattgt gggagttaat aagtaccagc tggagaagga agatgccgtc 1500

gaggttctgg caattgacaa tacatccgtg agaaaccgac agattgagaa gctgaaaaaa 1560

attaagtctt ccagagacca ggccctggcg gagcgctgtc tggctgcact cactgagtgc 1620

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ataaagaggg ttcataaatt catggagcgg gagggtaggc gtcccagatt actggtggcc 1860

aagatgggac aggacgggca cgatagggga gcaaaggtga tcgctactgg gttcgccgac 1920

ttaggatttg acgtggacat aggcccctta ttccagacgc caagagaagt cgcacagcag 1980

gcggtagacg cagacgtgca cgcagtcggg gtgtccacac tggccgcggg gcacaagacc 2040

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tgtggaggag tcatacctcc tcaggactac gaattccttt tcgaggtggg ggtgtctaat 2160

gtattcgggc ctggcacccg aattcccaag gccgcggtgc aggtactcga cgacatcgaa 2220

aaatgtctgg agaaaaaaca gcagtccgtg 2250

<210> 91
<211> 2250
<212> DNA
<213> Artificial Sequence

<220>
<223> Codon optimized sequence that encodes an MCM polypeptide with the I671V mutation

<400> 91
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gagtcaagtg ggtcccggct aattcagcag cgtctgctgc atcagcaaca gcctcttcac 120

cctgagtggg cagctctcgc caagaagcag ctcaagggca agaatccaga ggatctgatc 180

tggcacactc ccgagggcat tagcatcaaa cccttgtatt caaagcgcga caccatggac 240

ttacccgagg agctgcctgg cgtgaaaccc ttcacgcggg gaccatatcc aactatgtat 300

actttcaggc cttggacaat tcgtcagtac gctggttttt ccacagtaga ggagagcaac 360

aagttctaca aagataacat aaaggccgga cagcaggggc tgtcggtcgc tttcgatctg 420

gctacccacc ggggctatga ttcggacaac ccaagggtta gaggtgatgt gggaatggcc 480

ggtgtcgcga tcgataccgt tgaagacacc aaaattctat tcgacggaat tcccctggag 540

aaaatgtctg tttctatgac tatgaatggc gcagtcattc ccgtccttgc caattttatc 600

gtcaccggag aagagcaagg ggtcccaaaa gaaaaactga ctggcaccat tcagaacgat 660

attctgaagg agtttatggt taggaatacc tacatctttc ctccagaacc aagcatgaag 720

ataatcgccg acatctttga gtacacagct aaacacatgc cgaaattcaa cagcatcagc 780

atcagcggat atcacatgca agaggcaggg gctgatgcta tcctcgaact ggcgtacact 840

ctcgctgatg ggctggagta cagcagaaca gggctgcagg cagggctgac tatcgacgaa 900

ttcgctcccc gcctgagctt cttctggggc attgggatga acttttatat ggagattgct 960

aaaatgcggg cgggaagacg gctatgggct catctgatcg agaaaatgtt tcagcctaag 1020

aactccaagt cgctcctgct gagggcccat tgccagacca gcggttggag cctgaccgag 1080

caggacccgt acaacaacat cgtgagaaca gccatcgagg ccatggctgc ggtctttggg 1140

ggtacccaga gtctccatac gaattctttt gacgaggccc tcggacttcc gacagtcaag 1200

agcgcccgga tcgctagaaa tactcaaatc atcatacagg aggaatctgg cattcccaaa 1260

gtcgcagacc cgtgggggg cagttacatg atggagtgtc tgacgaacga cgtgtatgat 1320

gccgcgttaa agctgatcaa tgagatcgag gagatggggg ggatggccaa ggcagtagcg 1380

gaaggcattc ccaaactccg aattgaggag tgcgccgcgc gacgccaggc ccgaatcgac 1440

tctggaagcg aggtgatcgt gggagtgaac aagtatcagc tggagaagga ggacgctgtg 1500

gaagttctcg caattgacaa cacttcggtg aggaatcgac agatcgagaa actgaagaag 1560

atcaaatcaa gtcgcgacca agcgctggcc gaaaggtgtc tggcggcctt gactgaatgc 1620

gccgccagcg gcgacggcaa tattcttgcg ctggcggttg atgcttcccg ggctagatgc 1680

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attaaaaggg tccacaagtt catggaacgc gagggccgtc gcccccgcct gctggttgcg 1860

aagatgggcc aggacgggca cgacagaggc gctaaagtca ttgcaaccgg tttcgccgat 1920

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gccgtggatg ctgatgtgca tgccgttggt gtgagtacat tggcagctgg ccacaaaacg 2040

ctcgtgcctg aactgattaa ggagctgaat tcgctggggc ggcctgatat tttggtgatg 2100

tgcggtggag taatccctcc tcaggactat gagttcctgt ttgaggtcgg ggtttcaaac 2160

gtgtttgggc cgggaaccag gatccccaaa gctgcagtcc aagtcctgga cgatatcgag 2220

aaatgcctgg aaaagaaaca gcaatccgtg 2250

<210> 92
<211> 2250
<212> DNA
<213> Artificial Sequence

<220>
<223> Codon optimized sequence that encodes an MCM polypeptide with the I671V mutation

<400> 92
atgctccggg caaaaaacca gctctttctg ctgagccctc attacctgag gcaagtgaag 60

gagtcaagtg ggagtcggct gatacagcag aggttactgc accaacaaca accactgcat 120

cctgaatggg cagcactggc aaagaagcag ctcaagggaa aaaaccccga agacttaatt 180

tggcacacac ctgaaggaat cagcattaag ccgttgtatt cgaagaggga tacaatggat 240

ctcccggagg aactgcccgg agttaagcca ttcacccggg gaccataccc tacaatgtat 300

actttccgcc cttggaccat ccgtcaatat gccggctttt ccactgtgga agagagcaat 360

aaattctaca aggataatat caaggccgga cagcaaggcc tatctgtggc gttcgacctg 420

gcaacccacc gtgggtacga tagtgacaac ccaagggtcc gtggggacgt ggggatggct 480

ggggtggcta ttgatacagt ggaagacaca aaaatcctct ttgacggaat acctctggaa 540

aagatgagtg tctccatgac aatgaacggc gccgtgatcc ccgtgctggc caacttcatc 600

gtgaccggag aggagcaagg ggtgcctaag gaaaagctca cagggaccat ccagaatgat 660

atcctcaaag aattcatggt gaggaataca tacatctttc cgcccgagcc aagcatgaag 720

attatcgctg acatcttcga gtatacggct aagcacatgc ctaaatttaa cagtattagt 780

atttctggct atcacatgca ggaagcaggg gctgatgcta tcctggagct ggcgtacaca 840

ctcgccgatg ggttggaata cagtaggacc ggactacagg ctgggttaac cattgatgag 900

ttcgcacctc gccttagctt cttctggggt ataggcatga atttttacat ggagatcgca 960

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gggacccagt ccttgcacac caattcattt gatgaggctc tcggtctgcc aactgttaaa 1200

agcgctagaa tcgcccggaa tacacagatt attatccaag aagagagcgg aatcccaaag 1260

gttgcggacc catgggggg cagttacatg atggagtgtc ttactaacga tgtgtacgac 1320

gcagccttaa aactgataaa tgagatcgaa gagatgggag gcatggccaa ggccgtggcc 1380

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gaagtgctgg caatagacaa cacctccgtg cgcaaccggc agatcgagaa actgaagaag 1560

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aaaatggggc aagatggtca cgatcgggga gccaaagtta tcgctactgg attcgcagat 1920

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gcagtcgatg ctgatgtcca tgccgtaggg gtgtccacct tagctgctgg ccacaaaact 2040

ctcgtgccag aactgatcaa agaactgaat agcttgggta gaccagatat tttggtgatg 2100

tgtggaggcg tgatcccacc acaggattat gagttccttt ttgaggtggg ggtgtctaac 2160

gtttttggtc caggaaccag aatcccaaag gctgctgtgc aggtgctgga tgatattgag 2220

aagtgcctcg aaaagaagca gcagtctgtc 2250

<210> 93
<211> 2250
<212> DNA
<213> Artificial Sequence

<220>
<223> Codon optimized sequence that encodes an MCM polypeptide with the I671V mutation

<400> 93
atgctgcgtg ccaaaaatca gctttttttg ctctccccac attacctgcg acaggtcaaa 60

gagtcctccg gtagccgact gattcaacag agattgcttc atcagcagca gccgttacat 120

cccgagtggg cagctctggc aaagaaacag ctgaagggca agaatcctga ggatctcatt 180

tggcacacgc cagagggaat ctcaattaag cccctgtata gcaagcgcga caccatggat 240

cttcctgagg agctgcctgg agtgaagcct tttactaggg gaccctaccc taccatgtat 300

acttttcggc cttggacaat tcgacagtac gcaggattct ccacagtcga ggaaagtaat 360

aaattttaca aagataacat caaagccggg cagcaggggc tgtctgtggc tttcgatctg 420

gccacccatc ggggatacga ttcagacaat cctcgggtcc gaggggatgt cggcatggcg 480

ggggtggcga tagacacagt ggaggatacg aaaattctgt tcgacggcat tcctctggag 540

aagatgtctg tcagcatgac catgaacggg gcagtaatcc ccgttttggc gaatttcata 600

gttactgggg aagaacaggg agtacccaaa gagaagctca caggtaccat ccaaaacgat 660

atattgaagg aattcatggt caggaatacg tacatcttcc ctccagaacc atcgatgaaa 720

ataatcgctg acatttttga atatactgcc aaacatatgc ccaagtttaa cagtattagc 780

ataagtggat accacatgca ggaagccggc gccgacgcca ttctcgagct tgcttacacc 840

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tccgcccgga ttgcccgcaa tacccagatc atcattcagg aagaaagtgg gatccccaaa 1260

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gaagtgctgg caattgataa tacctcagtc cggaatagac agattgagaa gcttaaaaaa 1560

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tgtggcgggg tgatcccgcc ccaggattac gaattcctat ttgaggtggg ggtttccaat 2160

gtttttggcc cagggactcg aattcccaag gctgctgtac aggtgctaga cgatatagag 2220

aagtgcctgg agaagaagca gcagtctgtg 2250

<210> 94
<211> 2250
<212> DNA
<213> Artificial Sequence

<220>
<223> Codon optimized sequence that encodes an MCM polypeptide with the I671V mutation

<400> 94
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gagtcgtctg gcagtcgact gattcaacaa agattactcc accaacagca gcctctgcac 120

ccagagtggg ccgccctggc taagaaacag ctgaagggga aaaaccctga ggacctgata 180

tggcacacac ctgaaggcat ctccattaaa ccattgtata gtaaaagaga taccatggat 240

ctgcctgagg agcttcctgg ggtgaaaccg tttactaggg gtccataccc caccatgtat 300

acttttcgcc cttggacaat caggcagtac gcgggatttt caacagtgga ggagagtaat 360

aagttttata aggataatat caaagcggga cagcagggtc tcagcgtagc tttcgacctg 420

gccacacatc gtggatacga ttccgataac ccaagggtgc ggggggatgt ggggatggct 480

ggtgtggcca tcgacaccgt tgaagatact aagatcttgt ttgatggaat tccccttgaa 540

aagatgtcag tcagcatgac aatgaatggg gccgtcatcc cagtgctggc caatttcata 600

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atcctcaagg aatttatggt ccggaataca tacattttcc ctccggaacc ctcaatgaag 720

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gaggtgttgg caattgataa cacctccgtt agaaacaggc agatcgagaa actaaaaaag 1560

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accgttggcg aaatcacaga tgctctcaag aaggtctttg gtgagcacaa agcaaacgac 1740

cggatggtct ccggagctta ccggcaggaa tttggagaaa gcaaggagat tacctcagct 1800

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tgtggcgggg tgataccccc tcaggattat gaattcttat ttgaagtggg cgtcagtaat 2160

gtttttgggc ctggtactcg gatcccaaag gcggcagtgc aagtcttaga tgacattgaa 2220

aaatgtctcg agaaaaagca gcagagcgtc 2250

<210> 95
<211> 2250
<212> DNA
<213> Artificial Sequence

<220>
<223> Codon optimized sequence that encodes an MCM polypeptide with the I671V mutation

<400> 95
atgctgcgag caaagaatca gctgttcctc ctgtccccac actatctacg ccaagtgaag 60

gagtcgagcg gatctaggct aatccaacaa agactgctgc atcagcagca accactgcac 120

ccggaatggg ctgcgctcgc taagaaacag ctgaaaggta aaaacccaga ggatcttatc 180

tggcacactc ccgaaggtat cagcattaaa cctctttaca gtaagcgcga tactatggac 240

ctccccgaag aactaccagg cgtgaaaccg tttactcgag gcccataccc caccatgtac 300

acatttaggc cttggacaat acgacagtac gccggattct caaccgtgga agaaagcaac 360

aaattctaca aagataatat caaggcgggc cagcagggat tgagtgtagc cttcgacctg 420

gcgacccaca gagggtatga ctccgacaac ccccgggtgc ggggcgacgt cggaatggca 480

ggggtcgcga ttgataccgt tgaagatacg aagatcttat ttgacgggat tccactagaa 540

aagatgtcag ttagtatgac aatgaatgga gccgtgattc ccgtgctggc caactttatc 600

gtgaccggag aagagcaggg agtgccaaag gaaaagctga caggaacaat ccagaacgat 660

atattaaagg aatttatggt gagaaacaca tatatatttc cacctgaacc ctctatgaaa 720

ataatagcgg atatattcga atataccgcc aaacatatgc ccaagttcaa ctccatttcc 780

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gggacccaga gtctgcatac taattcattc gatgaagcac tggggttacc taccgtgaaa 1200

agcgctcgaa tcgcaaggaa cactcagatc attatccagg aagagagtgg catccctaaa 1260

gtggccgatc cctggggcgg ctcatatatg atggagtgcc tgactaatga tgtgtacgac 1320

gctgctttga aactgataaa tgagatcgag gagatgggcg gcatggccaa agccgtggcc 1380

gaagggatcc ctaagttacg gatcgaggag tgtgccgctc ggcgacaggc tcggatcgac 1440

tctggctccg aggtcattgt cggcgtaaac aagtatcagc tggaaaagga ggatgccgtg 1500

gaggtgctcg caatcgataa cactagtgtg aggaatagac agattgaaaa actgaaaaaa 1560

attaagagca gccgagacca agcccttgct gaaagatgcc tcgccgcact caccgaatgc 1620

gcagcctcag gcgatggcaa tattcttgcc ttggcagtgg acgcatcaag ggcacgctgc 1680

accgttggag aaatcaccga cgcacttaaa aaagtgttcg gtgaacataa ggccaatgac 1740

cggatggtca gcggcgccta taggcaggag tttggagaga gtaaagaaat tacttccgcc 1800

atcaagcgcg tccacaaatt catggagcgg gagggccggc gccccaggct gctggtggca 1860

aaaatgggac aggatgggca cgatcgggga gccaaagtga tagcaactgg gtttgcagat 1920

ctcggcttcg acgtggatat cgggcccttg ttccagacgc ctagggaggt ggctcagcag 1980

gctgttgacg cagatgtcca cgctgtgggc gtctcaactc tggctgccgg ccataaaacc 2040

cttgtgcctg agctgatcaa ggagctgaat agtctgggta ggccggatat cctggtcatg 2100

tgtgggggg tcatccctcc ccaggattat gaatttctct tcgaggtcgg cgtatctaac 2160

gtcttcggcc caggaacgag gatccccaag gcggccgtgc aggtacttga cgatattgag 2220

aaatgtcttg aaaagaaaca gcagagtgtg 2250

<210> 96
<211> 2250
<212> DNA
<213> Artificial Sequence

<220>
<223> Codon optimized sequence that encodes an MCM polypeptide with the I671V mutation

<400> 96
atgctgcgtg ccaaaaacca actgtttctc ctatcgcctc actatctccg ccaggttaag 60

gaatcttcgg gctcccggct aatacagcag agactgctac atcagcagca acctctacat 120

ccagagtggg cagcgctggc gaagaagcag ctgaagggaa agaacccaga ggatcttatc 180

tggcataccc ccgaggggat atctattaaa ccactgtaca gcaaacgaga caccatggat 240

ctgccagaag agcttccggg ggtgaaacca ttcacacggg gaccatatcc aacaatgtac 300

acgttccggc catggaccat ccgacagtac gccggctttt caactgtgga ggaatccaac 360

aagttttaca aggataatat taaggcagga cagcaggggc tgtctgtcgc tttcgacctc 420

gccacccacc gcggttacga tagcgacaac ccccgcgtca ggggggatgt cggcatggct 480

ggcgtggcca tcgacaccgt cgaagacacc aagatcctgt tcgatggaat cccgctggaa 540

aaaatgtcag taagcatgac catgaatggc gccgtaatcc ctgtactggc aaactttatt 600

gtgacaggcg aagagcaggg agtccctaag gagaagctga cagggaccat acagaatgat 660

attcttaaag agttcatggt gagaaacact tatatttttc ctccagagcc ttcaatgaaa 720

ataatagccg atatctttga gtacaccgcc aaacatatgc ccaagtttaa tagcatttct 780

atatccggtt accatatgca ggaagcaggt gcagacgcta ttctggaatt ggcctacacc 840

ctggctgatg gacttgaata cagccgcacc ggactccagg ccgggcttac aattgacgag 900

ttcgccccac gcttgtcctt tttttggggt attggcatga acttctacat ggagatagcc 960

aagatgcgtg ccggtcggag gctgtgggca cacttgattg agaaaatgtt ccagcctaag 1020

aattctaagt ctctgcttct gagggcccac tgtcagacta gtggttggtc actgaccgaa 1080

caggatccgt ataataacat tgtgcgcacg gccattgaag ccatggcggc cgtttttggc 1140

ggcacacaga gcctccacac caatagcttc gacgaggctc tgggtctgcc tacagtgaaa 1200

tcggcccgga tcgctagaaa cacacagatc attattcagg aagaaagcgg cataccaaaa 1260

gtggccgacc cttggggcgg ctcttatatg atggaatgtc tgactaatga tgtttatgat 1320

gccgccttaa aactcattaa tgaaatcgaa gaaatggggg gcatggctaa ggcggtggcc 1380

gagggcatac caaaactgag gatagaagag tgcgccgccc ggcgacaggc caggattgat 1440

agtggttctg aggttatcgt tggcgtaaac aaatatcagc tagagaaaga ggacgccgtg 1500

gaagtcctgg ccatcgacaa cacgagcgta cggaacaggc agattgagaa gctgaaaaag 1560

ataaagagca gtcgcgacca ggcactggcg gagcgatgcc tggccgcact gaccgagtgc 1620

gctgcaagtg gcgatggcaa tatcctggct ctcgcagttg atgcctccag ggccagatgc 1680

accgtgggag agatcacaga tgcccttaaa aaggtatttg gagagcataa ggccaacgac 1740

cgcatggtct ctggggcgta cagacaagag tttggagagt ctaaagagat tacatccgcc 1800

attaagagag tacacaagtt tatggagcgc gaaggaaggc gtccccgcct gctggtagcc 1860

aagatgggcc aagacggcca tgatagaggc gctaaggtta tcgccactgg cttcgcagat 1920

ttaggatttg acgtcgacat cggacccttg tttcagaccc ccagagaggt cgctcagcaa 1980

gctgtggatg ctgacgtcca tgcagtgggg gtctcaacgc tggcagcggg acataaaact 2040

ctcgtgcctg agttgatcaa ggaactcaat tccctggggc gccctgatat ccttgttatg 2100

tgtggtggag tcattcctcc ccaagattat gaatttctat tcgaagtggg cgtctctaat 2160

gtctttggcc ctgggacaag gattccaaag gcagctgtgc aggtgttaga cgatatagaa 2220

aaatgtctcg aaaagaaaca gcaatccgtg 2250

<210> 97
<211> 2250
<212> DNA
<213> Artificial Sequence

<220>
<223> Codon optimized sequence that encodes an MCM polypeptide with the I671V mutation

<400> 97
atgttgaggg ccaagaacca gttgttcctc ctgtctccac actacctgcg acaggtcaag 60

gagagcagcg gaagccgact cattcagcaa agactcctcc accagcagca gcccctgcac 120

cccgagtggg ccgcactggc taagaaacag ctgaaaggaa agaacccaga ggatctcata 180

tggcatacgc ctgaggggat cagcattaag ccccttaca gcaagagaga tactatggac 240

cttcccgaag agcttcccgg ggtgaaacca ttcacacggg gtccctatcc gaccatgtac 300

acgttccgtc cctggactat ccggcagtat gctggatttt ctaccgtgga ggagtccaac 360

aagttttata aggataatat caaagccggg cagcagggcc tttccgttgc ttttgacctg 420

gccacccatc gcggctacga ttcagataac cctcgcgtaa ggggtgatgt gggaatggcc 480

ggtgtagcaa ttgacacggt ggaagacaca aaaatcctgt tcgacggtat ccctcttgag 540

aaaatgtccg tctcaatgac catgaacggc gctgtgattc ccgtactcgc caacttcatt 600

gtgacaggcg aggaacaggg cgtccccaaa gagaagctaa ccggaaccat tcaaaacgac 660

atcttaaagg agttcatggt ccgcaacacc tacatattcc cacctgaacc ctccatgaag 720

atcattgcag atatttttga atacaccgcg aagcacatgc ctaaatttaa ctctattagc 780

atctccgggt accacatgca agaagcgggg gctgacgcca ttctggagct cgcttacact 840

ttggcggatg gactggaata cagcagaacg gggctccaag ctgggctgac tattgacgag 900

tttgcacccc gcctcagctt cttttggggc atcgggatga atttctatat ggaaattgct 960

aagatgcggg ctggccgtag actctgggca cacctcatcg agaaaatgtt tcaaccaaag 1020

aactctaaga gtctactgct cagggctcac tgtcagacct ccggctggag tctcacagag 1080

caggaccctt ataataacat tgtcaggaca gcaatagagg ctatggctgc cgtcttcggc 1140

ggtacccaga gcttgcacac caacagcttc gatgaagcac tcggcctgcc aacagtgaag 1200

tcggcgcgga tcgctagaaa cacccagatc ataattcagg aggagagtgg tattccgaag 1260

gtcgcagatc catgggggg gtcctatatg atggagtgcc taacaaatga tgtatacgac 1320

gcagctttga agctgatcaa cgagattgaa gaaatgggag gcatggccaa agcggtggcg 1380

gaggggattc caaagcttcg gattgaagag tgcgccgccc gccggcaggc ccgaattgac 1440

tcaggctcag aagtcattgt tggcgtcaat aaataccagc tggaaaagga ggacgccgta 1500

gaagtgctcg ctattgataa tacatccgtg agaaacagac agattgagaa gctgaagaaa 1560

ataaagagct ctcgcgatca ggctttagcc gaaaggtgtc tggctgcact taccgagtgt 1620

gcagcgtccg gagacggtaa cattctggcc ctagcagtgg atgctagcag agcccgctgc 1680

acagtgggcg agatcacaga tgctttaaaa aaggtgtttg gagaacataa ggcaaatgac 1740

cgcatggtct cgggagctta tcgccaggaa ttcggcgagt ctaaagagat tacaagtgct 1800

attaaaagag tgcataagtt tatggagcgg gagggtagga ggcctcgatt attggttgcc 1860

aagatggggc aggatgggca tgaccgggga gcgaaagtca ttgcaactgg ctttgctgat 1920

ctgggatttg atgttgacat aggaccgctg ttccaaactc cacgcgaagt agcccagcag 1980

gctgtagatg cggacgtgca cgccgtgggg gtttccaccc tggctgcagg acataagaca 2040

ctggtgcctg aacttattaa ggagctgaac tccttaggga ggcccgatat ccttgttatg 2100

tgtggcggtg tgatcccccc acaggactat gaatttctgt ttgaagtagg cgtgtcaaac 2160

gtcttcggcc ccggcacacg gatcccgaag gctgccgttc aagtcttgga cgacatcgaa 2220

aagtgcctcg aaaagaagca acagtctgtc 2250

<210> 98
<211> 2250
<212> DNA
<213> Artificial Sequence

<220>
<223> Codon optimized sequence that encodes an MCM polypeptide with the I671V mutation

<400> 98
atgcttagag ccaagaacca gctgtttctc ttgtctcctc attatcttag acaggtcaaa 60

gagagtagcg ggtcgaggct tatacagcag cggcttctac atcagcagca gcctctgcac 120

cccgagtggg cggcactagc aaagaagcaa ctcaaaggca aaaatccaga ggaccttatt 180

tggcacacgc ctgaggggat atcgatcaag ccgctttaca gcaagcgcga cacaatggac 240

ctcccagaag agctccctgg cgtgaaacca ttcacccgcg ggccctaccc tacgatgtat 300

acgttccgcc cctggaccat aagacagtat gccggtttta gcactgtcga agagtctaat 360

aagttctaca aagataatat taaagctggg cagcagggac tgtccgtcgc ttttgacctg 420

gcgacccatc gtgggtacga tagcgacaat ccgcgcgtcc ggggcgatgt tgggatggca 480

ggcgtcgcaa tcgatactgt ggaggacacc aagatcctgt ttgacggcat ccccctggag 540

aagatgtcag tgagcatgac aatgaacggt gctgtcatcc ccgtgctcgc aaactttatc 600

gtcacgggag aagagcaggg tgtgccgaag gagaagttaa cagggaccat tcagaacgat 660

atcctgaagg agtttatggt caggaacacc tatatttttc cacccgagcc atctatgaag 720

attatcgccg acatatttga atatactgca aagcatatgc ctaaattcaa tagtatttca 780

atctcgggct atcatatgca agaggccggg gccgatgcaa tactggagct tgcttatacg 840

ttagctgacg ggcttgagta tagtaggacg gggcttcaag ctggactgac cattgatgaa 900

ttcgctccca ggctgtcctt cttttggggg atcggtatga atttctacat ggagatcgcc 960

aagatgcgag ctggccgcag actatgggca cacctcatcg agaaaatgtt tcaaccaaaa 1020

aactccaaat cccttctcct acgggcgcat tgccagacca gcggatggag cctcactgag 1080

caggatccat ataataatat agtgaggacc gctattgagg ctatggctgc cgtgtttggc 1140

ggaacccaga gcctgcacac caactccttc gatgaagccc tggggctccc cacggttaaa 1200

agcgcgagaa tcgctcggaa cacacagatt attatacagg aagaatctgg tatccctaag 1260

gtggctgatc cttggggcgg atcctatatg atggaatgct tgacaaatga cgtgtatgat 1320

gccgccctga agcttatcaa cgaaattgaa gagatgggcg gcatggccaa ggcagtagcc 1380

gaaggcatcc ctaaactgcg gatagaagag tgcgctgcac gccgtcaagc tagaatcgac 1440

agtggcagtg aggttatcgt cggcgtcaac aagtatcagc tggaaaagga ggatgccgtt 1500

gaggtattgg cgatagacaa taccagcgtc cgtaacaggc agattgaaaa actgaaaaag 1560

atcaagagct cacgcgatca ggctctagcc gaaagatgct tagccgccct gacggagtgt 1620

gctgcaagcg gcgacggcaa catcttggcc ctggccgtag atgccagcag agctcgctgc 1680

accgtgggtg agatcactga tgccttgaaa aaggttttcg gggaacataa ggccaatgac 1740

cgcatggtgt ccggcgcata ccgacaggaa tttggagaga gtaaagagat tacttcagcc 1800

ataaaacgtg ttcacaagtt tatggaaaga gagggtagga gaccgcggct gctagttgca 1860

aaaatgggcc aggatggcca cgacaggggt gctaaggtga tcgcgaccgg atttgcagac 1920

ttgggcttcg atgtggatat tggcccgctg ttccaaactc cgcgagaagt ggcccagcaa 1980

gcagtcgatg ccgacgttca tgcagtcggc gtcagtactc tggccgccgg gcacaagact 2040

ttagttcccg aacttatcaa ggagctcaat agtttgggga gaccagacat cctggtgatg 2100

tgcggaggag ttatccctcc acaagactat gaattcctgt ttgaagtggg cgtgtccaac 2160

gtcttcggcc ccggaacacg aatacccaag gcggcagttc aggttcttga tgatatcgag 2220

aagtgtttgg agaaaaaaca gcagtccgtg 2250

<210> 99
<211> 2250
<212> DNA
<213> Artificial Sequence

<220>
<223> Codon optimized sequence that encodes an MCM polypeptide with the I671V mutation

<400> 99
atgctgagag ccaaaaatca gttgttcttg ttaagtccac attacctgag gcaggtcaaa 60

gagtcaagcg gcagcaggct catccaacag agactgttgc atcaacagca gcctctccac 120

cccgaatggg ccgcacttgc caagaaacag ttgaaaggca agaaccccga ggaccttatc 180

tggcatacac cagagggaat cagcatcaaa cccctataca gcaaaaggga cactatggac 240

cttccagagg agctcccagg cgtcaaaccc tttacacgtg gtccctatcc tacgatgtac 300

accttcagac cttggaccat ccgccagtac gccggcttta gtacggtaga agagagcaac 360

aagttttaca aagataacat aaaagctggg cagcaaggac tgtccgtggc cttcgaccta 420

gcgactcacc ggggctacga ctccgacaat ccaagggtcc gtggcgatgt agggatggcc 480

ggggtggcaa tcgatactgt agaagataca aaaattttgt ttgacggcat ccccctggag 540

aagatgtcag tttccatgac tatgaatggg gccgtgatcc ccgtgttggc gaatttcata 600

gtgacagggg aagaacaggg agtacccaag gagaagctca cggggacgat ccagaacgac 660

atcttgaaag aatttatggt gcgcaatact tacatcttcc ccccggaacc ttctatgaag 720

atcattgccg acattttcga gtatacagct aagcacatgc caaaatttaa ttcaatctct 780

atttcaggat accatatgca ggaggccggc gccgatgcca tcttggagct agcctatacc 840

ctcgctgatg gactggaata ctcaaggact gggttgcagg cgggactaac aatcgacgaa 900

ttcgccccac gtcttagctt tttttggggg attggaatga acttctatat ggaaatagca 960

aaaatgagag cgggcagaag actctgggcg catctcatcg aaaaaatgtt ccaacccaag 1020

aattccaaga gcctcctgct gagagctcat tgccagacat ctggctggtc gttaaccgaa 1080

caagacccct ataacaacat cgttcgcact gccatcgagg ccatggcggc ggtattcggt 1140

ggaacacagt cgctgcacac aaacagtttc gatgaggccc ttggcctccc aactgttaag 1200

tctgcgagaa ttgcccggaa cacgcagatt ataatacagg aagagtctgg cattccaaag 1260

gtcgcagacc cctgggggggg atcctacatg atggaatgtc tgacaaatga cgtttatgat 1320

gcggccctta agttgataaa cgagatcgaa gaaatgggag gcatggctaa agccgttgca 1380

gaaggcattc ccaagctgcg catcgaggag tgcgccgcta ggaggcaggc taggatagac 1440

tcaggcagcg aagtcattgt aggcgtgaat aagtatcagc tcgagaagga ggatgcggtg 1500

gaagtgcttg cgatcgacaa tacctctgtt cgcaaccggc aaatagaaaa acttaagaaa 1560

atcaagtcct cccgcgatca ggctttagcc gaacggtgcc tggccgcttt aacggagtgc 1620

gccgcttcgg gggacggtaa tattctggct ctcgccgtag acgcctccag agccagatgc 1680

acggtgggtg aaataacgga cgctctgaag aaggtgtttg gggaacacaa agcgaacgac 1740

cgcatggtgt caggtgctta ccgacaggaa tttggtgaga gtaaagagat caccagcgcc 1800

attaaacggg tgcataagtt tatggagcga gaaggccgta gacctaggct actggtggct 1860

aagatgggac aggatggcca tgaccgcggg gcaaaggtca tcgccaccgg ctttgctgac 1920

cttgggttcg acgtcgacat tggtcccttg ttccagaccc ctcgggaagt ggcccagcaa 1980

gccgtggacg ctgacgtgca cgctgtgggc gtgtcaacac tggccgccgg acacaaaact 2040

cttgtccccg aactgatcaa ggagctgaac tcattggggc ggcccgatat tttggtgatg 2100

tgtggaggag tcatcccacc tcaagactac gagttcctat tcgaagtggg cgtctctaac 2160

gtctttgggc ctggtactcg catcccgaaa gcggccgtgc aagttttaga cgacatagaa 2220

aaatgcctgg agaaaaagca gcagtccgtt 2250

<210> 100
<211> 2250
<212> DNA
<213> Artificial Sequence

<220>
<223> Codon optimized sequence that encodes an MCM polypeptide with the I671V mutation

<400> 100
atgttgcggg ctaagaacca acttttcctt ctctctcccc actacctgag acaggtgaag 60

gaatcaagcg gctcccgact gatccagcag cgactgctgc atcaacagca acccctacat 120

ccggaatggg ccgcgctcgc taagaaacaa ctgaagggca aaaatcccga agatttgatc 180

tggcataccc cagagggcat ttcaattaaa cctctctata gtaagagaga cactatggac 240

ctgccggagg agttgcctgg ggtcaagcca tttacccggg ggccataccc cacgatgtat 300

actttccgcc catggacgat ccggcagtat gctggttttt caacggtgga agagtcgaac 360

aagttttata aagataatat caaggccggc caacaggggt taagtgtcgc ctttgatctg 420

gccacgcacc gtggatacga cagcgataat cctcgcgtga gaggcgatgt ggggatggca 480

ggggtcgcca ttgacaccgt cgaagacact aagatcctct tcgatgggat ccccttagag 540

aagatgagtg ttagtatgac aatgaatgga gcagttatac ctgttttggc caatttcatc 600

gtaaccggcg aggagcaagg ggttcctaag gagaagctca caggtactat ccagaacgat 660

atcctgaagg agttcatggt tcgcaatacc tatatctttc ctccagagcc cagcatgaaa 720

atcatcgcag atattttcga gtatactgct aaacatatgc caaagtttaa ttcaattagc 780

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ttcgcccctc ggctgtcctt cttttggggg attgggatga atttctatat ggaaattgca 960

aagatgcgcg cgggccgacg actgtgggcc catctaatcg aaaagatgtt tcagcctaag 1020

aactccaagt ctttactgct gcgtgctcac tgccagacta gtgggtggtc attgacagag 1080

caggacccat ataacaatat agtgaggacc gcaatcgagg ctatggctgc cgtcttcgga 1140

ggaacgcaga gcctccatac taacagcttt gatgaggccc tgggccttcc cactgtaaag 1200

agcgcccgca tcgcaagaaa cactcagatc attatccagg aagaatctgg aatccccaaa 1260

gtcgcagacc cctggggcgg ctcctatatg atggagtgct tgactaacga cgtgtacgat 1320

gccgccctca agctgattaa tgaaatcgaa gagatgggcg ggatggccaa agcggttgct 1380

gagggtatcc ccaaactgcg aatcgaagag tgcgctgcac gccgccaggc tcgtatagat 1440

tccgggagcg aggtaattgt tggggtaaac aaataccagc tggagaagga agacgctgtt 1500

gaagttctag ctattgacaa cacatccgtc cggaatcggc agatcgagaa acttaagaag 1560

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gccgtggacg ccgatgtaca cgctgtgggt gtttctaccc tcgcggctgg gcataaaaca 2040

ttggtgccag aactgattaa ggaactgaat agtctgggcc gcccggatat tttagtcatg 2100

tgtggtggag tgatcccccc gcaggactac gagttcctat ttgaggtggg agtgagcaat 2160

gttttcggcc ctggcactag gattcctaaa gccgccgtgc aggtgttaga tgacattgag 2220

aaatgcctcg agaaaaagca acagtctgtg 2250

<210> 101
<211> 2250
<212> DNA
<213> Artificial Sequence

<220>
<223> Codon optimized sequence that encodes an MCM polypeptide with the WT mutation

<400> 101
atgctccgcg ctaaaaatca gctgtttcta ctgtctccgc attaccttcg gcaagtcaaa 60

gaatcctctg gcagccgact cattcaacag cgcctgctgc accagcagca gcctctccat 120

cccgagtggg ctgctctggc caagaagcag ctcaagggga aaaatcctga ggatctgatc 180

tggcataccc ccgaagggat cagcatcaag cctctgtact ctaagcggga taccatggat 240

ctgccggaag agttacctgg cgtgaagcct ttcaccaggg ggccttatcc gacaatgtat 300

accttcagac cttggaccat tcggcagtac gctggattca gcaccgttga agaatctaat 360

aagttttata aagataatat taaagcggga caacaggggc tgtcagtggc cttcgatctc 420

gctacccacc gtggttacga cagtgataac cctcgagtta gaggtgacgt gggcatggcg 480

ggcgtagcca tagacaccgt agaagacacc aagattctgt tcgatggcat ccctctggaa 540

aagatgagcg tctctatgac catgaatggg gccgtcattc cagtgcttgc caactttatt 600

gtcacgggcg aggagcaggg ggtccccaaa gaaaaactga ccgggactat ccagaacgat 660

attctgaagg aattcatggt tcggaatacc tacatcttcc caccagagcc aagtatgaaa 720

ataatcgcag atatcttcga gtataccgct aagcacatgc ccaagttcaa ctctatttct 780

atttcaggct accatatgca ggaggccggc gccgacgcaa tccttgaatt agcctataca 840

ctagctgatg gactcgagta tagtcgtacg ggtttgcagg ccgggctaac cattgacgag 900

ttcgcccctc gactttcctt cttctgggga ataggaatga acttctatat ggaaatcgcc 960

aagatgcgag ccggaagacg actgtgggct caccttatcg aaaagatgtt ccagcccaaa 1020

aacagcaagt ccctgcttct gcgcgctcac tgccagacga gtggctggag tcttacagaa 1080

caggatccat ataacaacat tgtgcggact gcgatcgaag ccatggccgc cgtattcgga 1140

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agcgctagga ttgccagaaa cacgcagatc atcatccaag aagagagtgg catacctaag 1260

gtggccgacc cctgggggg atcctatatg atggaatgcc tgacaaacga tgtgtacgat 1320

gccgctctta agctgattaa cgagattgaa gagatgggcg ggatggcaaa agccgtggcc 1380

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gaagtgctag ccatcgataa caccagcgtg cggaaccgac agattgaaaa actgaagaag 1560

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tgtgggggg tgatccctcc ccaggactac gagttcctct tcgaggtggg agtgagcaac 2160

gtcttcgggc caggtacacg tatacccaaa gcagctgttc aggtgctaga tgacatcgag 2220

aagtgcttag aaaaaaagca acagtcagtc 2250

<210> 102
<211> 2250
<212> DNA
<213> Artificial Sequence

<220>
<223> Codon optimized sequence that encodes an MCM polypeptide with the WT mutation

<400> 102
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cccgagtggg ccgccttggc aaaaaaacaa ctgaaaggta agaacccgga agatttaatt 180

tggcatacac cggaaggaat ttctatcaaa cccctgtact ctaagaggga cacaatggat 240

ctgccagagg agctgcctgg ggtcaagccc ttcacgagag gcccctaccc caccatgtat 300

acgttccggc cttggacaat caggcaatac gccgggtttt caacagtgga agagtcgaac 360

aagttttaca aagacaatat taaggccgga cagcagggcc tttccgtagc attcgatctg 420

gcaacacacc gcgggtacga tagtgataac ccccgggtta ggggcgatgt aggtatggcc 480

ggggtagcta ttgacaccgt tgaagacacc aagatccttt ttgatggcat cccactcgag 540

aagatgtctg tgagcatgac aatgaatggg gcggtgatac cggtcctggc aaacttcatt 600

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atcctcaaag agtttatggt tagaaatacc tacattttcc cacccgagcc ttctatgaaa 720

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gccgcctctg gcgacggcaa tatcctagcc ctggctgtgg atgcgtcacg ggcccgatgt 1680

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aagatgggcc aggatggtca cgaccgcggc gcaaaagtga tcgctaccgg attcgccgac 1920

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tgtgggggcg tgattccccc tcaggattat gagttcttgt ttgaggtggg cgtgagcaac 2160

gtcttcggtc caggcaccag aattcccaag gccgctgtgc aggtgttaga cgatattgaa 2220

aagtgcttgg aaaaaaagca gcagagcgtg 2250

<210> 103
<211> 2250
<212> DNA
<213> Artificial Sequence

<220>
<223> Codon optimized sequence that encodes an MCM polypeptide with the WT mutation

<400> 103
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ccggagtggg ccgccttagc caagaagcag ttaaagggga agaatcccga ggacctgatt 180

tggcacacac ccgaagggat ttctatcaag cctctctatt ctaaaaggga caccatggat 240

ctgcccgaag agctgccggg agtcaagccc ttcacaagag ggccataccc tacgatgtat 300

acattcagac catggacgat taggcagtac gctggattca gtactgtgga agaatcaaat 360

aaattctata aggacaatat caaggccggc caacaggggt tatcagtggc tttcgacctg 420

gctactcacc gaggctatga ctccgacaat ccccgggtcc ggggggacgt tggaatggca 480

ggagtggcaa tcgatacagt cgaggatacc aagatcctgt tcgatggtat ccctctggag 540

aaaatgtctg tctccatgac catgaacggg gcagttatcc ccgtgctggc taatttcatt 600

gtaacaggag aggagcaggg ggtaccgaag gagaagctta ccggtacgat acaaaatgat 660

atcctgaaag agtttatggt gaggaacact tacatcttcc cacctgagcc atctatgaaa 720

ataatcgcag acattttcga atataccgcc aaacatatgc ctaagttcaa ctcaatcagc 780

atctctggtt atcatatgca ggaggccggc gctgacgcca ttctcgaact ggcatataca 840

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caggatccct acaacaatat cgtgagaact gcgattgagg cgatggccgc agtttttggg 1140

gggacacagt ccttgcatac gaatagcttc gatgaggcac tggggctgcc tactgttaag 1200

agcgctagga ttgctcgaaa cactcaaatc atcattcagg aagagagcgg aatccctaag 1260

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gaagggatcc ctaaactgcg aatcgaagag tgtgcagcga gacgacaagc ccggattgac 1440

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gaagtgctcg caatcgataa tacctctgtc cgcaatagac agatcgagaa attgaagaag 1560

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aagatggggc aggacggaca tgacaggggt gccaaggtga ttgctacagg gttcgctgac 1920

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gctgtcgacg ccgatgtgca tgccgttggg atttctacgc tggctgcggg tcataagacc 2040

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tgtgggggg tgattccccc tcaagactac gagttcctgt tcgaggtcgg agtttctaac 2160

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aagtgtctgg agaagaaaca gcaatcagtt 2250

<210> 104
<211> 2250
<212> DNA
<213> Artificial Sequence

<220>
<223> Codon optimized sequence that encodes an MCM polypeptide with the WT mutation

<400> 104
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gaaagtagcg gatctcgcct catccagcaa cggctcctgc accagcagca acccctacac 120

cctgaatggg ccgcactggc taaaaaacaa ctgaaaggaa aaaaccctga agacttaatc 180

tggcacaccc ccgaaggcat ttctatcaaa cctctgtaca gtaaaagaga caccatggat 240

ctgccagaag aactgcccgg ggttaaacct ttcacccgcg gcccttatcc tactatgtat 300

acctttcgac catggactat ccgccagtat gcaggcttct ccactgtcga agagtcaaac 360

aagttctaca aggataatat taaggcaggt cagcagggac tgtcagtagc ttttgactta 420

gctactcata gaggctatga tagcgacaac cccagagtta gaggcgacgt aggaatggca 480

ggagtggcta tcgatacagt ggaggacaca aagattctgt ttgacgggat tcctttggag 540

aaaatgtccg tgtccatgac catgaacggt gctgtgatcc ctgtcctcgc taattttatc 600

gtgacagggg aggaacaggg cgtgcctaag gagaagctta caggtacaat acagaacgat 660

attctcaaag aattcatggt aagaaacact tacatatttc caccagagcc ctccatgaaa 720

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aagtgtcttg agaaaaagca gcagagcgtt 2250

<210> 105
<211> 2250
<212> DNA
<213> Artificial Sequence

<220>
<223> Codon optimized sequence that encodes an MCM polypeptide with the WT mutation

<400> 105
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cccgaatggg ccgcgctcgc gaagaagcag ttgaaaggga aaaaccctga agacctcatt 180

tggcataccc ccgaaggcat tagcatcaaa ccactgtata gcaaacggga taccatggac 240

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accttcggc cttggactat tcgacagtac gcgggattct ccacagtgga ggaatcaaat 360
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aagtgtctgg agaaaaagca gcagtcagtg 2250

<210> 106
<211> 2250
<212> DNA
<213> Artificial Sequence

<220>
<223> Codon optimized sequence that encodes an MCM polypeptide with the WT mutation

<400> 106
atgctgaggg ccaaaaacca gttgttccta ctgagccctc attatctcag gcaggtgaag 60

gagagttccg gttcccgtct gatccagcag cggctgctgc accagcaaca acctctccac 120

cccgagtggg ccgctctggc gaagaagcaa ctcaaaggaa agaatccaga ggatcttata 180

tggcatacac ctgaaggaat tagcattaag cccctctatt ccaagcgtga cacaatggac 240

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actttccgac cctggactat caggcagtac gcaggattca gcaccgtgga ggagtcaaac 360

aagttctata aggacaacat caaggccggc cagcaagggc tttctgttgc attcgacctg 420

gccacgcacc ggggttacga ctcggacaat ccaagggtcc ggggcgacgt cggcatggcg 480

ggagtggcca ttgacacagt agaggacacg aagattctat ttgacggtat ccctctcgag 540

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gtcaccggtg aggagcaggg agtacctaaa gagaagctga cgggaacgat tcaaaacgat 660

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ataatcgctg atatatttga gtacacagca aaacacatgc ccaagttcaa ctccataagt 780

atcagcgggt accatatgca ggaggccgga gctgacgcaa tcctggaact ggcatatacc 840

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gcagtcgatg ctgatgtgca cgcagtggga atcagtacct tggccgcagg gcacaagacc 2040

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tgcggcggcg tcataccccc acaggactac gagtttctgt ttgaggtagg agtgtctaac 2160

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aaatgtctcg aaaagaagca gcagtccgtt 2250

<210> 107
<211> 2250
<212> DNA
<213> Artificial Sequence

<220>
<223> Codon optimized sequence that encodes an MCM polypeptide with the WT mutation

<400> 107
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gagagttccg gcagtcgctt aattcagcag agactgctcc atcagcagca gcctcttcac 120

ccagaatggg ccgcactggc taagaagcaa cttaagggaa aaaacccgga ggaccttatt 180

tggcacacac ccgaaggtat atctatcaag ccactgtaca gcaaaagaga tacgatggac 240

ctgccagagg agctccccgg ggtcaaaccg ttcaccagag ggccctaccc taccatgtac 300

acctttcgtc cgtggacaat taggcaatac gccggtttca gcacagtgga ggagagcaac 360

aagttctata aagataatat taaagccgga cagcaggggc ttagtgtggc ctttgactta 420

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ggagtcgcaa tagatacagt cgaagacact aagattctct tcgacggcat tcctcttgaa 540

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<210> 108
<211> 2250
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<213> Artificial Sequence

<220>
<223> Codon optimized sequence that encodes an MCM polypeptide with the WT mutation

<400> 108
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<210> 109
<211> 2250
<212> DNA
<213> Artificial Sequence

<220>
<223> Codon optimized sequence that encodes an MCM polypeptide with the WT mutation

<400> 109
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cccgaatggg cagcactcgc taagaagcag ttgaagggta aaaaccctga agatctgatt 180

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aaattctata aggataatat aaaggctggc cagcaggggc tgtcagtagc atttgatctg 420

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<210> 110
<211> 2250
<212> DNA
<213> Artificial Sequence

<220>
<223> Codon optimized sequence that encodes an MCM polypeptide with the WT mutation

<400> 110
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<210> 111
<211> 2250
<212> DNA
<213> Artificial Sequence

<220>
<223> Codon optimized sequence that encodes an MCM polypeptide with the I69V mutation

<400> 111
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<212> DNA
<213> Artificial Sequence

<220>
<223> Codon optimized sequence that encodes an MCM polypeptide with the I69V mutation

<400> 112
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cctgagtggg cagccctggc taaaaaacag ctaaaaggaa agaatcctga ggatctgatc 180

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<212> DNA

<213> Artificial Sequence

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<223> Codon optimized sequence that encodes an MCM polypeptide with the I69V mutation

<400> 113
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tggcatacac cagaaggcat ttcagtcaag cccctctata gtaagaggga tactatggat 240

ctgcccgagg agctgcccgg tgtaaaaccg tttacacggg gcccataccc aaccatgtat 300

accttcaggc cttggacaat ccgtcagtat gctggcttct ccacggttga ggaatctaac 360

aagttttaca aggataacat caaagctgga cagcagggtc tgagtgtggc attcgactta 420

gcaacacatc ggggatacga cagtgacaat ccccgggtga gaggcgacgt gggcatggcg 480

ggagtggcta ttgatacagt cgaagatact aaaatcttgt ttgatgggat tcccctggag 540

aagatgagcg tgtcgatgac catgaacggg gctgttatcc ctgtgcttgc aaactttata 600

gtaacagggg aggaacaggg cgtgcctaag gagaagttga ccggcaccat ccagaacgat 660

attcttaagg agttcatggt gaggaataca tatatcttcc ctccagagcc aagtatgaag 720

atcatagccg atatttttga atataccgcc aagcacatgc ccaaattcaa ttctatctca 780

atttcaggct atcatatgca ggaggccgga gcagacgcta ttctggagct tgcatacaca 840

ctcgcagatg gcctcgaata ctcccgaacc ggactccagg caggccttac gatcgacgag 900

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tccggctcag aggtcatcgt cggcgtcaat aaataccaac tagaaaagga agacgcagtg 1500

gaggtgctgg cgattgacaa taccagcgtc cgcaatagac agatcgagaa gctcaagaaa 1560

attaaaagtt ccagggatca ggcgctcgca gagcggtgtc ttgctgccct aaccgaatgt 1620

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attaagcgcg tacataagtt catggaaaga gaagggcggc ggcctcgact cctggtggcc 1860

aaaatgggac aggacggtca tgaccggggt gctaaagtca ttgcaacggg tttcgcagac 1920

ctcggttttg atgttgacat cgggccgctc ttccagacac ccagagaagt agctcagcag 1980

gcagttgatg cggatgtaca tgcggtgggc atcagtacgc tggcggcagg ccacaagacc 2040

ctggtgccag aattaatcaa ggagctcaat agtctgggtc gcccagacat tctggtaatg 2100

tgcgggggag taatcccacc ccaagattac gaattcctgt tcgaggtcgg cgtcagcaac 2160

gtctttggtc cagggactcg catccctaaa gccgctgtgc aggtgctgga tgacatcgaa 2220

aaatgcctag agaaaaagca gcaatccgtg 2250

<210> 114
<211> 2250
<212> DNA
<213> Artificial Sequence

<220>
<223> Codon optimized sequence that encodes an MCM polypeptide with the I69V mutation

<400> 114
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gagtccagcg ggtcccggct gatacagcag aggctgctgc accagcagca gcccttgcac 120

ccagaatggg ccgctttggc caagaaacag ctgaaaggga aaaaccccga agacctcatt 180

tggcataccc cagaagggat ttctgtcaaa ccactctatt caaagaggga caccatggat 240

ctgcctgagg agctgcctgg cgtgaaacct ttcacaagag gcccataccc aaccatgtat 300

acattcaggc catggaccat ccgccagtat gctggtttct ccaccgtaga agagtccaat 360

aagttttata aggataatat aaaagcagga caacagggac tgtcagtcgc cttcgatctg 420

gccacgcata gggggtacga cagtgataac ccacgggtgc ggggtgacgt cggaatggct 480

ggagtggcca tcgacaccgt tgaggataca aaaatcctgt ttgatggtat ccctctcgaa 540

aaaatgagcg tgtcaatgac gatgaatggc gctgtcatcc cagttttggc caactttatt 600

gtgacgggtg aggagcaggg tgtgcccaag gagaaactca ccggcacaat ccagaatgat 660

attttgaagg aatttatggt aagaaacact tatatcttcc cacccgagcc gagcatgaaa 720

attatcgccg acatttttga gtacacagcc aagcacatgc ctaaattcaa tagcatctcg 780

atctctggat atcacatgca ggaagccggc gctgatgcca tactcgagct cgcctacaca 840

cttgccgacg gactcgagta cagccgaact ggccttcagg ccggtctgac tatcgacgaa 900

ttcgctccta gactgtcgtt cttttggggc attgggatga atttctatat ggagatcgcc 960

aaaatgcggg ccggacgcag actctgggct catctcattg agaagatgtt tcaacccaaa 1020

aattcaaaat cccttctcct gagggcccat tgccagacaa gcggctggtc cctcacagag 1080

caggaccctt ataacaatat cgttagaacc gccattgaag ccatggccgc tgtgtttgga 1140

ggcactcaat ctttacatac aaattccttt gacgaggctt tagggttgcc taccgtcaaa 1200

tccgccagaa ttgccaggaa cacacagatt attatccaag aagagtccgg aatccccaaa 1260

gtggctgacc cctggggtgg tagttatatg atggaatgtt tgactaacga tgtatacgat 1320

gccgccctga aactgatcaa tgagatcgag gagatgggcg gtatggcaaa ggccgtcgcc 1380

gaaggcattc caaagctgcg gatagaggag tgcgctgccc gtagacaggc ccgaatagac 1440

agcggctctg aggtaatcgt gggggtcaac aagtaccagt tggaaaagga ggacgctgtc 1500

gaggttctgg ccattgacaa caccagcgtc cggaaccgcc agattgagaa gctgaagaag 1560

attaagagtt cccgggacca ggccttagcc gagcggtgtt tggcagccct cacagaatgt 1620

gctgcctcgg gcgacggcaa tattctggcc ctcgctgtcg atgcatccag ggcacgctgc 1680

acagtggggg aaattacaga tgcactgaag aaggtattcg gcgagcataa ggccaatgac 1740

cgtatggtca gtggggccta taggcaagaa tttggtgagt ccaaggagat tacatcagcc 1800

ataaagagag ttcataagtt tatggagaga gaggggcggc ggccacgtct tctggttgct 1860

aaaatggggc aagatggaca cgatcgtggg gccaaagtga tcgcaaccgg cttcgctgac 1920

ctggggttcg acgtggatat cggccctctg ttccagactc cccgcgaagt ggctcagcaa 1980

gctgtggatg cagatgttca cgctgttggg atttcaacac tggccgccgg acacaagacg 2040

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tgcgggggggg tcatcccccc gcaggactat gagttcctgt ttgaggttgg cgttagcaat 2160

gtttttggcc ctggcactcg tattccaaaa gctgctgtgc aggtgcttga cgatatcgag 2220

aagtgccttg agaagaaaca gcagagtgtg 2250

<210> 115
<211> 2250
<212> DNA
<213> Artificial Sequence

<220>
<223> Codon optimized sequence that encodes an MCM polypeptide with the I69V mutation

<400> 115
atgctcaggg ccaagaacca actgtttctt ctgtctcctc actatctgcg ccaagtaaag 60

gagtccagcg gaagtcgctt gatccagcaa cggttattgc atcagcagca gcccttacac 120

cccgaatggg ccgccctggc caagaagcaa ctgaagggca agaaccctga agatcttatc 180

tggcacaccc ctgaaggcat ttcggttaaa cccctgtata gcaaacggga taccatggat 240

ttgccagaag aacttcccgg cgtgaagccc ttcacccgcg gcccataccc tactatgtat 300

actttccggc catggacaat taggcaatac gcgggctttt ccactgtaga ggaatctaat 360

aagttctaca aggacaatat caaggctggc agcaaggac tcagcgtagc attcgacttg 420

gccacgcata gaggctatga cagcgacaat ccccgcgtaa ggggagacgt ggggatggcc 480

ggagtggcca tcgacaccgt ggaggatacg aagatcctgt ttgacggaat cccattggaa 540

aaaatgagcg tgtctatgac catgaacggc gccgttatcc ccgtcctcgc aaattttatc 600

gtgacggggg aggagcaggg ggtgcccaaa gagaagctga ccggaactat tcagaacgat 660

attctgaagg agttcatggt cagaaacact tacattttcc ctcctgagcc atcaatgaaa 720

atcatcgccg atatctttga atacacagcg aaacatatgc ctaagttcaa tagcatctct 780

attagtggct accacatgca ggaagctgga gccgatgcta tcctggaatt agcttacacg 840

ttggcagatg ggctcgaata cagccgcacc ggccttcagg ctgggctcac tatcgatgag 900

tttgcgccac gcctgtcatt tttttggggt attgggatga atttttacat ggaaatcgca 960

aagatgagag ccggccggag attgtgggcc catctgattg agaagatgtt ccaacccaag 1020

aattccaagt ccttgttatt acgcgcacat tgtcagacca gtggttggag tctcactgag 1080

caggatcctt ataataatat cgtgcgcacc gctattgagg ctatggcggc cgtttttggt 1140

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gaagggatcc ctaagctcag gattgaggag tgtgcagcca gacgccaggc ccgcatcgac 1440

tcaggtagtg aggtgatcgt cggggtgaac aagtaccagc tcgaaaagga ggacgccgtt 1500

gaggtcctcg ctattgacaa cacctccgtc aggaataggc aaattgagaa attaaagaag 1560

attaagtcct cccgggacca agccttagcc gaaagatgtc tggcagctct gaccgagtgc 1620

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atcaagcgag tgcacaagtt catggagcgg gagggcagga gaccgaggtt attggtggct 1860

aagatgggac aggacggcca cgatcgcgga gctaaagtga tcgctaccgg atttgcagac 1920

ctgggtttcg acgtagatat tggtcccctg tttcaaaccc caagggaggt cgctcaacag 1980

gccgtcgatg ctgatgtgca cgctgtgggc atcagcacct tggctgctgg acacaaaact 2040

cttgtgcccg aactgatcaa ggagcttaat tcactgggaa ggcccgacat cctggtgatg 2100

tgcggaggag tgatcccacc tcaggattac gagttcctct ttgaggttgg ggtgtctaat 2160

gtgttcggtc ccgggacccg tatcccaaaa gcggctgtcc aggtccttga cgatatcgag 2220

aaatgcctag agaagaaaca acagagcgtc 2250

<210> 116
<211> 2250
<212> DNA
<213> Artificial Sequence

<220>
<223> Codon optimized sequence that encodes an MCM polypeptide with the I69V mutation

<400> 116
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gagtctagcg gctcaaggct gatacagcaa cggctcctgc atcagcaaca gcctctgcac 120

cccgaatggg cagcccttgc caaaaaacaa ctcaagggca agaatccaga ggatttgatt 180

tggcacacgc ctgaagggat cagcgtaaag ccgctttact ctaaacgcga cactatggac 240

ctgccagaag aactgccggg agtgaagccc ttcacgcggg gtccataccc caccatgtac 300

acctttcggc catggactat tagacagtac gccgggttca gtaccgtgga ggagtctaat 360

aagttttaca aggataatat caaggctgga cagcagggtt tgagcgtggc ctttgacctt 420

gcaacccacc gggggtacga cagcgacaac ccccgggtga ggggggacgt aggtatggcc 480

ggggtggcaa ttgacaccgt agaagatact aagattttgt tcgatggaat tcctttggag 540

aaaatgagtg tgtctatgac catgaacgga gcagtgatac ccgttctagc caattttatt 600

gtgaccgggg aggagcaagg tgtgcctaaa gagaaactga ctggcacaat tcagaacgat 660

atcctgaagg agttcatggt tagaaacaca tatatatttc ccccagaacc gagtatgaag 720

attatagccg atatcttcga atatacagca aaacacatgc ctaaatttaa tagcatctca 780

atctccggtt atcatatgca ggaagcagga gccgatgcga tactggagtt agcttacacg 840

ctcgccgacg gcttagaata ttcaagaact gggttacagg cagggctaac aatcgatgag 900

tttgccccaa gactgtcctt cttttgggga atcggaatga acttttacat ggaaattgcc 960

aaaatgaggg ccggaagacg gctttgggca catttgatcg agaagatgtt tcagcccaag 1020

aactccaaga gtctcttgct gcgagcgcac tgtcaaactt ccggttggag cctcaccgag 1080

caagacccgt ataacaacat cgtcaggact gcaattgaag ccatggctgc agttttcggt 1140

gggacacaat ctctgcacac caattccttt gacgaagcac tggggcttcc gaccgtgaag 1200

tcagctcgga tcgctagaaa tacccagata attatccagg aagaaagtgg catccctaag 1260

gtggctgatc cttggggcgg gagttatatg atggagtgtc ttacaaatga tgtctacgac 1320

gcggcgctta agctgatcaa cgaaattgag gaaatgggag gaatggcaaa ggccgtcgct 1380

gaaggcatac ccaagttgag gatcgaggaa tgtgctgccc gcaggcaagc cagaattgac 1440

agcgggtcag aggtgatagt cggcgtgaac aagtaccagc tcgaaaaaga agatgctgtc 1500

gaagttttgg caatagataa tacttccgta aggaaccgcc agatagaaaa gctcaaaaag 1560

attaagagtt caagggacca ggcattagca gagaggtgcc tggcagccct gactgagtgt 1620

gccgcgtcag gggacgggaa tatactggcc ctggctgttg acgcaagtag agcccgctgt 1680

accgtgggag aaatcacaga cgcccttaaa aaggttttcg gtgaacacaa ggccaacgat 1740

cggatggtgt ccggcgccta ccggcaggaa tttggcgaat ctaaggaaat cacctcagcc 1800

attaagcgcg ttcacaagtt tatggaaagg gaagggcgga gaccaaggct gctggtggcc 1860

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gcagttgatg ctgatgttca tgccgttggc atttctaccc tggccgcagg acacaaaacc 2040

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tgcgggggag tgattccccc ccaggactac gaattcttat tcgaggtggg tgtgagcaat 2160

gtcttcggac cagggacacg gatacccaag gccgccgttc aggtgctgga cgacatcgag 2220

aaatgtttgg aaaaaaaaca gcagtccgtt 2250

<210> 117
<211> 2250
<212> DNA
<213> Artificial Sequence

<220>
<223> Codon optimized sequence that encodes an MCM polypeptide with the I69V mutation

<400> 117
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gaatccagcg gttccaggct gatccagcag cgtctgctgc atcaacaaca gccccttcac 120

cctgagtggg ctgccttagc taagaagcag ttaaagggaa aaaacccaga ggatctcatc 180

tggcacaccc cagagggcat ctctgtgaag cccttataca gcaagagaga taccatggac 240

ctacccgagg agcttcccgg agttaagccc tttactcgag gtccttatcc tactatgtac 300

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aaattttaca aggacaacat caaggctggc caacagggac tctcagtagc tttcgacctc 420

gccacccacc gcggatatga cagtgacaat ccacgcgtga gaggcgacgt cggaatggcc 480

ggagtcgcta tcgacacagt ggaggatact aaaatcctct ttgacggaat ccctctcgaa 540

aaaatgtctg tgtccatgac gatgaatggc gcagtgatcc cagtgttggc taatttcata 600

gtgaccggcg aagagcaagg tgtgccaaaa gagaagctga ccgggacaat tcagaacgat 660

atactcaagg aatttatggt tcgtaacact tatatattcc cgcccgagcc atccatgaag 720

attattgctg acatctttga gtacacagct aagcacatgc ctaaatttaa cagtatcagt 780

atctctggct atcacatgca ggaggcgggg gcagatgcaa ttcttgaact ggcctacacc 840

ttagcggatg ggttagaata cagcaggacc gggttgcagg ccgggcttac aatcgacgag 900

ttcgcccctc gcctgagctt cttctggggc attggaatga acttttatat ggagatagct 960

aagatgcggg ccgggcgtcg actctgggct cacctcatcg aaaagatgtt tcagcccaag 1020

aattcaaaaa gccttctgct gagagctcac tgccagacat ccggttggtc ccttaccgag 1080

caagacccat acaataacat cgtgcgcacc gcaatcgaag ctatggccgc cgtttttggg 1140

ggcacgcagt ccttacacac aaattcattt gacgaggcgc tcggtctccc cacggtgaaa 1200

tccgcgagga ttgcgcggaa tactcaaatc attattcagg aggagagtgg aatcccgaag 1260

gttgcggatc catggggcgg ttcatatatg atggagtgcc ttacaaatga tgtgtatgac 1320

gcagcactta aattgattaa cgagatcgag gaaatgggcg ggatggccaa ggctgtggcc 1380

gaaggcatcc caaaactgcg gatcgaggaa tgtgctgcta gaaggcaggc tcggatcgac 1440

tcaggaagcg aagtcatcgt gggcgtcaac aaataccagc tagaaaaaga agacgccgtg 1500

gaggtgctcg ccatcgacaa taccagtgta agaaatcgcc agatcgaaaa gcttaaaaaa 1560

attaagtcct cccgggacca ggcgttggcc gaacgctgcc ttgccgctct gaccgagtgt 1620

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aaaatgggtc aggatggcca cgaccgaggg gccaaggtga tcgccaccgg atttgccgac 1920

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gtgtttggac ctggcacacg catacccaag gcagctgtgc aggtgctgga tgacattgag 2220

aagtgcctgg agaagaagca gcagtccgtg 2250

<210> 118
<211> 2250
<212> DNA
<213> Artificial Sequence

<220>
<223> Codon optimized sequence that encodes an MCM polypeptide with the I69V mutation

<400> 118
atgctgcgag ccaagaatca gctcttttta ctttcacctc attatctgcg tcaggttaag 60

gaaagctcag gctctagact gattcagcaa aggttactcc accagcaaca acccctgcat 120

ccggagtggg ccgcactggc taagaagcag ttgaagggca agaatccgga agacctcatc 180

tggcacaccc cagaggggat atctgtgaag ccgctttatt ctaaacggga cactatggat 240

ctgccagaag agctgcctgg cgttaagcca ttcacccgcg gaccctatcc caccatgtac 300

acctttagac catggacaat ccgacagtat gcgggcttca gcacagtgga agagtctaat 360

aaattctaca aagataacat aaaggccggc cagcagggcc tctccgtcgc gtttgattta 420

gctacacata gaggctacga ttcagacaac ccaagagtgc gaggcgacgt tggaatggct 480

ggggttgcta ttgatactgt agaggataca aagattctct ttgacggtat accgttggag 540

aaaatgtctg tctccatgac tatgaatggg gccgtgatcc cagtcctggc caacttcata 600

gtgacaggcg aggaacaggg cgttccaaag gaaaagctga ctggaacaat ccaaaacgat 660

attctgaaag agttcatggt ccggaacact tatattttcc cacccgaacc ctcaatgaag 720

atcatcgcag atatattcga atatactgca aaacacatgc ccaaatttaa ttccatctct 780

atcagtggat accacatgca ggaggccggc gcggacgcta tactggagtt agcctacacg 840

ctcgccgacg gcctggagta tagccggacc ggtctccagg ctggtctgac tattgatgag 900

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ggcacccagt ctctgcacac taactccttt gatgaggcac tgggacttcc gactgttaag 1200

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gtggcggacc catgggggg gtcttacatg atggaatgtt taaccaatga cgtgtatgat 1320

gccgccttga agctaatcaa tgagattgag gagatgggag gcatggccaa ggctgtggca 1380

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agcgggtctg aagtcattgt aggggtgaac aaataccagt tggagaaaga ggacgcagtg 1500

gaggtactcg ccatcgataa tactagcgtc cggaaccgac aaattgaaaa gctcaagaag 1560

atcaaatcta gtagggacca ggccctcgcg gaacggtgtc tggcagcact gacagagtgc 1620

gccgccagtg gagacggtaa tatcctggct ctggcggtcg acgcaagtag ggctcggtgc 1680

actgtgggcg aaattaccga cgcgcttaaa aaggtgttcg gggagcacaa agctaacgat 1740

agaatggtga gcggagcata tcgtcaagaa ttcggcgaat caaaggaaat tacttctgca 1800

attaaaagag tacataagtt tatggagagg gaaggacgcc gccccagact gctggtggcc 1860

aaaatgggac aagatggaca cgatcgaggt gccaaagtca ttgccacagg atttgcggac 1920

ctaggattcg acgtggatat tggcccactg ttccagacgc cgagggaagt ggcccaacag 1980

gcagtagacg ccgatgtaca tgccgtggga ataagcaccc tggctgctgg ccataaaact 2040

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<210> 119
<211> 2250
<212> DNA
<213> Artificial Sequence

<220>
<223> Codon optimized sequence that encodes an MCM polypeptide with the I69V mutation

<400> 119
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ccggaatggg ccgccctcgc gaaaaaacaa ctgaagggca aaaaccccga ggacttaatc 180

tggcacaccc ctgaaggcat ctccgtgaaa ccactctatt caaaacgaga cacaatggac 240

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gctacccata ggggatacga ctccgataat ccacgcgtcc gtggcgacgt gggcatggcc 480

ggagttgcca tcgatacagt cgaggacacc aaaatactct ttgacggaat cccgctggaa 540

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aagtgtctag agaaaaagca acagtcagtt 2250

<210> 120
<211> 2250
<212> DNA
<213> Artificial Sequence

<220>

<223> Codon optimized sequence that encodes an MCM polypeptide with the I69V mutation

<400> 120

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ccagagtggg ccgccctggc caagaaacag ctcaaaggga aaaatccgga ggatctgatt 180

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<210> 121
<211> 2250
<212> DNA
<213> Artificial Sequence

<220>
<223> Codon optimized sequence that encodes an MCM polypeptide with the A499T mutation

<400> 121
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cctgaatggg ctgcgttagc caagaagcaa ttgaaaggca agaatccaga ggaccttatt 180

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<210> 122
<211> 2250
<212> DNA
<213> Artificial Sequence

<220>
<223> Codon optimized sequence that encodes an MCM polypeptide with the A499T mutation

<400> 122
atgctgcgtg ctaaaaatca actgttcctg ctgagcccac actacctaag acaggtgaag 60

gagtccagcg ggtcaagact gattcagcag cgcctttac accagcaaca gcctctgcac 120

cccgagtggg ctgccctcgc caaaaaacag ttgaagggca aaaacccaga agatctaatt 180

tggcataccc ccgaaggcat tagcatcaaa ccactgtaca gcaaacggga tacgatggat 240

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<210> 123
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<212> DNA
<213> Artificial Sequence

<220>
<223> Codon optimized sequence that encodes an MCM polypeptide with the A499T mutation

<400> 123
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aaatgcctgg aaaaaaagca acagagtgtg 2250

<210> 124
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<212> DNA
<213> Artificial Sequence

<220>
<223> Codon optimized sequence that encodes an MCM polypeptide with the A499T mutation

<400> 124
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<210> 125
<211> 2250
<212> DNA
<213> Artificial Sequence

<220>
<223> Codon optimized sequence that encodes an MCM polypeptide with the A499T mutation

<400> 125
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gccacccata ggggctacga ttccgataat cccagggtca ggggggacgt gggcatggcc 480

ggcgtggcca tcgacaccgt agaagatacc aagatcctct ttgatggaat tcccctcgag 540

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aaatgcctgg agaaaaagca gcaatccgtg 2250

<210> 126
<211> 2250
<212> DNA
<213> Artificial Sequence

<220>
<223> Codon optimized sequence that encodes an MCM polypeptide with the A499T mutation

<400> 126
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cctgaatggg ctgccctcgc caagaagcaa cttaaaggaa agaatcccga ggacctcatc 180

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gccactcacc gaggttacga tagcgacaat cctcgggtga ggggagatgt gggaatggct 480

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<210> 127
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<212> DNA
<213> Artificial Sequence

<220>
<223> Codon optimized sequence that encodes an MCM polypeptide with the A499T mutation

<400> 127

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cccgaatggg cagctctggc aaagaagcaa cttaaaggga agaacccgga agacctaatc 180

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aagtgtctgg aaaaaaagca gcagtccgtg 2250

<210> 128
<211> 2250
<212> DNA
<213> Artificial Sequence

<220>
<223> Codon optimized sequence that encodes an MCM polypeptide with the A499T mutation

<400> 128
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<211> 2250
<212> DNA
<213> Artificial Sequence

<220>
<223> Codon optimized sequence that encodes an MCM polypeptide with the A499T mutation

<400> 129
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<213> Artificial Sequence

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<223> Codon optimized sequence that encodes an MCM polypeptide with the A499T mutation

<400> 130
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actgtggggg agatcacaga cgcactgaag aaggtcttcg gggagcataa agcaaacgac 1740

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attaagagag tccacaagtt tatggaaaga gagggtaggc gcccccgcct cctggtcgcc 1860

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gcagtggacg cggatgtaca cgccgtaggc atctctacat tggcggctgg tcacaagacg 2040

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<210> 131

<211> 2250
<212> DNA
<213> Artificial Sequence

<220>
<223> Codon optimized sequence that encodes an MCM polypeptide with the R532H mutation

<400> 131
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cctgagtggg ccgccttagc caagaagcag ctcaaaggta agaacccaga agatctgatc 180

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<210> 132
<211> 2250
<212> DNA
<213> Artificial Sequence

<220>
<223> Codon optimized sequence that encodes an MCM polypeptide with the R532H mutation

<400> 132
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ccggaatggg cagcacttgc taaaaaacag ctcaagggaa agaatcctga agatcttatc 180

tggcacactc cggagggcat ctcaatcaaa ccgttgtata gcaaacgcga tacaatggat 240

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gccacacata gaggatacga ttcggacaat ccacgcgtac ggggagatgt cggcatggct 480

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<210> 133
<211> 2250
<212> DNA
<213> Artificial Sequence

<220>
<223> Codon optimized sequence that encodes an MCM polypeptide with the R532H mutation

<400> 133
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cccgagtggg cagcattggc caagaagcag ctgaaaggta agaatcccga ggacctgatc 180

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gctactcaca gaggctacga tagcgataac ccccgggtac gtggcgatgt gggtatggcc 480

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<210> 134
<211> 2250
<212> DNA
<213> Artificial Sequence

<220>
<223> Codon optimized sequence that encodes an MCM polypeptide with the R532H mutation

<400> 134
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ccagagtggg ctgcactggc caaaaagcaa cttaagggca aaaatccaga ggatctgatc 180

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<212> DNA
<213> Artificial Sequence

<220>
<223> Codon optimized sequence that encodes an MCM polypeptide with the R532H mutation

<400> 135
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<212> DNA
<213> Artificial Sequence

<220>
<223> Codon optimized sequence that encodes an MCM polypeptide with the R532H mutation

<400> 136
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cctgagtggg ccgctcttgc gaagaaacag ctcaagggga agaatcctga ggacctgatt 180

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gaaggaattc ccaagctgag aattgaagaa tgcgcagccc ggcgtcaagc caggatcgac 1440

agcggatccg aagttatcgt gggggtaaat aaatatcagc ttgaaaaaga ggatgcagtg 1500

gaagtcttgg caatcgacaa tacgtctgta cggaatcggc agatcgaaaa gctcaagaag 1560

ataaagtcaa gtagggatca ggcccttgct gagcattgcc ttgctgcttt aacagaatgt 1620

gccgccagcg gggatggcaa catcctagcc ctagctgtgg acgcttcgag ggctaggtgt 1680

accgtggggg agataaccga tgcactgaag aaggtctttg gagagcacaa agcaaacgat 1740

cgcatggtga gtggggccta cagacaggaa ttcggtgaaa gcaaagaaat tacaagcgca 1800

atcaagagag tgcataagtt catggaacga gagggaagga gacctcggct gctggtggcg 1860

aaaatgggtc aagacgggca cgacagagga gccaaagtta ttgcgaccgg attcgctgat 1920

ttggggtttg acgtcgatat cggaccactg ttccagaccc cccgagaagt agcgcagcag 1980

gctgtggatg cagacgttca tgctgtaggt atttcaacac tggcagcagg ccacaagacc 2040

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tgcggaggtg tgatcccccc acaggactat gagttcctgt tcgaggtggg agtgtcaaac 2160

gttttcggcc ctggaacgcg aatccccaaa gcagcagtgc aggtcctaga tgacatcgaa 2220

aaatgcttgg agaagaagca gcaatccgtg 2250

<210> 137
<211> 2250
<212> DNA
<213> Artificial Sequence

<220>
<223> Codon optimized sequence that encodes an MCM polypeptide with the R532H mutation

<400> 137
atgttgcgag ctaagaatca gcttttcctc ctatcccctc actacctccg acaagtgaag 60

gagtccagtg gttctagact gatccagcaa aggcttctgc accagcagca accgttgcac 120

cctgagtggg ctgctctcgc caagaaacaa ctgaagggga aaaatcctga agatctcatc 180

tggcacaccc ctgaaggcat ttccatcaag cccctctaca gcaaacgaga taccatggat 240

ctgcccgagg agctgcccgg agtaaagcct tttaccaggg ggccctatcc caccatgtat 300

actttccggc cttggactat tagacagtat gccgggtttt ctacggtgga ggagtcaaat 360

aagttttaca aggataacat caaggctggt cagcaaggcc tgtcagtggc ttttgatctc 420

gcgactcatc ggggttacga ttccgataat ccacgggtgc gaggagatgt gggcatggct 480

ggggtcgcca ttgacacagt ggaggacaca aagatccttt tcgacggcat ccctctggag 540

aaaatgagcg tgagcatgac catgaatggt gccgtgatac cagtgctggc caattttatc 600

gtgactgggg aggagcaggg agtgcccaag gagaagctga caggaacaat tcagaatgac 660

atactgaagg agtttatggt aagaaacacc tacatctttc ccccagaacc cagcatgaag 720

ataattgccg acatcttcga atataccgcg aagcacatgc cgaagttcaa ctctatcagc 780

atctctggat atcacatgca ggaagcagga gccgacgcca tccttgagct tgcgtacact 840

ttggccgacg gccttgagta ctcacggacc ggccttcagg caggacttac aatagacgag 900

ttcgccccga gactgtcctt tttttggggg attgggatga acttttacat ggagattgcc 960

aaaatgcggg ccgggagaag attatgggcg cacctgatcg agaaaatgtt ccagcctaag 1020

aactccaagt cactgcttct gcgggcccac tgtcagacca gcggctggag tctgactgag 1080

caggaccctt acaacaacat cgtgcgcacc gcaatagagg ccatggctgc tgtgtttgga 1140

gggacccagt ctcttcatac caattccttc gacgaggcac tgggcctgcc caccgtgaaa 1200

tctgcccgta ttgcccggaa cactcagatc atcatccagg aagagtctgg cattccgaaa 1260

gtggcggacc cctggggagg atcgtatatg atggagtgtt tgaccaatga tgtctacgac 1320

gctgcactga aacttatcaa cgagatcgag gaaatgggtg ggatggccaa ggctgttgcc 1380

gaggggatcc ctaaactccg aattgaagaa tgtgccgcac gccggcaggc ccgcatagac 1440

tcgggctcag aggtcattgt tggggtaaat aaataccagt tggagaagga ggatgccgtt 1500

gaggtcctgg ccatcgataa caccagcgtg agaaataggc aaattgagaa gctgaaaaaa 1560

attaagtctt caagggatca ggccctggcg gagcactgtc tagccgccct aactgagtgt 1620

gccgcctcag gcgatggcaa cattctggct ctggctgtgg acgcgtcccg cgctaggtgt 1680

acagtgggtg agattacaga cgcactcaaa aaggtgttcg gggaacacaa ggctaacgac 1740

cgtatggtgt caggagccta ccggcaggag tttggcgaat cgaaggaaat aacatcagcc 1800

attaagaggg tgcacaagtt tatggagaga gagggaagac gcccccggct gctagtggca 1860

aaaatgggcc aagatggcca cgaccgggga gcgaaagtta ttgcaacagg gttcgcagat 1920

ttgggattcg acgttgacat cggtccgctg tttcagacac cccgagaggt ggcacagcag 1980

gctgttgacg cggatgtgca cgccgtgggg atttctacgc tcgccgccgg acataagacg 2040

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tgtgggggag tcatcccgcc acaggactac gagttcctgt tcgaagtcgg ggtctctaat 2160

gtgtttggac cgggcactag aatcccaaag gccgctgtgc aggtcctgga cgatatcgag 2220

aaatgtctcg aaaaaaagca gcagtcggtg 2250

<210> 138
<211> 2250
<212> DNA
<213> Artificial Sequence

<220>
<223> Codon optimized sequence that encodes an MCM polypeptide with the R532H mutation

<400> 138
atgctgaggg ccaagaatca actgttcctt ctgtcccctc actatctgcg ccaggtcaaa 60

gagtcatccg gcagcaggct catacagcaa aggctgcttc accagcagca acccctacac 120

ccagaatggg cagctttggc gaaaaagcag ttgaaaggta agaacccgga agacctgatc 180

tggcacaccc ccgagggcat ttcaatcaaa cccctgtata gcaaacggga cacaatggac 240

cttcctgagg aattgccagg ggtgaaaccc ttcacccgag ggccataccc aactatgtac 300

actttcagac cttggaccat cagacagtat gctggattta gcacggtgga ggaatcaaac 360

aagttttaca aagataatat caaggccggt cagcaggggc tgagcgtcgc gttcgacctg 420

gcgacacacc ggggatatga ttccgataat cctcgggtca gaggggatgt ggggatggcc 480

ggcgttgcca ttgataccgt cgaggacacc aaaatactgt tcgacggaat ccccctcgag 540

aaaatgagcg tgtctatgac aatgaatggg gctgttattc cggtcctggc aaattttatc 600

gtcacaggag aggagcaggg ggttcctaaa gagaagctga caggtacaat ccagaatgat 660

atcctcaagg aatttatggt caggaatacc tacatcttcc cgcctgagcc atcaatgaag 720

attatcgccg acatttttga atatactgcc aaacacatgc ccaaattcaa ttctatctcc 780

atatctgggt accatatgca ggaggccggc gccgacgcca tccttgaact cgcttataca 840

ctcgccgatg gactggagta ttctcgcact gggttacagg ccggcctcac tattgatgaa 900

ttcgcaccaa gactaagctt tttctggggg atcggcatga atttctatat ggaaatcgct 960

aagatgcggg ccggaagaag actgtgggct catctgattg agaaaatgtt tcagcccaag 1020

aacagtaaat ccctgctgct ccgcgcacac tgccagacat caggttggtc tcttaccgaa 1080

caggacccct ataataacat cgtgaggact gccattgaag caatggctgc tgtgttcggg 1140

gggacccaat ctctgcacac aaactctttc gacgaagccc tgggcctacc tacagtcaag 1200

agcgccagaa tcgcaaggaa cactcagatc attatacagg aagagtcagg gatacctaag 1260

gttgccgatc cctggggcgg ctcctacatg atggagtgcc taacaaatga cgtgtatgac 1320

gccgcactca agctgatcaa cgaaatagaa gagatgggag gtatggcaaa agcagtagct 1380

gaaggcatac ctaaattgcg gatcgaggag tgcgccgcga ggaggcaagc cagaatcgat 1440

agtggaagtg aggtaatcgt aggcgtgaat aagtatcagc tggagaaaga agacgccgtg 1500

gaggttctag ccatcgataa cacctcagtg aggaaccgtc agattgaaaa gcttaaaaag 1560

atcaaatcat cacgggatca ggctctagcc gagcactgcc tggccgcact gactgaatgc 1620

gcagcttctg gcgatggaaa tatcctggca ctagcagtgg acgcgtctcg ggctcgatgt 1680

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aggatggtga gtggggctta ccgacaggag tttggcgaaa gtaaagagat cacatcagct 1800

atcaaaagag tgcataagtt tatggaacgc gagggacgga ggcctcggtt gctggtggcc 1860

aaaatgggcc aggatggcca cgatcgcggg gccaaggtca ttgctactgg ctttgctgat 1920

ttgggatttg acgtggacat cggtcctttg ttccaaacgc ccagagaggt ggcccaacag 1980

gcggtggatg ccgacgtgca cgcggtcggc atctctactc tggcagcagg acacaaaacc 2040

ctggtcccag agctgataaa ggagctgaat tcacttggcc gccccgacat cctcgtgatg 2100

tgcgggggtg ttattcctcc ccaagactac gagttcctgt tcgaagtggg cgtcagcaat 2160

gtgtttggac ctgggacgag aatacccaag gccgccgtgc aggttttgga tgatatcgag 2220

aaatgcctag aaaagaagca acagtcggtc 2250

<210> 139
<211> 2250
<212> DNA
<213> Artificial Sequence

<220>
<223> Codon optimized sequence that encodes an MCM polypeptide with the R532H mutation

<400> 139
atgctacggg ccaagaatca gctttttctc ttatcccctc actatctgcg acaggtaaag 60

gagagctccg ggtcacgcct gattcagcaa cggttactcc accaacagca accgttgcat 120

cctgagtggg ccgcactcgc aaagaagcag ctgaaaggga agaacccaga agacctcata 180

tggcatacgc ccgaaggaat ctccatcaag ccccttaca gcaagagaga cacaatggat 240

ctgccggaag aattgcccgg cgtgaagcct tttactcggg gaccatatcc aactatgtat 300

actttcagac cctggaccat tcgccaatat gccggctttt ctacagtgga ggaaagtaac 360

aagttttata aggataatat aaaagccgga cagcaggggc tgagtgtggc ctttgatctt 420

gccacacaca ggggctacga ttcggacaat ccccgcgtca ggggtgacgt gggaatggct 480

ggcgtggcta tcgataccgt ggaagacact aagattttgt tcgacggaat cccactcgaa 540

aagatgtcag tttctatgac catgaacggc gccgtgatcc ctgtcttggc gaatttcatc 600

gtaacaggcg aggagcaggg tgtgccaaag gaaaagctca cagggaccat ccagaacgac 660

atcctcaagg aatttatggt gcggaataca tatattttcc caccagagcc tagcatgaag 720

atcatcgcag acatctttga gtataccgct aaacacatgc ccaagtttaa cagtatttcc 780

atttcaggct accacatgca ggaagcggga gctgacgcaa tccttgagtt ggcatatacg 840

ttggccgatg gactggagta tagccgcacc gggcttcagg caggccttac aatcgatgag 900

ttcgcaccca ggttaagttt cttttggggt attgggatga atttttacat ggaaatagca 960

aagatgcggg ccggcagacg gctgtgggcg catctgatag agaagatgtt ccagccgaag 1020

aacagtaaat cactgctgtt gcgggctcac tgccagacca gcggatggtc tctgactgaa 1080

caagacccct acaacaatat cgtgagaact gccatcgagg ctatggccgc agtctttgga 1140

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gccgcactca agctgattaa tgagattgag gagatggggg gcatggcaaa agctgtggcc 1380

gaaggcatcc ccaaactcag aatagaagaa tgcgccgcca ggcgacaggc taggatagat 1440

tcaggctccg aagtcattgt gggcgtgaac aaatatcaat tggagaagga ggacgccgta 1500

gaggtgctcg caatcgacaa tacatccgtt aggaacagac aaatcgaaaa actgaagaaa 1560

attaaaagct cacgcgatca ggctctggca gagcattgtc tggccgctct gacagagtgc 1620

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attaagaggg tgcacaagtt catggagcgt gagggacggc ggccaaggct gctcgtggcg 1860

aagatgggac aggatgggca tgaccggggc gctaaagtga ttgcaacagg gtttgcagat 1920

ctgggatttg atgtagacat tggcccctta ttccaaaccc cgagggaggt agcacagcag 1980

gcagtagatg ccgatgtgca cgccgtgggg atttccacct tggcagccgg tcacaaaacg 2040

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tgcgggggtg tgattccgcc ccaggattat gagttcctgt tcgaggtagg tgtgagcaac 2160

gtgttcggcc ctgggactcg gataccgaag gccgctgtgc aagtcctgga cgatattgaa 2220

aagtgcctcg agaaaaagca gcagtccgtc 2250

<210> 140
<211> 2250
<212> DNA
<213> Artificial Sequence

<220>
<223> Codon optimized sequence that encodes an MCM polypeptide with the R532H mutation

<400> 140
atgctgcgcg ctaagaatca gcttttcctg ctcagccctc actatcttcg tcaggtaaaa 60

gagtctagcg gttccaggct catccagcag agattgttac accagcagca gcctctgcac 120

cctgaatggg ccgcactcgc aaagaaacag ctgaaaggaa agaacccgga agacctcatc 180

tggcatacac cagagggcat ctcaatcaag ccactttact ccaaacggga tactatggac 240

ctccctgagg agctgcctgg cgtaaagccc tttactcgtg gaccgtaccc tacgatgtat 300

acctttagac catggaccat caggcagtac gcaggcttta gtactgtcga ggagagcaat 360

aaattttata aagataatat caaggccggg cagcagggac tctcagtcgc gtttgacctg 420

gccactcatc gcggttacga cagcgacaat cctcgagtga gaggggacgt gggcatggct 480

ggtgtcgcga tagacactgt ggaagataca aagatcctat ttgacggaat tcctcttgag 540

aaaatgagtg tttcaatgac aatgaatggg gcggtgatcc ctgtgcttgc caactttatc 600

gttactggcg aagaacaagg cgttccaaaa gagaaactga ctggaaccat tcaaaatgac 660

attttaaagg aattcatggt ccgaaatact tacatctttc cacccgagcc aagtatgaag 720

attattgcag acatctttga gtatactgcc aaacacatgc ctaagttcaa cagcatttct 780

atctcagggt accacatgca ggaggccggc gcagacgcaa ttctggagct ggcgtataca 840

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ttcgctccca gactctcttt tttctgggga ataggcatga atttttatat ggagatagcg 960

aagatgagag ccgggaggcg gctatgggcg cacttgatcg aaaaaatgtt tcaaccaaag 1020

aattcgaagt cgctcttgct gcgcgctcac tgccaaacgt ccggctggtc actgactgaa 1080

caggatcctt acaacaacat tgtcaggact gccattgagg cgatggcagc agtgtttggg 1140

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gaggggattc ccaaactgag gatagaggaa tgcgccgccc ggcgccaggc gcgcattgac 1440

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gaggtccttg ccatagataa cacatcagtg cggaaccgcc agattgagaa gcttaaaaag 1560

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gccgccagcg gggacggcaa catacttgcc ttagccgtgg acgcctcgag agcaaggtgc 1680

acagtcggag agattaccga cgctcttaag aaggtcttcg gagagcacaa ggctaatgac 1740

agaatggttt ctggcgcata taggcaggag tttggtgaat caaaggaaat cacatctgca 1800

atcaagagag ttcacaagtt catggaacgg gaggggcgga ggcctcgact gctggtcgca 1860

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tgtggtggag tgataccacc ccaggactac gaatttctgt ttgaagttgg tgtgtctaat 2160

gtattcggcc ctggcacacg aattcctaaa gctgctgtgc aggtgttgga tgacatcgaa 2220

aagtgcctcg agaagaagca gcagtctgtt 2250

<210> 141
<211> 2250
<212> DNA
<213> Artificial Sequence

<220>
<223> Codon optimized sequence that encodes an MCM polypeptide with the T598A mutation

<400> 141
atgctccggg caaagaatca gttatttctg ttaagcccgc attacttgag acaagtgaag 60

gagtccagcg gatctcggtt aatccagcaa cgactgctgc accagcaaca gcctcttcac 120

cctgaatggg ctgcactggc caagaagcaa ttgaagggca aaaaccccga agacctgatt 180

tggcacaccc cggagggaat ctcgataaag cccttgtact ccaagaggga taccatggat 240

ctccccgaag aattgcctgg cgtcaaaccg ttcactcggg ggccataccc caccatgtac 300

acattccgcc cttggacaat cagacaatat gccggattct ctaccgtgga ggaatccaac 360

aaattctaca aagataatat caaggctggg cagcagggac tatcggttgc atttgacctg 420

gctacccacc gcgggtatga cagtgataac cccagagtaa ggggagatgt cggcatggct 480

ggcgtggcca tcgatactgt tgaagacacc aaaatcctgt tcgacgggat tcctctcgaa 540

aaaatgtctg tgtccatgac tatgaacggc gcagttattc ctgtgctggc caatttcatt 600

gtaacgggcg aggagcaggg agtgccaaag gagaagctta cgggcaccat acagaacgac 660

atcctaaagg agttcatggt gagaaatact tacatctttc cccccgaacc ctctatgaag 720

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atttccggct accacatgca ggaggccggc gccgatgcca tcctagaact cgcctatacc 840

ctcgcagacg gattggaata cagtcgcact ggcctccaag caggactgac aatcgatgag 900

tttgctccca gactttcctt cttctggggc attggaatga acttttatat ggaaattgca 960

aaaatgaggg ccggcaggcg cctgtgggct cacctcattg aaaagatgtt ccagcccaaa 1020

aacagcaagt ctttgttgtt aagagcccat tgtcaaacat ctggatggag cctgaccgaa 1080

caggacccat acaataacat tgttaggacg gccattgagg ccatggcggc cgtattcggc 1140

ggtacccaat ccttacacac caatagcttt gacgaagcct tgggcttgcc tacagtgaag 1200

tctgccagga ttgcgcgcaa tacccagatt ataatccagg aggagagcgg cattccaaaa 1260

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gaggggattc ccaaattacg gattgaagag tgtgccgcga ggaggcaggc cagaattgat 1440

agtggatccg aggtgatcgt tggggtgaat aagtatcaac ttgagaaaga ggacgccgtt 1500

gaggtgctcg ccatcgacaa tacatcagtc agaaacaggc aaatcgagaa gctgaaaaag 1560

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tgcggtggag tcatccctcc tcaggattat gagttcttgt tcgaagtggg ggttagtaat 2160

gtgttcggcc caggcacacg aatccctaag gccgccgtgc aggttctgga cgatattgaa 2220

aagtgcctgg aaaagaagca acagtcggtg 2250

<210> 142
<211> 2250
<212> DNA
<213> Artificial Sequence

<220>
<223> Codon optimized sequence that encodes an MCM polypeptide with the T598A mutation

<400> 142
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gagagctccg gaagcagatt gatccaacag cggctgctgc atcagcagca gccactacat 120

ccagaatggg ccgctctggc aaagaagcag ttgaaaggta aaaatcctga ggatctgata 180

tggcacaccc cagagggtat atccattaaa ccccttttact ctaagagaga cacgatggac 240

ctccctgaag agttgcccgg ggtgaagccc ttcactcgcg ggccatatcc aacaatgtac 300

acattccgcc cgtggacaat ccggcagtat gccggatttt ccactgtgga agaatctaac 360

aagttttata aggataatat aaaggcgggc caacagggtc tgtctgtggc cttcgatctg 420

gccactcatc gcggctacga ctcagacaat ccaagagtga gaggcgacgt cggcatggct 480

ggtgtcgcca tcgacactgt agaagatacc aaaatcctct tcgacggaat acccctggaa 540

aagatgtcag tttctatgac tatgaatggc gccgtcatcc ctgtcctcgc aaacttcata 600

gtgacaggag aagaacaggg agtacctaaa gagaagttaa ctgggacaat ccagaatgat 660

atcctgaaag agtttatggt acgcaatact tacatcttcc cacctgagcc cagtatgaag 720

attatcgctg atattttcga atatacagcc aaacacatgc caaaattcaa ctctatctca 780

atcagtggct accacatgca ggaggccggc gccgacgcaa tccttgaact ggcatacacg 840

ctggccgatg gcctggaata tagtcggact ggcctgcagg ccgggctgac tattgacgaa 900

tttgcacccc gtctgtcttt tttttgggga atcggcatga atttttacat ggagatcgcc 960

aagatgaggg ctggcaggcg tctgtgggct cacctgatcg aaaagatgtt ccaacccaaa 1020

aattcgaagt ccctgctttt aagggctcat tgccagacca gtggctggtc tctcaccgag 1080

caagatccct ataacaacat cgtgagaact gccattgaag ccatggcagc agtattcggc 1140

ggcacgcaaa gtctccacac aaattcattt gatgaagcct tggggttacc caccgtaaag 1200

agcgctcgca tcgcccggaa tacccagatt attattcagg aggagtcggg tatccctaag 1260

gtcgctgatc catggggagg ctcttacatg atggaatgcc tgacgaacga cgtttacgat 1320

gcagcactga aactcattaa tgagatcgaa gagatgggag gtatggccaa ggccgtggcc 1380

gagggcatcc ctaaactgag gatagaggag tgtgctgcac gaaggcaggc acgtatcgac 1440

tctggctctg aagttatcgt gggggtgaat aagtatcagc tcgagaaaga ggacgccgtc 1500

gaagtgctgg ctatagacaa tacctctgta cggaatagac aaattgagaa actcaagaag 1560

ataaagagta gcagagacca agctcttgcg gagcgatgcc ttgccgcttt gactgagtgc 1620

gccgcctctg gcgacggaaa cattctggct cttgcagtgg acgcctcgcg ggcccggtgc 1680

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attaaaagag ttcacaagtt tatggaacgc gagggccgac gacctagatt gctagttgcg 1860

aaaatgggtc aggacgggca tgatagaggg gccaaggtta tcgctaccgg attcgctgac 1920

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tgcggcggcg taatcccacc ccaggactat gagtttctgt tcgaagtcgg cgtcagcaat 2160

gttttcggcc cgggcactcg cattccgaaa gccgcagttc aggtgctcga cgacatcgaa 2220

aaatgcctgg agaagaagca gcagtctgta 2250

<210> 143
<211> 2250
<212> DNA
<213> Artificial Sequence

<220>
<223> Codon optimized sequence that encodes an MCM polypeptide with the T598A mutation

<400> 143
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gagagcagtg gttcaagact gatacagcaa cggcttctcc accaacagca accactgcac 120

cccgaatggg ccgctctggc taagaaacag ctcaagggca agaatccaga ggatctcata 180

tggcataccc ctgaaggcat cagcattaaa ccccttttata gcaagaggga taccatggat 240

cttcccgagg agcttcccgg cgtaaagccc tttacaagag ggccttatcc taccatgtac 300

acgtttaggc catggacaat taggcaatat gctggattta gtacagtgga agaatctaat 360

aaattctata aagacaatat taaggcaggc cagcaaggtt tgagtgtggc ctttgatctg 420

gctacccacc gcggttacga tagtgacaac cctagggtac gcggagatgt cggtatggct 480

ggagtcgcta tagatacggt cgaagataca aaaattttgt tcgacggaat tcccctggag 540

aagatgtctg tgagcatgac gatgaatggg gctgtgatac ccgttctggc aaacttcatc 600

gtgaccggag aggagcaagg cgtcccgaag gaaaagctga ccgggaccat ccagaatgac 660

atcctcaagg aattcatggt aaggaatacc tacatattcc ccccggagcc ttctatgaag 720

atcattgcgg acattttcga gtacactgca aagcatatgc cgaaatttaa ctccatttca 780

atttctggtt accacatgca ggaggccggc gccgatgcaa ttctggaact cgcttacact 840

ctcgccgatg ggctcgaata cagtcggaca ggactccagg caggacttac tatcgatgag 900

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aagatgcgtg cgggtcggag gctgtgggcg catcttattg aaaagatgtt ccagccaaaa 1020

aatagcaagt ctctcttact cagggcccac tgtcagacgt cagggtggtc tttaacggag 1080

caagatcctt ataacaacat tgtcaggacg gccatcgagg ctatggccgc agtcttcggg 1140

gggactcagt ctctgcacac aaacagcttt gacgaggccc tgggtctacc aacggtcaaa 1200

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gaggggatcc caaaacttag aatcgaggaa tgcgctgcgc gcagacaggc tagaatagat 1440

agcgggtcag aggtgatagt gggggtgaac aaataccaac tcgagaaaga agatgccgtt 1500

gaagtgctgg ctatagataa cactagtgtc cggaacagac agatcgaaaa attgaaaaag 1560

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attaaacgtg tacacaaatt catggaaaga gaggggcgcc gcccgcgctt actggtggcc 1860

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gtgtttggcc ccggtacccg tatccctaag gccgcagtgc aggtactgga cgacatcgag 2220

aagtgcttag agaagaagca gcagtctgtc 2250

<210> 144
<211> 2250
<212> DNA
<213> Artificial Sequence

<220>
<223> Codon optimized sequence that encodes an MCM polypeptide with the T598A mutation

<400> 144
atgcttaggg caaagaacca actatttttg ctgagtccgc attaccttag gcaggttaag 60

gaaagtagtg gctcccgtct gattcagcaa aggctactgc accagcagca gccactgcac 120

cctgagtggg ccgcgttggc gaagaaacag ctgaagggca agaatccaga agaccttata 180

tggcacaccc ccgagggcat ctcaatcaaa ccgttatatt cgaagaggga taccatggat 240

ttgcccgagg agctgcccgg cgtcaagccc tttactaggg ggccttatcc gacaatgtac 300

acattccgac cttggaccat tcgtcagtac gcgggtttct ctacagttga agagagcaac 360

aagttttata aggacaatat caaggcgggc cagcaggggc tgagtgtcgc ctttgatctc 420

gctacacacc gaggatacga tagtgacaac cccagggtta ggggcgatgt tgggatggct 480

ggagtggcca ttgatacagt agaggatact aaaatcctct ttgacggcat acccctggaa 540

aaaatgagtg tctccatgac tatgaatgga gcagtaatcc cagttttagc aaatttcatt 600

gttacgggag aggagcaggg ggtgcccaaa gagaagctga ctggcacaat ccagaacgat 660

atattaaagg aatttatggt gaggaatacg tacatcttcc ctcccgagcc ttcaatgaaa 720

atcattgcag acattttcga gtacacagct aagcacatgc ccaagttcaa ttccatttcc 780

atctcaggct accacatgca ggaggcaggc gccgatgcca tcttggagct ggcctatacg 840

ttggccgacg gcttggaata ttcccgcacc ggactccagg ccgggctaac cattgatgaa 900

ttcgccccaa ggctgtcatt tttctggggt atcggaatga acttttacat ggagatagct 960

aagatgagag ctggtcgacg cttgtgggct catttgatag agaagatgtt ccaacctaaa 1020

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caggacccct acaataatat tgtgaggaca gcaattgagg ccatggctgc tgtttttggc 1140

gggacacagt cccttcacac aaactcattt gatgaggccc tgggcctgcc caccgtgaag 1200

tcagcacgca ttgcaagaaa cacccagatt atcatacagg aagaatccgg tatccccaag 1260

gtcgccgacc cgtggggcgg tagctacatg atggagtgct tgacaaacga cgtatacgac 1320

gccgccctga aactgattaa cgaaattgaa gagatgggcg ggatggctaa ggccgtagcc 1380

gaaggtattc ccaaactgag aatcgaagaa tgcgccgcta gaaggcaggc acgcatcgac 1440

tccggttctg aggtcatcgt gggggtgaac aagtaccagc ttgagaagga ggacgctgtt 1500

gaggtcctgg ctatcgataa cacgtcagtg agaaatagac aaatcgagaa gctcaagaaa 1560

attaaatcca gccgcgatca ggctcttgcc gagaggtgcc ttgccgcact cacagagtgt 1620

gccgcctcag gcgacgggaa tatattggca ctggcggtgg atgcaagcag agcgagatgc 1680

actgtcggtg aaatcacaga cgcacttaag aaggtctttg gggaacacaa ggcaaacgat 1740

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atcaagagag tgcataaatt catggaacga gagggtaggc ggcctaggct gctggtggca 1860

aagatgggcc aggacggaca tgatcggggt gccaaggtta ttgcgacggg ctttgcggat 1920

ctgggatttg atgtcgacat cggcccactc tttcagactc ctcgcgaggt cgcccagcag 1980

gctgtggatg cggacgttca cgctgtcggg atctcaacac tcgctgccgg ccacaagacg 2040

ttagtgcctg aattaattaa agaactgaat agcttaggcc ggccagacat attggtgatg 2100

tgcggtggcg tgattcctcc ccaggactat gaatttctct ttgaggtggg ggtctcgaat 2160

gtgttcggcc caggcaccag gatccctaag gctgcagttc aggtgctcga tgatatcgag 2220

aagtgcctag agaagaaaca gcagtcggta 2250

<210> 145
<211> 2250
<212> DNA
<213> Artificial Sequence

<220>
<223> Codon optimized sequence that encodes an MCM polypeptide with the

T598A mutation

<400> 145

atgttacgcg ccaaaaatca gcttttctta ctttcacccc attacctgcg ccaggtcaaa 60

gaaagctccg gatctcgact tatccagcaa agactacttc atcagcaaca gccgttgcac 120

cccgaatggg cagccctagc aaaaaagcag ctcaaaggga aaaaccctga ggaccttatc 180

tggcatactc ccgaaggaat ctcaatcaag cccctctact ctaaaaggga taccatggat 240

ctgcccgaag agttgcctgg ggttaaaccc ttcactcgag ggccataccc cactatgtac 300

acatttcgtc cgtggactat ccgacaatat gccgggtttt ctacggtaga agagagtaat 360

aagttttaca aagacaatat taaggccggt cagcaggggt taagcgtggc gttcgactta 420

gctacgcatc gcggctatga ctccgacaac ccccgggtta ggggggacgt gggcatggct 480

ggcgttgcaa tcgataccgt ggaagatacc aaaattcttt tcgacggaat acctttggag 540

aaaatgagcg tctctatgac catgaacgga gcagtgattc ccgtgcttgc caatttcatc 600

gtcactggcg aagaacaagg ggtgcccaag gaaaaattaa ctggcacaat ccaaaacgac 660

atcctgaagg aattcatggt gcggaacacc tatatctttc cacctgagcc tagtatgaag 720

atcatcgccg acatcttcga atatactgct aagcatatgc ccaagttcaa cagtatttca 780

atatcgggat atcacatgca ggaggcaggt gccgacgcca tcctggaact ggcctacaca 840

ttggctgacg ggctggaata ctccagaacc gggctgcagg cgggtctgac catcgacgag 900

tttgctcctc ggttatcttt tttctgggga atcggaatga atttctatat ggagatagct 960

aaaatgcgcg ccgggcgaag actctgggcc cacctgatcg aaaaaatgtt ccagcccaaa 1020

aatagtaaga gtctccttct ccgggcgcac tgtcagactt caggatggtc gctcaccgag 1080

caagatccat acaataatat tgtccggacc gctatcgagg ctatggcagc agtttttggc 1140

ggaacccagt ctctgcacac aaattccttc gatgaggctt tgggactccc aacagtgaag 1200

agcgccagaa tagcacggaa cactcaaatc attatccagg aggaaagtgg tatcccaaaa 1260

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gagggcattc ctaaacttag aatcgaggaa tgcgccgcta gacggcaggc gagaattgac 1440

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gaagtgctgg ccatagataa tacctccgtc aggaaccggc agatcgagaa gttgaagaag 1560

atcaaaagca gccgggacca ggccttggct gaacgctgcc tcgctgcact gaccgaatgc 1620

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attaagagag ttcacaaatt tatggagcgg gaggggcgcc gcccccgcct gctcgtcgca 1860

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gtgtttggcc cagggacgcg gataccaaaa gccgcagtgc aggtcctgga tgacattgag 2220

aaatgtctgg agaaaaagca gcagagtgtg 2250

<210> 146
<211> 2250
<212> DNA
<213> Artificial Sequence

<220>
<223> Codon optimized sequence that encodes an MCM polypeptide with the T598A mutation

<400> 146
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gaatcaagcg gttcaaggct gatccagcag cgcctgcttc accaacaaca gccacttcac 120

ccggaatggg ccgctctggc caagaaacaa ctcaagggga aaaacccaga ggacctcatc 180

tggcatactc ccgagggaat ctctattaag cctctttact ccaagaggga taccatggat 240

ctgcctgaag agctgccagg agtgaagcca ttcacccgag gaccttatcc gacaatgtat 300

acattccgcc cttggacgat ccggcagtac gctggcttca gtaccgtgga ggagagcaac 360

aagttctaca aggataacat taaggctggc cagcagggac taagcgtagc tttcgacctc 420

gccactcata ggggttacga cagcgacaat ccgagagtca gaggggacgt tggcatggct 480

ggcgtcgcca tcgataccgt ggaggatacc aagattcttt tcgatggaat cccactagaa 540

aagatgtccg tgtcaatgac aatgaatggc gctgttatcc ctgtgcttgc aaacttcatc 600

gtcacagggg aagaacaggg ggtgcctaaa gagaagctta ctggcacaat ccagaacgac 660

atactcaaag agtttatggt tcggaatacc tatattttcc ctcccgaacc ttcgatgaag 720

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attagcggct atcacatgca agaggccggt gccgatgcca tcctagagct ggcctacact 840

ctcgccgacg gcctggagta ctcacgcact ggtctgcagg ctggcctaac catcgatgaa 900

ttcgcaccca ggttgagttt tttctgggga atcgggatga atttctatat ggagatagca 960

aagatgcgcg ctgggcggag actgtgggcc cacctgatcg aaaagatgtt tcaacccaag 1020

aactcaaaaa gcctattgct ccgcgctcac tgtcagactt ctggatggag tttgactgag 1080

caagacccgt ataacaacat tgtgagaaca gcaattgagg ccatggccgc tgtcttcgga 1140

ggcacacaat ccctccatac aaattccttt gatgaggcgc tcggcctccc aacggtgaag 1200

agtgcacgaa ttgcccgtaa tactcagatc attattcaag aggagagtgg aatcccaaag 1260

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gcagccctga aactgatcaa cgagatagag gagatgggag gaatggccaa ggctgtggct 1380

gagggaatcc caaagctgag aatcgaagag tgcgccgcac gaagacaggc cagaatcgac 1440

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gaggtcttgg ccattgacaa tacttctgtg agaaatagac aaatcgagaa acttaagaaa 1560

atcaagtcaa gtagggacca ggccctcgcg gagcggtgtc tcgcagccct gacggagtgc 1620

gccgccagcg gcgacgggaa catcctcgcg ctggccgtgg atgcatccag agctcgctgt 1680

accgtgggcg aaattactga tgcactcaaa aaggtctttg gggaacacaa agcaaacgac 1740

cgcatggtct ctggagccta ccgccaagag tttggcgaga gcaaagagat agcatctgcc 1800

atcaagaggg tgcacaaatt catggagcga gaagggagga ggccccgctt gctcgttgcg 1860

aagatgggac aggatggcca cgaccgtggc gctaaagtaa ttgccaccgg gtttgccgac 1920

cttggctttg atgtggatat cgggccactg ttccagactc ctcgcgaggt agcccagcag 1980

gccgtggatg cggacgtcca cgcagttgga attagcacct tggcggcggg ccacaagact 2040

ctggtacctg aacttatcaa ggaactgaac tctctgggtc gtccagatat tctggtcatg 2100

tgcggcgggg tgattcctcc gcaggactac gaatttctat ttgaggtcgg ggtttccaac 2160

gtctttgggc cgggcactag gataccaaag gccgctgtcc aggtgcttga cgatatcgag 2220

aaatgcctgg agaagaagca gcagagtgta 2250

<210> 147
<211> 2250
<212> DNA
<213> Artificial Sequence

<220>
<223> Codon optimized sequence that encodes an MCM polypeptide with the T598A mutation

<400> 147
atgctgaggg caaagaatca gctgttcctg ctgtcccctc actacctccg tcaagtgaag 60

gagagctctg gttcgcggtt aattcagcag agactgcttc atcaacagca acccctccac 120

cccgaatggg ctgccctggc caagaaacag ctcaaaggta agaaccctga ggacctgatc 180

tggcacacac ctgaagggat cagcatcaag cctctctact ccaagcgcga cactatggat 240

ctgccagagg agctccctgg cgtaaaacca ttcacccggg gaccctatcc tacaatgtac 300

acctttcggc cttggactat cagacagtac gctgggttct ctacagtaga agagagcaat 360

aagttttaca aggataatat aaaagctggt cagcagggcc tcagtgtagc cttcgaccta 420

gctacacaca gaggatatga ttccgataat ccgagagttc ggggagatgt cggcatggcc 480

ggagtggcaa tagacaccgt ggaagatact aagatcctgt tcgatggcat tccgctcgaa 540

aaaatgagtg tcagcatgac tatgaacggc gctgtgatcc ccgtgcttgc aaactttatc 600

gtaaccgggg aggaacaggg tgtgccaaaa gagaaactca caggaacaat tcagaacgat 660

attcttaagg agttcatggt cagaaacaca tacattttcc cacccgagcc ttcaatgaaa 720

atcatcgccg acatattcga gtacaccgct aaacacatgc caaaatttaa ttcaattagt 780

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ggcacgcagt ctctccacac taactccttc gacgaagccc taggtcttcc aacagtgaag 1200

tccgctagaa ttgcccgaaa tacccagatc attattcaag aggaatctgg aatccctaag 1260

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gaaggcatcc ccaagctgcg gatagaagaa tgtgcggcac gcagacaagc ccgcatagac 1440

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gaggtactgg ccattgacaa tacaagtgtc aggaaccgac agattgagaa gctgaagaaa 1560

attaaatcct ctagggacca ggccctggct gaaaggtgtc tggcggcatt gaccgaatgc 1620

gcagcaagcg gcgacggaaa catactggca ttggcggtag acgcaagccg tgctcgatgt 1680

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attaaaagag ttcacaaatt tatggagcgc gagggaagga gaccccggct gctcgtcgca 1860

aagatgggcc aagacggcca tgatcgcggc gcaaaagtca tcgcaacggg ctttgccgat 1920

ctcgggtttg atgtcgatat tggcccactg ttccagacac ccagggaagt ggctcagcaa 1980

gccgtcgatg ccgatgttca cgccgtgggc atctcaacac tagctgccgg ccataagaca 2040

ctagtaccag aactgatcaa ggaactgaat tctcttggta gacccgacat cctcgtgatg 2100

tgtggcgggg ttatcccgcc gcaagactac gagtttcttt ttgaggtcgg tgtgtcgaat 2160

gtcttcggac ccggcactcg gattcctaaa gctgcagtgc aagtgttgga cgacatcgag 2220

aagtgcctgg aaaagaagca acagagtgtt 2250

<210> 148
<211> 2250
<212> DNA
<213> Artificial Sequence

<220>
<223> Codon optimized sequence that encodes an MCM polypeptide with the T598A mutation

<400> 148
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gagtctagcg gttccagact cattcagcaa cgcttgcttc accagcagca gccgctccac 120

cctgaatggg cagccctggc aaagaagcag ctaaaaggta agaatccaga ggatctgatc 180

tggcacacac ccgaggggat ctccattaag cccctatact ctaagagaga cactatggac 240

ttacctgaag aactgccagg tgtgaagcct tttaccagag ggccatatcc taccatgtat 300

acattccgac catggactat ccgtcaatat gcggggttca gcaccgtaga ggagtcaaac 360

aaattttata aggataatat caaagctgga cagcagggcc tgtccgtcgc attcgatcta 420

gcaacacaca gaggatatga ttcagacaat cctcgggtgc gggggacgt cggaatggcg 480

ggggtcgcca tcgacaccgt ggaggacacc aagatactct tcgatggcat tcccctcgaa 540

aaaatgtccg tgtctatgac catgaacggc gcggtcattc ctgtgctggc taactttatc 600

gtaaccggag aagagcaggg cgtgccaaaa gaaaagctga ctggaacaat ccagaatgat 660

atcttgaaag agttcatggt gcggaacaca tacatcttcc caccggaacc ttcaatgaag 720

atcattgctg atattttcga atacactgca aaacacatgc ccaaattcaa tagcataagt 780

ataagcggat atcacatgca ggaggctgga gccgacgcca ttcttgaact ggcgtatacc 840

ctggcggacg gattggaata tagcagaaca ggactacagg cagggttgac catcgacgag 900

ttcgccccaa ggctgagttt cttctgggga attgggatga atttttacat ggagattgcc 960

aagatgcgcg ccggtcgtcg actctgggca catcttatcg aaaagatgtt ccagcccaag 1020

aatagcaagt cactgctcct gagagcgcac tgccaaacgt ctggctggag cttgactgag 1080

caggacccct acaataatat cgtgagaacg gctatcgaag ctatggccgc tgtttttggg 1140

ggcactcagt ctctgcacac aaacagtttt gatgaagcac tcggcctccc aaccgtcaag 1200

tcagcaagga tcgccaggaa cacccaaatc ataatacagg aagagagcgg catccccaaa 1260

gtggcagatc catgggggg aagctatatg atggaatgct tgacaaatga cgtgtacgat 1320

gcagccctga aactgattaa cgagattgag gaaatgggtg ggatggctaa agccgtagcc 1380

gagggcattc caaaactgcg catagaggaa tgtgcagcta ggaggcaggc tagaatagat 1440

agcggcagtg aggtcatcgt tggtgtcaac aagtaccagc tggaaaagga agatgccgtt 1500

gaggtcctgg ctattgacaa cacctcggtc agaaatcggc agatagagaa gctgaagaag 1560

ataaagagta gtagagatca agcccttgcc gaacgttgcc tcgccgccct gaccgagtgc 1620

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attaagaggg tgcacaaatt tatggagaga gagggccggc gcccccgact gttggtggca 1860

aaaatgggac aggatggaca tgacagaggc gcaaaagtca ttgccaccgg atttgccgat 1920

ctgggctttg acgtggacat tgggccgttg tttcagactc cgagggaggt cgctcagcag 1980

gccgtggatg ctgacgttca tgccgtggga atcagcaccc tggccgccgg acataaaacc 2040

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gtgtttggcc cggggacccg tatcccgaag gccgcagttc aggtgttgga tgacattgag 2220

aaatgcttag agaagaagca gcagagcgta 2250

<210> 149
<211> 2250
<212> DNA
<213> Artificial Sequence

<220>
<223> Codon optimized sequence that encodes an MCM polypeptide with the T598A mutation

<400> 149
atgctgcggg caaagaacca actcttcctc ctaagcccgc attacctgag gcaggtcaag 60

gagagttccg gctctcgttt aattcaacag cggctgctgc accagcagca gccattacac 120

cctgagtggg cggcgctagc aaagaaacag ttgaagggaa agaaccctga ggatctgatc 180

tggcacaccc ctgaggggat ttccatcaag ccactctatt ctaagcggga cactatggat 240

cttccagaag aactgcccgg cgtaaagccc ttcacccgcg gcccttaccc taccatgtac 300

accttccgac cttggaccat caggcagtac gcaggattct caactgtgga ggaatctaac 360

aaattttaca aggacaacat aaaggccgga cagcaggggt tatctgtcgc cttcgacctg 420

gccacacacc gagggtacga ctctgataac ccgagagtac gcggggacgt gggaatggct 480

ggagtcgcaa tcgacacagt ggaagacacc aagatcctgt tcgatggcat cccactggaa 540

aagatgagtg tcagcatgac aatgaatgga gccgttattc ctgtgctggc taactttatc 600

gtgacgggag aggagcaggg ggtgccgaag gaaaagctga cgggtaccat ccagaatgac 660

atcctgaagg aattcatggt gcggaatact tatatttttc ctccagagcc atccatgaag 720

atcatcgctg acatcttcga atacaccgcc aaacatatgc cgaagtttaa cagtatctct 780

atctctgggt accacatgca ggaggccggg gcagacgcta tcttagagtt ggcctataca 840

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tttgcgcccc gcctgtcttt tttttggggg attgggatga acttctatat ggagattgca 960

aaaatgagag ctggcaggcg cctatgggcg cacctgatcg aaaagatgtt ccagccaaag 1020

aattctaagt ctcttctcct gagagcccac tgtcagacca gtggttggtc cttaaccgag 1080

caggacccat acaataatat agtacgtaca gctattgaag ccatggccgc ggtgtttggc 1140

ggaacacaga gcctccacac caacagcttt gacgaggccc tgggcttacc aaccgtcaaa 1200

tccgcaagga tcgccaggaa tacacagatt attatacagg aggaaagtgg cattcctaag 1260

gtggcagatc cctggggcgg ttcttacatg atggaatgcc tgacaaatga tgtctacgat 1320

gccgccttga aactgatcaa tgaaatcgaa gagatgggtg gcatggcaaa agctgttgca 1380

gagggaattc ctaagctgcg gattgaagaa tgtgcagctc gccggcaggc tagaatcgac 1440

tccggtagcg aagtcattgt tggagtcaac aagtaccagc tagagaaaga ggacgcagtc 1500

gaggtgctgg ccattgacaa cactagcgtg cggaatagac agatcgagaa gctgaaaaaa 1560

ataaagtcct cacgcgatca ggcgctggca gaacggtgct tagcagctct taccgagtgc 1620

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attaaaaggg tgcataaatt tatggaacga gagggaagac ggcctcgatt actagtcgcc 1860

aagatgggac aggatggcca cgaccgaggg gccaaggtca tcgctacggg gttcgcagat 1920

ctcggctttg atgttgatat cggaccactg ttccagaccc ctcgagaggt cgcccagcag 1980

gccgtcgatg ccgacgtcca cgcagtgggc atatccacgc tggcagctgg gcataaaact 2040

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tgtgggggcg taatcccacc tcaggattac gagtttcttt ttgaagtggg agtaagcaac 2160

gtcttcgggc cagggaccag gattccaaag gcggctgtcc aggtgctgga cgacatagag 2220

aagtgtttag aaaagaaaca gcagagtgtt 2250

<210> 150
<211> 2250
<212> DNA
<213> Artificial Sequence

<220>
<223> Codon optimized sequence that encodes an MCM polypeptide with the T598A mutation

<400> 150
atgcttcgag ccaagaatca gctcttcctc ttgagcccac actatctgag gcaggtcaag 60

gagtcatctg ggtctcggtt gattcagcaa cgccttctgc accagcagca gccgctccat 120

cccgagtggg ccgccctggc caaaaaacaa ctcaagggaa aaaatccaga ggatttgatc 180

tggcatacac ccgaagggat ctccataaag cctttgtata gtaagcgcga cacaatggat 240

ctcccagagg agctgcctgg tgtaaaacct ttcaccagag ggccctaccc caccatgtac 300

acctttagac cgtggacaat cagacagtac gctgggttct caacagtgga agagtccaac 360

aagttttaca aagataacat caaagcgggc cagcaggggc tcagcgtggc cttcgactta 420

gccacccacc gagggtatga cagcgataat ccgcgtgttc gcggggatgt cgggatggcc 480

ggcgtggcca ttgacaccgt ggaagataca aagatcctat tcgatggaat cccactggaa 540

aagatgagcg tctctatgac tatgaacgga gctgttatcc cagttctggc aaacttcata 600

gtaactggtg aagaacaggg cgtgcctaaa gagaagttga cagggactat ccagaacgac 660

atcttgaagg agttcatggt gaggaacacg tacatttttc cacctgagcc atcaatgaag 720

attatcgctg acatattcga atataccgca aagcacatgc ctaagttcaa ctcaatttcc 780

atctcaggct accacatgca ggaggccggc gcggacgcta ttctggaatt ggcttatacc 840

ctcgcggatg gactcgaata ttcgcggaca ggcctccaag ccgggttgac catcgatgag 900

tttgcaccca gactcagctt cttttggggc atcggaatga acttctatat ggagatagca 960

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aacagtaaaa gccttctcct cagagcacac tgccaaacca gcggttggtc cttaacagaa 1080

caggatcctt ataacaatat tgtgaggacc gccattgagg ctatggccgc agtctttggc 1140

ggtacgcaga gcctccatac caatagcttt gacgaagctc ttgggcttcc tacagtgaaa 1200

agcgcccgga tcgcaaggaa cacccagatt atcatccagg aagagagtgg catacccaaa 1260

gtggctgatc cttggggagg aagctatatg atggagtgcc tcaccaacga tgtgtacgat 1320

gcagccttga agttgatcaa cgagatcgag gaaatggggg gcatggctaa ggctgttgcc 1380

gaaggtatcc caaaacttag gatcgaggaa tgcgctgcac gccgtcaggc tagaatcgac 1440

agtggtagcg aggtgatcgt gggcgtgaac aagtatcagc tcgagaaaga agatgcagtc 1500

gaggtgttag caatcgacaa taccagcgtc cggaaccgac agattgaaaa actaaagaaa 1560

attaagtcct caagagatca ggccttggct gagagatgtc ttgccgctct cacagagtgt 1620

gccgcttcag gggatggaaa tattctcgca ctggccgtgg atgcctctag agctagatgt 1680

accgtggggg aaatcaccga tgcattgaag aaggtctttg gggagcacaa agcaaacgac 1740

cggatggtta gcggcgccta tcgccaggag ttcggcgaat caaaggagat tgcctcagcc 1800

atcaaacgtg tacataaatt catggagagg gaaggtcggc gcccacgtct cctggttgcc 1860

aagatgggtc aggatggcca tgaccggggg gcgaaagtga tcgcaacggg ctttgccgat 1920

ttaggcttcg atgtggatat cggacccttg tttcagaccc ctcgtgaagt ggcacaacag 1980

gccgttgacg ccgatgtaca cgccgtcggc atcagcaccc tggccgcagg ccacaagaca 2040

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tgcggagggg tgattccccc gcaggattac gagtttctgt tcgaggttgg agtgtccaat 2160

gtgtttggcc ctggcaccag gattccaaag gccgccgtac aggtgcttga tgatatcgag 2220

aagtgcctgg aaaagaagca acaatcggtt 2250

<210> 151
<211> 2250
<212> DNA
<213> Artificial Sequence

<220>
<223> Codon optimized sequence that encodes an MCM polypeptide with the I671V mutation

<400> 151
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gagagcagcg gctcaaggct gatccaacag aggttgctgc accagcagca gccccttcat 120

cccgagtggg cagctctggc caagaaacag ttgaagggca agaaccccga ggacctgatt 180

tggcataccc ccgagggcat cagcatcaag cctctgtact ccaagcgcga caccatggac 240

ctccccgagg aactgcccgg ggtgaaacca tttacacgcg gcccctaccc caccatgtac 300

accttccggc catggacgat taggcagtac gctggcttca gcacggtgga ggagagcaat 360

aagttctaca aggacaacat caaggcaggg cagcaggggc ttagcgtggc ctttgacctg 420

gccacacacc gggggtacga cagcgacaat cccagggtgc ggggcgacgt tggcatggcc 480

ggcgttgcta tcgataccgt ggaggatacg aagatactgt ttgacgggat ccccctggag 540

aaaatgagcg tgagcatgac aatgaacggc gctgtgatcc ctgtcctcgc taacttcatc 600

gttaccggcg aggaacaggg agtacctaag gaaaagctga ctggaactat tcagaatgac 660

attctcaagg aattcatggt caggaacact tatatctttc cccctgaacc gtctatgaaa 720

atcatagcag acatttttga gtataccgcc aagcacatgc ccaagtttaa cagcatctcc 780

atctctggct accacatgca ggaggcaggc gccgacgcta ttctggagct ggcgtacact 840

ctcgccgacg gactggagta ctctcgcact ggactccagg ccgggctgac catcgatgag 900

ttcgcaccga ggctgtcctt cttctggggc attggaatga acttttacat ggagatcgct 960

aagatgcgag caggccggag actgtgggcc cacctgattg aaaaaatgtt ccaacctaag 1020

aattccaaga gcctgctgtt gagagcccac tgccagacca gcggctggtc gctgaccgag 1080

caggacccct acaataacat agtgcggacc gctattgaag ccatggccgc cgtttttggc 1140

ggcactcaga gcctgcacac caacagcttt gacgaggccc tgggcctgcc cactgtgaag 1200

agtgccagaa tcgccaggaa tacccagatt atcattcagg aggagtcagg aatacccaaa 1260

gtggccgacc cctgggggg tagctacatg atggagtgcc tgacaaacga cgtgtacgat 1320

gccgccctca agctgatcaa cgagatcgag gaaatgggcg gcatggccaa ggctgttgcc 1380

gaaggcatcc ccaagctccg gattgaagag tgtgcggcca ggagacaggc taggatagac 1440

agcggcagcg aagtgatcgt cggcgttaac aaataccagc tggaaaagga agatgctgtg 1500

gaggtgctgg ccatcgacaa cacctccgtt cggaacagac aaatcgagaa gctgaagaaa 1560

atcaagagca gcagagacca ggcccttgct gagcgctgtc tggccgcact aaccgaatgc 1620

gccgccagcg gcgatgggaa tatcctggcc ctggccgtgg acgcttctag ggcaagatgc 1680

acagtgggcg agatcacaga cgctctgaag aaggtcttcg gcgagcataa agccaacgac 1740

cggatggtga gcggagcata ccggcaggag ttcggcgaga gcaaagaaat tacctctgcc 1800

atcaaacgcg tgcataagtt tatggagcgg gagggcagga gaccgcggct gttggtggcc 1860

aaaatgggac aagatggcca cgatcgcggt gccaaggtga tcgccaccgg gttcgctgac 1920

ctgggcttcg acgttgatat aggccctctt ttccagacac ctcgggaggt ggctcaacag 1980

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gtgttcggtc ctggcacacg gatccccaag gccgccgtcc aggttctgga cgacatcgag 2220

aagtgcctgg aaaagaaaca gcagtccgtg 2250

<210> 152
<211> 2250
<212> DNA
<213> Artificial Sequence

<220>
<223> Codon optimized sequence that encodes an MCM polypeptide with the I671V mutation

<400> 152

atgctgagag ccaaaaatca gctcttccta ctgagccctc attacctgag gcaggtgaag 60

gagagctcag ggagccggct catccagcag agactgctcc atcagcagca gccgctgcac 120

ccggagtggg ccgccctggc caagaaacaa ctgaagggca agaacccaga ggaccttatt 180

tggcacaccc cagagggcat tagcatcaag cctctctata gcaagagaga caccatggac 240

ctccccgagg agctgcccgg cgtgaagcct ttcacccgtg gcccctaccc aaccatgtac 300

acattcaggc cctggactat ccggcagtac gcgggcttct ctaccgtgga ggagtccaac 360

aagttctaca aggacaatat taaagctggc cagcagggac tgagcgtggc cttcgatttg 420

gccacccaca gaggatacga cagcgacaac cccagggtga ggggcgacgt tggaatggcc 480

ggcgtggcca ttgatactgt cgaggacacc aagatcctgt tcgatgggat acccctcgaa 540

aaaatgtctg tgtccatgac aatgaatggg gccgtgatcc cagtgttggc caattttatc 600

gtgacaggag aggagcaggg cgtgcccaag gagaagctga ccggcaccat ccagaacgac 660

atcttgaaag aattcatggt tagaaatacc tacatctttc ctcccgaacc cagcatgaag 720

atcatcgccg atatcttcga gtataccgcc aaacacatgc ccaaattcaa ctccattagc 780

atatccggat accatatgca ggaggctggc gccgacgcca tcctggagct ggcgtacacc 840

ctggccgatg gcctggaata ttctaggacc ggcctgcagg ctggactcac aatcgatgag 900

ttcgcccccc gcctgagctt cttctggggc atcggcatga acttctacat ggagatcgct 960

aagatgagag cgggacgccg cctgtgggct cacctgatcg aaaaaatgtt ccaacctaag 1020

aatagcaagt ctctgctcct gcgggcacac tgtcaaacct ccggctggtc ccttacagaa 1080

caggacccgt acaacaacat cgtgagaacc gccatcgaag ccatggcggc cgtgttcggg 1140

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tctgccagga tcgccaggaa cactcagatt atcatccagg aggagagcgg cattcctaag 1260

gtagctgacc cctgggggg aagctacatg atggaatgcc tcaccaacga cgtgtacgat 1320

gccgccctga agctgattaa tgagatcgag gaaatggggg gcatggccaa ggctgtagcc 1380

gagggaatcc ccaagctgag aatcgaggag tgcgccgcca ggcggcaggc ccgcatcgat 1440

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gaggtgttgg caatcgacaa tacctccgtg agaaataggc agatcgagaa gctaaagaag 1560

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agaatggtgt ccggcgccta caggcaggag tttggcgaga gcaaggagat cacatctgct 1800

attaagagag tgcataagtt catggagaga gagggacggc ggcctagact gctggtagca 1860

aagatgggcc aggacggcca cgatcgggga gcaaaggtca ttgctaccgg gttcgccgac 1920

ctgggcttcg acgtggacat tggccccctc ttccagaccc cccgcgaagt tgctcagcag 1980

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gtgttcggcc ccggaacaag aatcccgaag gccgctgtgc aagtcctgga cgacatcgaa 2220

aagtgcctcg agaagaagca gcagtctgtg 2250

<210> 153
<211> 2250
<212> DNA
<213> Artificial Sequence

<220>
<223> Codon optimized sequence that encodes an MCM polypeptide with the I671V mutation

<400> 153
atgctgaggg ccaagaacca gctgttcctc ctgtctcctc actacctgag acaggtgaag 60

gagtccagcg gtagcagact gatccagcag aggctgcttc accagcagca gcccctccat 120

ccggagtggg ctgcactggc aaaaaagcag cttaagggaa aaaaccccga ggacctgatt 180

tggcacaccc cagagggaat tagcattaaa cccctctaca gcaaacggga cacgatggac 240

ctgcccgagg aactgcccgg cgtgaagccc ttcacacggg gcccataccc cacaatgtat 300

acattccgtc cttggaccat tcgccaatac gccgggttca gcacggtgga ggaatccaac 360

aagttctaca aggacaacat caaggccggc cagcaaggcc tcagcgtcgc ctttgacttg 420

gccacccaca gaggctacga ctccgacaac cccagagtga gaggcgacgt gggtatggcc 480

ggcgtggcca tcgacactgt tgaggacacc aaaatcctat ttgacggcat acccctggaa 540

aagatgtccg tgagcatgac aatgaatggc gctgtgatcc ccgtgctcgc taacttcatc 600

gtgaccggcg aggagcaggg tgtccctaag gagaaactta ccggcacaat ccagaacgac 660

attctcaagg agtttatggt gcgcaacacc tacattttcc ccccagagcc tagcatgaag 720

atcattgccg acatcttcga gtacaccgcc aagcatatgc caaagtttaa ctccatttca 780

atctctggct accatatgca ggaagctggc gctgacgcca tcttagagct ggcctacacc 840

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tttgcaccca gactgagctt cttctggggc atcggcatga acttctatat ggagatcgct 960

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ggaacccagt ccttacacac aaatagcttt gacgaagccc tggggctgcc aaccgtgaaa 1200

agcgccagaa tcgcccggaa tactcagata atcatccagg aggagtccgg gatccccaag 1260

gttgccgacc cctgggggg aagttacatg atggagtgct tgaccaacga tgtgtacgat 1320

gctgctctga agctgattaa cgagattgag gagatgggag gcatggctaa ggctgtcgcg 1380

gagggcatcc ctaagctgag aatcgaggag tgcgccgccc gccggcaggc caggattgac 1440

agcggatctg aggtgatcgt gggggtgaac aagtaccagc tggagaagga ggacgccgtt 1500

gaggttctgg ctatcgacaa caccagcgtc agaaacaggc agatcgagaa gctgaagaaa 1560

atcaaaagca gcagagacca ggccctggca gaaagatgcc tggctgccct gaccgagtgc 1620

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gtctttggcc ccggaactcg gatccccaag gccgcagtac aggtgctgga cgacatcgaa 2220

aagtgcctgg agaagaagca acagtctgtg 2250

<210> 154
<211> 2250
<212> DNA
<213> Artificial Sequence

<220>
<223> Codon optimized sequence that encodes an MCM polypeptide with the I671V mutation

<400> 154
atgctgcgcg ctaaaaacca actattcctg ctgtcccccc attacctgag acaggtgaag 60

gagagctccg gaagcaggct gatccaacag agacttctgc accagcagca gcccctgcat 120

cccgagtggg ccgctctggc taagaaacaa ctgaagggaa agaaccccga ggacctgatc 180

tggcacaccc cagagggcat atccatcaag cccctgtatt ctaagaggga cactatggac 240

ctgcccgagg agctccccgg cgtcaagcct ttcacacgcg gaccttaccc cacaatgtac 300

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aaattctata aggacaatat taaggccgga caacagggcc tgagtgtggc attcgacctg 420

gccacacaca gaggttacga ctccgataat cctagggtga gaggcgacgt gggcatggct 480

ggagtggcca tcgataccgt cgaggacaca aagatcctgt tcgacggcat ccccttggag 540

aaaatgtccg tgagcatgac catgaacggc gccgtgattc ccgtgctggc caactttatt 600

gtaaccggcg aggagcaggg cgtccccaag gagaagctga ccggcaccat ccagaacgat 660

atcctcaagg agttcatggt acggaatacc tacatttttc cccccgaacc ctccatgaag 720

atcatcgccg acatcttcga gtacaccgcc aagcacatgc ccaagttcaa ctccatcagt 780

attagcggct atcacatgca ggaggccggc gccgacgcca tcctggaact ggcctacaca 840

ctggccgacg gtctggagta cagcagaacc ggcctgcaag caggcctgac catcgacgag 900

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aaaatgcgcg ctggcaggcg actctgggcc cacctgatag aaaaaatgtt ccagcccaag 1020

aactccaagt ccctgctcct cagggcccac tgtcagacta gcggctggag cctcaccgag 1080

caggacccat ataataacat tgtaagaaca gccatcgagg ccatggccgc agtgttcgga 1140

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tccgctagaa tagcccggaa cacccagatc attatccagg aagagtccgg gatccccaag 1260

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gctgccctga agcttatcaa cgaaatcgag gagatgggcg gcatggccaa agccgtcgcc 1380

gaggggattc caaagctccg gatcgaggag tgcgccgcca gaaggcaggc cagaatcgac 1440

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atcaagagag tgcacaagtt catggagagg gagggcagga gaccacggct gctggttgcc 1860

aagatgggcc aagacggtca cgacagaggg gctaaagtga ttgccaccgg cttcgccgac 1920

ctgggcttcg acgtggacat cggtccactg ttccagaccc ctagggaggt ggcgcagcag 1980

gccgtggacg ccgacgtgca cgccgtcggc gtgagcacac tggctgccgg ccacaagaca 2040

ctagttcctg agctgatcaa ggaactcaac agcctgggcc ggcctgatat actggtgatg 2100

tgcgggggg tgatcccccc tcaggattac gagtttctgt ttgaggtggg cgtgtccaac 2160

gtcttcggcc ccgggaccag aatcccaaag gccgcagtgc aggtattaga cgacattgag 2220

aagtgcctgg agaagaaaca gcagtccgtt 2250

<210> 155
<211> 2250
<212> DNA
<213> Artificial Sequence

<220>
<223> Codon optimized sequence that encodes an MCM polypeptide with the I671V mutation

<400> 155
atgctacgag ctaagaatca gctcttcctg ctgagccccc actacctccg ccaggtcaag 60

gagtcgtcgg ggagccggct cattcagcag cggctcctgc accagcagca gccgctccat 120

ccggagtggg ccgccctggc caagaagcag ctcaagggca agaaccccga ggacctgatc 180

tggcacacac ccgagggcat ctcgatcaag cccctgtatt ccaagcgaga taccatggac 240

ttgcccgagg agctgcccgg tgtgaagccc tttacgaggg gtccatatcc gactatgtac 300

acgtttcggc cttggaccat ccgacaatac gccggctttt ccaccgtgga ggagagcaac 360

aagttctata aggacaatat caaagccggt caacaagggc tgtcggtcgc gttcgacctg 420

gccacccaca ggggttacga ctccgataat cccagggttc ggggggacgt cggcatggcc 480

ggcgtggcaa tcgacaccgt ggaggatacc aagattcttt tcgatggcat ccccctcgag 540

aagatgtctg tctccatgac tatgaacggc gccgtgattc ccgtcctggc gaacttcatc 600

gtcaccgggg aggaacaggg tgtgcccaag gagaagctga ctggtaccat ccagaacgat 660

atcctaaaag aattcatggt ccggaatacc tacatatttc cgcccgagcc cagcatgaag 720

atcatcgccg acatcttcga gtataccgcc aagcacatgc ccaagttcaa ctcgatcagt 780

atcagcggtt atcacatgca ggaggcggga gcagacgcca tcctggagct ggcgtacacc 840

ctggccgacg gcctggagta cagtcgcaca ggactgcagg ctgggctgac aattgacgag 900

tttgccccca ggctctcctt tttctggggc atcggcatga acttttatat ggagatagcc 960

aagatgaggg ccgggaggag gctgtgggcc catctaattg aaaagatgtt ccaacctaaa 1020

aactccaaat ccctcctgct gcgggcccac tgtcagacta gcgggtggag cctcacggag 1080

caagaccctt acaataacat cgtccgcacc gccattgagg cgatggccgc cgtgttcggc 1140

gggacgcaat ctctgcacac caacagcttc gacgaagcgc tgggcctgcc aaccgtaaag 1200

agcgcccgta tagcgcggaa cacccagatc ataatccagg aggagtcggg catccccaag 1260

gtggccgacc cctgggggggg cagttatatg atggagtgcc tgacgaatga tgtctacgac 1320

gcggcactga aactcatcaa cgagatcgag gagatggggg ggatggccaa ggctgtcgcc 1380

gagggcatac cgaagctgcg gatcgaagag tgtgccgccc ggcggcaggc gaggatcgac 1440

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gaggtactgg caatcgacaa caccagcgtg cggaaccgtc agatcgaaaa gctcaaaaag 1560

attaagagct ccagggacca agccctggcc gaacggtgcc tggccgcgct gaccgaatgc 1620

gctgccagcg gtgatggcaa cattctcgcc ctggctgtcg atgcaagcag ggcccgatgc 1680

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atcaagcgcg tgcacaagtt catggagcgg gagggccggc ggcctcggct cctggtagca 1860

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ctgggtttcg atgtcgatat tggcccgctg ttccaaaccc cccgggaggt ggcccagcag 1980

gccgtcgatg cggacgtgca cgcggtggga gtgtccacgc tggcggcagg ccacaagacc 2040

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tgcgggggggg taatcccccc tcaggattac gagttcctgt ttgaagtggg ggtgtcaaac 2160

gttttcgggc ccggcacccg gatccccaag gcggccgtcc aggtgctcga tgatattgag 2220

aagtgtctgg agaagaagca gcagtcagta 2250

<210> 156
<211> 2250

<212> DNA
<213> Artificial Sequence

<220>
<223> Codon optimized sequence that encodes an MCM polypeptide with the I671V mutation

<400> 156
atgctgcggg ccaagaacca gctctttctc ctgtcccctc attacctgag gcaggtgaag 60

gagagcagcg gcagccgcct catccagcaa aggctgctcc accagcagca gccactgcac 120

cccgagtggg ccgcactggc caagaagcag ctcaagggca agaatcccga ggacctgatc 180

tggcacacgc cagaaggaat ctccatcaag cccctgtatt cgaaaaggga cacgatggac 240

ctcccagaag agctgcccgg cgtgaagccc tttacccgag gtccctaccc caccatgtac 300

accttccggc cctggaccat ccggcagtat gccgggttct ccaccgtgga ggagagcaat 360

aaattttaca aggataacat aaaggcaggg caacagggct taagcgtggc ctttgacctg 420

gcgacccaca ggggctacga ttcagacaac ccgcgtgtta ggggggacgt gggcatggcc 480

ggggtcgcca tcgacaccgt ggaggacacc aaaatcctct tcgacggtat acccctggag 540

aaaatgtccg tgtccatgac catgaacggg gcggtgatcc ccgtgctggc gaatttcatc 600

gtcaccggag aggagcaagg ggtgccgaag gagaagctga ccggcacgat acaaaacgat 660

attctgaaag agttcatggt ccggaacacc tacatttttc ccccggagcc ctccatgaag 720

atcattgcgg atatattcga gtataccgcc aaacacatgc ccaagttcaa cagcatcagc 780

atcagcggtt accacatgca agaggccgga gccgacgcta tcctggagct tgcctacacc 840

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ttcgccccca ggctatcctt tttctggggg atcggaatga acttctatat ggagatcgcc 960

aagatgcggg ccggccggcg gctgtgggcc catctgatag agaaaatgtt ccagcccaag 1020

aattcgaaaa gcctgcttct gcgggcacac tgccagacca gcgggtggag cctgacagag 1080

caggacccgt acaacaacat agtccgcact gccatcgagg ccatggccgc cgtcttcggt 1140

gggacgcaga gcctgcacac aaactcattc gacgaggctc tgggtctgcc caccgtgaaa 1200

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gagggaatac ccaaactgcg cattgaggag tgcgccgccc gaaggcaggc gcggatcgat 1440

agtgggtccg aggtcatcgt gggcgtaaac aagtaccagc tcgagaagga agacgccgtg 1500

gaggtgctgg ccatcgacaa tacgtcggtg cgcaatcgcc aaatagagaa gctgaaaaag 1560

atcaagagca gccgagacca ggccctggcc gagcgctgtc tggcggccct caccgaatgt 1620

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cggatggtgt ccggcgcgta ccgccaggag ttcggggaaa gtaaggagat tacctccgcg 1800

atcaaaaggg tgcacaaatt catggagcgg gagggccggc ggccccgcct tttagttgcc 1860

aaaatggggc aggacgggca cgaccggggc gctaaggtga tcgccaccgg cttcgccgac 1920

ctgggcttcg atgtggacat agggcccctc ttccaaaccc cgagggaggt ggcgcagcag 1980

gcggtggacg ccgatgtcca cgcggtcggc gtcagcaccc tggcggcggg gcataagaca 2040

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tgcggtggtg tgatcccccc gcaggactac gaattccttt tcgaagtcgg ggtgagcaac 2160

gtgttcgggc ccggcaccag aatcccaaag gcggcggtcc aagtgctcga cgatatcgaa 2220

aagtgcctag aaaagaagca gcaatcggtt 2250

<210> 157
<211> 2250
<212> DNA
<213> Artificial Sequence

<220>
<223> Codon optimized sequence that encodes an MCM polypeptide with the I671V mutation

<400> 157
atgctgcgcg cgaagaacca gctgtttctc ctgagcccac actacctgcg tcaggtgaag 60

gagagctccg gctcacggct gatccaacag aggctgctgc accagcagca gccccttcac 120

cccgagtggg ccgcactagc caagaagcaa ctcaagggta aaaacccgga ggacctcatc 180

tggcataccc ccgaggggat cagcatcaag cccctgtact cgaagcggga tactatggac 240

ctgcccgaag agctccctgg agtgaaaccc tttactcgag ggccttatcc tactatgtac 300

acctttcgcc cgtggactat caggcagtac gccggcttca gcaccgtgga agagtccaat 360

aagttttaca aggacaatat aaaggccggg cagcagggtc tcagcgtcgc cttcgactta 420

gccacccacc gcggctacga tagcgacaac cctcgggtac ggggagacgt gggaatggcc 480

ggcgtagcca tcgataccgt ggaggacaca aagatcctct tcgacggaat accgctcgaa 540

aagatgtcag tgtctatgac catgaacggg gcggtcatcc cagtactggc aaatttcatc 600

gtgacgggag aggagcaggg cgtgcccaaa gaaaagctga ccggcacgat acaaaacgac 660

atcctgaagg agtttatggt gcgcaacacc tacatcttcc cgcccgagcc ctcgatgaag 720

atcatcgcgg acatcttcga gtacaccgcc aagcacatgc ccaagtttaa cagcatcagc 780

atatccgggt accatatgca ggaggccggc gccgacgcca tcctcgaact ggcctatacc 840

ctcgccgacg gactggagta cagccggacc ggactgcagg ccgggctgac aatagacgag 900

tttgcacccc ggctctcctt cttctggggg atcgggatga acttttatat ggagatcgcc 960

aaaatgcgtg ccggtcggcg cctgtgggcg catctcatcg aaaaaatgtt tcagccaaag 1020

aacagcaaaa gcctgctgct gcgagcccac tgtcaaacca gcgggtggag cctgacggag 1080

caggaccctt ataacaacat tgtgcgaacc gccatcgaag ccatggccgc ggtgttcggg 1140

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tccgcgcgca tagcgcggaa tacccaaatc atcatccagg aggagagcgg tatcccgaaa 1260

gtggccgacc cttggggcgg aagctacatg atggagtgcc tgactaacga cgtgtacgat 1320

gccgccctga agctgataaa cgaaatcgag gagatgggtg gcatggcgaa ggccgtcgcg 1380

gaagggatcc ccaagctgcg gatcgaagaa tgcgcagcca ggcgccaggc ccggatcgac 1440

tccgggtccg aggtgatcgt gggcgtgaac aagtatcagc tggagaagga agatgccgtg 1500

gaggtgctgg ccatcgacaa cacctccgtg cggaacagac aaattgaaaa actcaaaaaa 1560

atcaagagca gccgcgacca ggccctcgcc gaaaggtgcc tggcggcgct gactgaatgc 1620

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accgtcggcg aaataacgga tgcgctaaag aaggtcttcg gggagcataa agcgaacgac 1740

cggatggtga gcggcgcata ccgacaggag ttcggagaga gcaaggagat cacatcagcc 1800

atcaagcgcg tccataagtt tatggaacgc gaaggccggc ggccccgact gctggtcgcg 1860

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ctggggtttg acgtggacat agggccctta ttccagaccc cgcgggaggt ggcccagcag 1980

gccgtggatg cggacgtaca tgctgtcggg gtgtcaacgc tggcagccgg gcacaagacc 2040

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tgcggcggag tgatcccgcc ccaggactac gagttcctct tcgaggtggg tgtctcaaac 2160

gtctttggcc ccggcacccg catccccaag gccgccgtac aggtccttga cgacattgag 2220

aagtgtctcg agaaaaagca gcagtccgtt 2250

<210> 158
<211> 2250
<212> DNA
<213> Artificial Sequence

<220>
<223> Codon optimized sequence that encodes an MCM polypeptide with the I671V mutation

<400> 158
atgctgcgcg ctaaaaacca gctctttctc ctgtcaccgc actacctgag acaggtgaaa 60

gagtcgagtg gctcaagact gatccaacaa aggctgctgc accagcagca gcccctgcac 120

cccgagtggg cggccctcgc caagaaacaa cttaagggca agaaccccga ggacctcatc 180

tggcatactc ccgaggggat ctcgataaag cccctctatt caaagaggga taccatggac 240

ctgccagagg agcttcctgg cgtgaaacca ttcacgcggg gcccataccc taccatgtac 300

acattccggc cgtggactat ccgccaatat gccggattca gtaccgtcga ggagagcaat 360

aaattctaca aagacaacat caaggcgggg cagcaggggc tgtccgtggc cttcgatctg 420

gctacccacc gcgggtacga ttccgataac ccccgtgttc gcggggatgt cgggatggct 480

ggcgtagcta tcgacaccgt ggaggatacc aagatcctgt tcgacggtat ccccctagaa 540

aagatgtccg tgagcatgac catgaatggc gccgtcatcc ctgtactggc caatttcatc 600

gtcaccgggg aggagcaggg ggtgcccaag gagaagctca cgggcaccat acagaacgac 660

attctgaagg agtttatggt gcgaaacacc tacatattcc cccccgaacc gtccatgaaa 720

atcatcgctg atatctttga gtacacggcc aagcacatgc ctaagttcaa cagcatctcc 780

atatccggct accatatgca ggaggccgga gctgacgcca tactggaact ggcctataca 840

ctggccgacg gactggagta tagccggacc ggcctgcaag ccgggctcac catcgacgag 900

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caggatccat acaacaacat cgtgcgcacg gccatcgagg ccatggcagc tgtattcggg 1140

ggcacccagt ccctgcacac caactccttt gacgaggccc tgggcctccc caccgtcaag 1200

agcgcgcgta ttgcgcgcaa cacccagatc atcatccaag aagagtccgg tattcctaag 1260

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gaagtcctgg ccatcgacaa cacctctgtg cgtaacaggc agatcgaaaa gctcaagaag 1560

atcaagtcca gccgcgacca ggccctggcc gagcggtgcc tggctgccct gaccgagtgt 1620

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accgtcgggg aaatcaccga cgccctgaag aaggtatttg gcgagcacaa agccaacgat 1740

aggatggtaa gcggcgccta caggcaggag ttcggggaat ccaaagagat cacctccgcc 1800

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aagatgggcc aggatggtca tgatcggggc gccaaagtga tcgcgaccgg gttcgccgat 1920

ctgggattcg acgtggacat cggccccctc ttccagacgc ccagggaggt agcgcagcaa 1980

gccgtggatg ccgacgtgca cgcggtgggc gtgtccaccc tcgcggccgg tcacaagacc 2040

ctcgtgcccg aactcatcaa ggagctgaac agcctggggc ggcccgacat cctggtcatg 2100

tgtggaggcg tcattccacc ccaggactat gagtttctct tcgaggtcgg cgtgtcaaac 2160

gtgtttggcc ccggcactag gatacccaaa gcggcagtcc aggtcctcga cgatatcgag 2220

aagtgtctcg agaagaagca acagtccgtg 2250

<210> 159
<211> 2250
<212> DNA
<213> Artificial Sequence

<220>
<223> Codon optimized sequence that encodes an MCM polypeptide with the I671V mutation

<400> 159
atgctccgtg ccaagaacca gctgttcctg ctgagccccc actatctccg acaggtgaaa 60

gagtcgtccg gaagcaggct gatccagcaa agactgctgc accaacagca accactgcat 120

cccgagtggg ccgcgctggc caagaagcag ctgaagggca agaaccccga agatctcatc 180

tggcacacac ccgagggcat cagcatcaag cccctgtatt ccaagaggga taccatggac 240

ctgccagaag agctgcccgg cgtcaagcct ttcacacgag gcccctaccc gaccatgtac 300

accttcaggc cctggacgat ccgacaatat gccggcttca gcaccgtgga ggagagcaac 360

aaattttaca aggacaacat caaggccggg caacaaggcc tatccgtcgc cttcgacctg 420

gcgacccacc gggggtacga cagcgataac ccccgcgtgc gtggagacgt gggaatggcg 480

ggggtagcta ttgacacggt agaggataca aagatcctgt ttgatgggat cccgctggaa 540

aagatgagcg tgtccatgac gatgaacggg gccgtgattc ccgtcctggc caatttcatc 600

gtcacgggtg aagaacaagg cgtacccaaa gaaaagctga ccggtaccat ccaaaacgat 660

atcctgaaag agttcatggt gaggaatacc tacatctttc cccctgaacc cagcatgaag 720

atcatcgccg acatcttcga gtataccgcc aaacacatgc ccaagttcaa tagtatcagc 780

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ggcacccaga gcctccacac aaactccttc gacgaagccc ttggcctgcc caccgtgaag 1200

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gccgccctca agctcatcaa tgagattgag gagatggggg gtatggccaa ggcagtggcg 1380

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gaggtcctgg ccattgataa cacctccgtg aggaacagac agatcgagaa gctcaagaag 1560

atcaagtcaa gccgtgacca ggccctcgcc gaacgctgtc tggctgccct caccgaatgc 1620

gccgccagcg gcgacgggaa catcctggcc ctggcagtgg acgccagcag agccaggtgc 1680

accgtgggcg aaataaccga cgccctgaag aaggtgttcg gcgagcacaa agctaacgat 1740

cggatggtct cgggggccta ccgccaggaa ttcggggagt ccaaggagat cacgagtgcc 1800

atcaaaagag tccataaatt catggagcgc gaggggaggc gacccaggct gttggtcgct 1860

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ctgggcttcg acgtggacat cgggccgctg ttccaaaccc cccgtgaggt cgcccagcag 1980

gcggtggacg ccgatgtgca cgccgtgggg gtgagcacac tcgccgccgg tcataagacg 2040

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gtgttcggcc cagggaccag gataccgaag gcggcggtcc aggtgctgga cgacattgaa 2220

aaatgtttgg aaaagaagca acagtccgtc 2250

<210> 160
<211> 2250
<212> DNA
<213> Artificial Sequence

<220>
<223> Codon optimized sequence that encodes an MCM polypeptide with the I671V mutation

<400> 160
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gaaagttcag gatccaggct gatccagcag aggctgctgc accagcagca gccgctgcat 120

ccggagtggg ccgcgcttgc caaaaagcaa ctgaagggga agaatcccga ggacctgatc 180

tggcataccc ctgaggggat ctcaattaag ccactgtact ccaagcggga taccatggac 240

ctccccgagg agctgcccgg ggtcaaaccc ttcacccggg gtccctaccc caccatgtac 300

actttccgac cctggaccat cagacaatac gccggcttct ccaccgtgga ggagagcaac 360

aagttctata aagacaatat caaggcagga cagcagggcc tctccgtggc ctttgacctc 420

gccacgcaca ggggttatga tagcgacaac ccccgcgtgc gaggcgatgt tgggatggcc 480

ggcgtggcga ttgacaccgt ggaagacacg aagatactct ttgacggcat ccccctcgag 540

aagatgtccg taagcatgac aatgaacggc gcggtcatcc ccgtgctggc caacttcatt 600

gttactggcg aggagcaggg ggtcccgaaa gagaaactga ccgggaccat acagaacgac 660

atactcaaag agtttatggt ccgcaataca tatatcttcc cccccgagcc ctcaatgaag 720

atcatagcgg acatctttga atacacggcc aagcacatgc caaagttcaa tagcatcagc 780

atctccggct atcacatgca ggaggcgggt gccgacgcca tcctggaact cgcctatacc 840

ctggcggacg gcctggagta cagccgcacg gggctccagg cgggtctgac catcgacgaa 900

ttcgcccccc ggctgtcctt cttttggggg atcggtatga atttttacat ggagatcgcc 960

aaaatgcgcg ccgggcgcag gctgtgggcc catctgatcg aaaagatgtt tcagcccaag 1020

aacagcaagt cgctgctgct gcgggctcat tgccagacat cgggatggtc cctcactgag 1080

caagatccct acaacaacat tgtgcgcaca gcgatcgagg caatggccgc agtgttcggg 1140

ggtacccagt ccctccacac aaactccttc gacgaggccc tggggctacc gacggtcaaa 1200

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gagggaatcc caaagcttcg aatcgaggag tgcgctgcca ggagacaggc ccgcatcgat 1440

tcaggtagcg aggtgatcgt tggggtgaat aagtaccagc tcgagaagga ggacgccgtg 1500

gaagtgctgg ccatagacaa cactagcgta cgcaacaggc agattgagaa gctgaagaaa 1560

atcaagtcga gccgagacca ggccctcgcc gaaaggtgcc tggccgcatt gaccgaatgc 1620

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gccgtcgacg ccgatgtgca tgcggtcggc gtgagcaccc tcgctgccgg tcataaaacc 2040

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gtctttgggc cgggaaccag gatcccaaag gctgcagtgc aggtgctcga cgatatagaa 2220

aagtgcctcg aaaaaaaaca gcagtccgtg 2250

<210> 161
<211> 2250
<212> DNA
<213> Artificial Sequence

<220>
<223> Codon optimized sequence that encodes an MCM polypeptide with the I671V mutation

<400> 161
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gagtcctccg gctccaggct gatacagcag cgcttactcc atcagcagca gcccctgcac 120

ccggagtggg ccgcgctggc taaaaaacag ctgaagggga agaaccccga ggacctcata 180

tggcacaccc cggagggtat cagcatcaag ccgctgtact ccaagcggga tacgatggat 240

ctccccgagg agctgccagg tgtgaaacct ttcacacggg ggccgtatcc caccatgtac 300

acctttcggc cttggacaat ccggcaatac gccgggtttt caactgtcga ggagtctaac 360

aagttttaca aggacaacat caaggcaggc caacagggcc tcagcgtcgc cttcgatctg 420

gccacccaca gggggtacga ttccgacaac cccagggtgc gcggggacgt gggcatggcc 480

ggcgtggcca tcgacaccgt cgaagatacg aagatcctgt tcgacgggat cccgctcgaa 540

aagatgagcg tgtcgatgac catgaacggg gccgtgatcc cagtgctcgc caatttcatt 600

gttaccgggg aagagcaggg cgtgccaaaa gaaaaactca cgggaactat ccaaaacgac 660

atcctgaaag agttcatggt aaggaacacc tatatcttcc cccccgagcc cagcatgaag 720

atcatcgcgg atatctttga gtataccgcc aagcatatgc ccaagttcaa ttcgatcagc 780

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ctggccgatg gactggagta ctcccggacc gggctgcagg ccggcctcac catcgacgag 900

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aactccaaat ccctgctgct ccgggcccac tgccagacgt ccggttggtc cctgactgag 1080

caagatccgt ataataacat cgtgcgcacc gccatcgagg cgatggccgc cgtcttcggg 1140

ggtacccagt ccctccacac caattccttc gacgaagccc tgggcctccc caccgtgaag 1200

tccgcacgta tcgcacggaa cacccagata atcatccagg aggagagcgg gatccccaag 1260

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gcggccctga agctgatcaa cgaaatcgag gagatgggcg gcatggcaaa ggccgtcgcc 1380

gaggggatcc ccaagctgcg aatcgaagaa tgcgccgcaa gaaggcaggc tcggatcgat 1440

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gaggtcctgg ccatcgataa cacctccgtc cggaatcgtc agatcgaaaa actgaagaag 1560

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aagatgggac aggacggcca cgatagaggg gcgaaagtca ttgccaccgg attcgccgac 1920

ctggggtttg acgtggacat cggtcctctg tttcagaccc cccgcgaagt ggcccagcag 1980

gccgtcgatg ccgatgtgca cgcggtgggg gtgagcactc tggccgccgg ccacaagacc 2040

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gtgttcgggc ctggtactcg cattcccaag gcggcggtcc aggtactgga cgatatcgaa 2220

aagtgcctcg aaaagaagca gcagtcggtg 2250

<210> 162
<211> 2250
<212> DNA
<213> Artificial Sequence

<220>
<223> Codon optimized sequence that encodes an MCM polypeptide with the I671V mutation

<400> 162
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gagtcgtcgg gttctcgcct cattcagcaa cgtctgctgc accagcagca gccgctgcac 120

cccgagtggg ccgccctggc gaagaagcag ctgaagggca agaaccccga ggacctgatc 180

tggcacaccc cggaaggtat cagcataaag ccgctctact ccaagcggga taccatggac 240

ctgcccgagg aacttcccgg cgtgaagccc tttacccgcg gtccctaccc gacgatgtat 300

accttccgtc catggactat acgtcaatat gcgggcttca gcaccgtgga ggagagtaac 360

aagttttaca aggacaatat caaggcgggc cagcaaggcc tgtcagtggc ctttgacctc 420

gccacccaca gggggtacga cagcgacaat cctcgagtgc gtggcgacgt cggcatggcg 480

ggtgtcgcca tcgacaccgt ggaggataca aagatccttt tcgacgggat ccccctcgaa 540

aagatgtccg tgagcatgac catgaacggg gcagttatac ccgtgctggc taacttcatc 600

gtgacaggag aggaacaagg ggtacccaag gaaaagctga ccgggaccat ccagaatgac 660

atcctgaagg agttcatggt gaggaacacc tatattttcc cacccgagcc ctccatgaag 720

atcatagccg acatatttga gtataccgcc aagcacatgc ccaagtttaa cagtatatcc 780

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ttcgcccccc gcctgtcctt cttttgggga atcggtatga acttctacat ggagatcgcc 960

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aacagcaagt ccctgctgct ccgggctcac tgtcagactt ccggctggtc cttgactgaa 1080

caggacccgt acaacaacat cgtgagaacg gccatagagg ccatggccgc cgtgtttggc 1140

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aagatggggc aagacggaca cgacaggggc gctaaggtca tagccaccgg gttcgccgac 1920

ctggggttcg atgtagacat tggccccctg tttcagaccc cccgcgaggt ggcgcagcag 1980

gccgtggacg ccgacgtcca tgccgtgggt gtcagcaccc tcgcggccgg gcataagaca 2040

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gtcttcggcc ccgggacccg gatccccaag gccgccgtgc aggtgctgga cgacatcgaa 2220

aagtgcctgg agaaaaagca gcagagtgtc 2250

<210> 163
<211> 2250
<212> DNA
<213> Artificial Sequence

<220>
<223> Codon optimized sequence that encodes an MCM polypeptide with the I671V mutation

<400> 163
atgctgcgag cgaagaacca gctctttctg ctgagccccc attacctaag gcaggtgaag 60

gaaagctccg gcagccgcct gatccagcag cggcttctgc accaacaaca gccactccac 120

ccggagtggg ccgccctggc caagaagcaa ctgaagggga agaaccccga ggacctaatc 180

tggcataccc cggaaggcat ctccatcaag cctctgtact ccaagagaga caccatggac 240

ctgcccgaag agctccccgg cgtgaagccc tttaccaggg gcccctatcc caccatgtac 300

accttccgtc cgtggacaat ccgccagtat gccggtttca gcaccgtcga ggagtccaac 360

aaattctaca aggacaacat caaggccggg caacaggggc tcagcgtggc cttcgatctg 420

gccacccacc ggggctatga cagcgacaac ccgcgagtgc ggggagatgt cggcatggcc 480

ggcgtggcta tcgacaccgt cgaggacacc aagatcttgt ttgacgggat cccgctggag 540

aaaatgagcg tctcaatgac gatgaatgga gccgtgatcc ccgtgctggc caacttcatc 600

gtcaccggtg aggagcaggg cgtgcccaaa gagaagctaa ccggcaccat ccagaacgat 660

atactcaagg agttcatggt gcggaacaca tatatcttcc cccccgagcc ctccatgaag 720

ataatcgcgg acatttttga gtacacggcg aagcacatgc ccaagttcaa tagcataagc 780

atctccggct accacatgca ggaggccgga gccgatgcca tcctcgaact tgcgtatacc 840

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gtcttcgggc cgggcaccag gataccaaag gccgcagtac aggttctcga cgatatcgag 2220

aagtgccttg agaagaaaca acagtccgtc 2250

<210> 164
<211> 2250
<212> DNA
<213> Artificial Sequence

<220>
<223> Codon optimized sequence that encodes an MCM polypeptide with the I671V mutation

<400> 164
atgctacgcg ccaaaaacca gctgttcctc ctcagtccgc attacctcag gcaggtcaaa 60

gagtccagcg gatcccggct catccagcag cgtctactcc accaacagca gccactgcac 120

ccggagtggg cggccctcgc taaaaagcag ctgaagggta agaacccaga agatctgatc 180

tggcacacgc ctgagggaat ctccattaaa ccgctctact ccaaacgcga caccatggat 240

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aagttctata aggacaacat taaggcaggg caacaggggc tgagcgtggc cttcgacctg 420

gccacccatc ggggatacga ttccgataat ccccgggtcc ggggcgacgt gggaatggcc 480

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aagatgtccg tgtccatgac catgaatggg gccgtaatcc ccgtgctcgc gaacttcata 600

gtcacgggcg aggagcaggg cgtgccgaag gagaaactca caggcactat ccaaaacgac 660

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gaggtgctgg ccatcgacaa cacctccgtg aggaaccgcc agatagagaa actgaagaag 1560

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aaatgcctgg aaaagaagca gcagtccgtc 2250

<210> 165
<211> 2250
<212> DNA
<213> Artificial Sequence

<220>
<223> Codon optimized sequence that encodes an MCM polypeptide with the I671V mutation

<400> 165
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gaatcctccg gaagcaggct gatacagcag agactcctgc atcagcagca gcctctacac 120

cccgagtggg ccgccctggc caaaaagcag ttgaaaggca aaaatcccga agatctgatc 180

tggcacaccc ctgaaggcat cagcatcaag ccactgtaca gcaagagaga caccatggac 240

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accttccggc cctggacaat tagacagtac gcaggcttca gcaccgtgga ggagtccaat 360

aagttttaca aggacaacat caaggctggg cagcaggggc tctcagtggc cttcgatctg 420

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aagatgtctg tgagcatgac catgaacggc gcagtgattc ctgttctggc caacttcatc 600

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gaggtgctgg ccattgacaa cacatctgtg agaaaccggc aaatcgaaaa gctgaaaaaa 1560

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gccgcgagcg gcgatggcaa catcctggct ctggccgtgg acgcaagcag agctagatgt 1680

acagtcggcg agattaccga tgcgctgaag aaggtgttcg gcgaacacaa ggccaacgat 1740

cggatggtga gcggcgctta tcgccaggag ttcggagagt ccaaggagat cacctccgca 1800

ataaagaggg tgcacaagtt tatggagcgc gagggaagac ggccccgact gctggtggcc 1860

aagatgggcc aagatggcca tgacagaggg gccaaggtga ttgccaccgg ctttgcagat 1920

ctgggcttcg atgtggacat cggccccctg ttccaaaccc ctagagaggt ggcccagcaa 1980

gccgtcgacg ctgacgttca tgccgtgggc gtctccaccc tggcggcagg acacaagaca 2040

ctggtgcctg agctgatcaa ggaactgaat agcctcggga gacccgatat cctggtgatg 2100

tgcggaggcg tgatcccccc tcaggactac gaatttctgt tcgaggtggg cgtctcgaat 2160

gtgttcggac ccggcacaag aattcccaag gctgctgtcc aggtcctgga cgacattgag 2220

aaatgcctgg agaagaagca gcagtccgtg 2250

<210> 166
<211> 2250
<212> DNA
<213> Artificial Sequence

<220>
<223> Codon optimized sequence that encodes an MCM polypeptide with the I671V mutation

<400> 166
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cccgagtggg ctgctctcgc taagaaacag ctgaagggca agaaccccga ggacctgatc 180

tggcacacac ctgagggcat atcaatcaaa cccctctatt cgaagcgaga caccatggac 240

ctgcccgagg aattacctgg cgtgaaacca ttcaccagag gcccttatcc caccatgtac 300

acttttaggc catggacaat tcggcagtac gcaggctttt ccactgtgga agagagcaat 360

aagttttaca aagataacat taaggccggt cagcagggcc tgagtgtggc atttgacctg 420

gctacccaca gaggctatga cagcgacaac cccagagtga gaggcgacgt gggcatggcc 480

ggcgtcgcta tcgacaccgt tgaagacacg aagattctgt tcgacggcat ccccctggag 540

aagatgagcg tttccatgac catgaacggc gctgtgatcc ccgtgctggc caatttcatc 600

gtgacaggag aggagcaggg cgtgcctaag gagaagttga ctggcaccat ccagaatgac 660

atcctgaagg aattcatggt gcggaacacc tacatcttcc cccctgaacc tagcatgaaa 720

atcatcgctg acatctttga gtacacagcc aagcacatgc cgaagttcaa cagtatcagc 780

atctctggct atcacatgca ggaggcaggc gctgacgcca ttcttgaact cgcctacacc 840

ctggccgacg gcctagagta ctccagaaca gggctgcagg ctggcctgac tatcgacgag 900

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aaatgcttag agaagaagca gcagagcgtg 2250

<210> 167
<211> 2250
<212> DNA
<213> Artificial Sequence

<220>
<223> Codon optimized sequence that encodes an MCM polypeptide with the I671V mutation

<400> 167
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gagtcctctg gaagcaggct catccagcaa agactgcttc accagcagca gccactgcac 120

cctgagtggg ccgccctggc taaaaagcag ctgaagggca agaaccccga ggatctgatt 180

tggcacacgc ccgagggcat ctccatcaag cctctgtact ccaagagaga taccatggac 240

ctgcccgagg aactccctgg cgtcaagcca ttcacacggg gcccctaccc cacaatgtac 300

acattccggc cttggacgat taggcagtat gctgggttct ctacagtaga ggagtccaac 360

aaattctata aggacaacat caaggccgga cagcaaggcc tttctgttgc cttcgacctc 420

gctacccacc gcggctatga tagcgataat cccagagtga ggggcgacgt gggcatggcc 480

ggggtggcta ttgacaccgt ggaggatact aagatcctgt ttgacggcat ccctctggag 540

aagatgagcg tgtctatgac catgaacggg gctgtgattc ccgtgctggc taatttcatc 600

gtgaccggag aggagcaggg cgtgccaaag gagaagctga caggaacaat tcagaacgac 660

attcttaagg agtttatggt gagaaacacc tatatattcc cccccgagcc cagtatgaag 720

atcatcgctg acatcttcga gtacacagct aagcacatgc ctaagtttaa cagcatcagt 780

atcagcggct accacatgca ggaggccggc gccgacgcta tcctcgagct ggcttacacc 840

ctggccgatg gcctcgagta ctcgagaacc gggctgcagg cgggactgac catcgatgag 900

ttcgccccca ggctcagttt cttctgggga atcggcatga acttctatat ggagatcgcc 960

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aatagcaagt cactgctgct gagggcacac tgccagacca gcggatggag cctgactgaa 1080

caggacccct acaacaacat cgttcggacc gcaatcgaag ccatggccgc agtgttcgga 1140

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gccgcactca agctgattaa tgagatcgaa gaaatgggag gaatggctaa ggctgtggcc 1380

gaaggaatcc caaagttgag aatcgaggag tgcgctgcca ggaggcaggc ccgcatcgac 1440

agcggaagcg aagttatcgt gggcgttaat aagtatcagc tggagaagga ggacgccgtg 1500

gaggtgctgg ctatcgacaa cacctcagtc agaaaccgcc agatcgaaaa actgaaaaaa 1560

attaagtcga gccgagatca ggcactcgcc gagcgttgcc tggccgccct gactgagtgc 1620

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cttggcttcg acgtcgacat tggacccctg ttccagaccc caagagaggt ggctcaacag 1980

gccgtggacg ccgatgtcca cgccgtgggc gtgtctaccc tggccgccgg ccacaagaca 2040

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tgcggcgggg tgatcccccc tcaggactac gaatttcttt tcgaagtcgg agtgagtaac 2160

gtgttcggcc ccggaacgcg catacctaag gctgctgtgc aggtgctgga tgatattgag 2220

aaatgtcttg agaagaagca gcagagcgtg 2250

<210> 168
<211> 2250
<212> DNA
<213> Artificial Sequence

<220>
<223> Codon optimized sequence that encodes an MCM polypeptide with the I671V mutation

<400> 168
atgctgaggg ccaaaaatca gcttttcctg ctcagtccac actatttgag acaggtaaag 60

gaatcttccg gctccagact gatccagcag agactgctgc accagcagca gcctctgcac 120

cccgagtggg ccgctctggc aaaaaaacag ctgaagggca agaaccctga ggacctcata 180

tggcacaccc ccgaggggat ctcaatcaag ccactgtaca gcaagagaga caccatggac 240

ctgccagaag aactgcccgg cgtgaaaccc ttcaccaggg ggccctatcc tacaatgtac 300

actttcaggc cttggaccat aaggcagtat gccggattct ccaccgtgga ggagagcaat 360

aagttctaca aggataacat caaagccggg cagcagggcc tgtccgttgc gttcgacctg 420

gccacccata gagggtacga tagtgacaac cccagggtca gaggcgacgt gggcatggcc 480

ggggtcgcga tagacaccgt ggaggacacc aagatcctgt ttgacggcat ccccctggag 540

aagatgagcg tgtcaatgac catgaacggc gccgtgatcc ccgtcctggc caatttcatc 600

gtgaccgggg aagagcaggg agtgcccaag gaaaagttga cagggaccat tcagaacgat 660

atcctgaagg agttcatggt ccggaatacc tacatcttcc cccccgagcc tagcatgaag 720

atcatcgccg acatcttcga gtacaccgcc aagcatatgc ctaagttcaa ttctatcagc 780

atttccggct accatatgca agaagctgga gcagacgcca tactggagtt ggcctacacc 840

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tttgcaccca gactgtcctt cttctggggc ataggcatga acttctacat ggagattgcc 960

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aacagcaagt ccctcctgct gagggcccac tgccagacca gcggatggag cctgactgaa 1080

caggacccct acaacaacat agtgagaacc gccatcgagg ccatggccgc agtgtttgga 1140

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tccgctagaa tcgccagaaa tacacagatc ataatccagg aggagtccgg catccctaag 1260

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gaggtcttgg ccatcgataa cacaagcgtg cggaaccgcc aaatcgagaa acttaaaaag 1560

attaagagca gccgggacca ggccctggcc gagaggtgcc tggcagccct cacagaatgt 1620

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attaaaagag ttcataagtt catggagcgg gagggcagac ggcctagact gctggtggct 1860

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gcagtagacg ccgacgtgca cgccgtgggc gtgtctacac tggccgccgg tcataagacc 2040

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tgtggcggag tgatcccacc ccaggactac gagttcctgt ttgaggtggg cgtgagcaac 2160

gtcttcggcc ccggaactag aatccccaag gccgcagtcc aggtgctgga cgacattgag 2220

aaatgcctgg agaagaagca gcaatccgtg 2250

<210> 169
<211> 2250
<212> DNA
<213> Artificial Sequence

<220>
<223> Codon optimized sequence that encodes an MCM polypeptide with the I671V mutation

<400> 169
atgctgcggg ccaaaaacca gctgttcttg ctgtctcccc actaccttcg acaggtcaag 60

gaaagctctg gcagccgtct catccagcag agactgctgc accagcaaca gccactccac 120

cccgagtggg ccgccctggc caagaagcag ctgaagggca agaacccaga ggatctgatc 180

tggcacaccc ccgaaggaat cagcattaaa ccactctaca gcaagagaga caccatggat 240

cttcccgagg aactccccgg cgtgaagcct ttcacccggg gaccttatcc cactatgtac 300

accttccgac cctggaccat tagacagtac gctgggttct ccacagtgga ggagagtaac 360

aaattttata aggataatat caaagccggc cagcagggcc tgtctgtagc cttcgatctg 420

gctacccata gaggatatga tagtgacaac cccagggtca gaggcgacgt gggcatggcc 480

ggcgtggcca ttgacaccgt ggaggatact aagattctgt tcgacggcat tccccttgaa 540

aagatgagcg tgagcatgac gatgaacggg gccgtgatcc ctgtgctggc taacttcatt 600

gtgaccggag aggagcaggg cgtccctaaa gagaaactaa caggaactat tcagaacgac 660

atcctgaaag agtttatggt gcggaatacc tacattttcc cccctgagcc ttctatgaaa 720

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aaaatgggcc aggacggtca cgaccggggc gctaaagtga tcgccaccgg cttcgccgac 1920

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gccgtggatg ccgatgttca tgccgtggga gtgagcactc tcgccgccgg ccataagaca 2040

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gtgttcggcc ccggtacccg gatccccaag gccgcagtgc aggttctgga cgacattgag 2220

aaatgcctgg agaagaagca gcaaagcgtg 2250

<210> 170
<211> 2250
<212> DNA
<213> Artificial Sequence

<220>
<223> Codon optimized sequence that encodes an MCM polypeptide with the I671V mutation

<400> 170
atgctcagag ccaagaatca gctatttctt ctgagcccac attatctgag acaggtgaag 60

gagagcagcg gaagcaggtt gatacagcag cggctcctgc atcagcagca gcctctgcat 120

cccgagtggg ccgcactggc aaagaagcag ctgaagggca agaaccctga ggacttgatc 180

tggcacacac ccgagggcat ctctatcaag cctctctata gcaagagaga tacaatggat 240

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accttccgcc cttggaccat taggcagtac gccggcttct ccacagtcga ggagagcaac 360

aagttctata aagataacat caaggcagga cagcaaggcc tgtccgtggc ctttgacctt 420

gccacacaca ggggctatga cagcgataat cctagagtgc gcggcgacgt aggcatggca 480

ggcgtggcaa tagataccgt ggaggacaca aagatcctgt ttgacggcat ccccctggaa 540

aagatgtccg tgagcatgac catgaacggg gcggtgatcc cagtgctggc caactttata 600

gtaaccggcg aagagcaggg cgtgcccaag gagaagctga ctggcacaat ccagaatgac 660

atcctgaagg agttcatggt gaggaacaca tacatctttc cccctgagcc cagcatgaag 720

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atctccggct accatatgca ggaggccggc gccgacgcca ttctggagct ggcctacacc 840

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atcaaacgcg tccataagtt catggagcgg gaaggcagga ggcctcggct gctggtggca 1860

aagatggggc aagatgggca cgatagaggt gccaaggtga tcgccaccgg attcgctgac 1920

cttgggttcg acgtagacat tgggccactg ttccagacac ccagagaggt cgcccaacag 1980

gctgtggatg ccgacgtgca cgcggtgggc gtgagtactc tggccgcggg ccataagacc 2040

ctggtgcccg aactgatcaa ggaactgaat agcctgggca ggcccgatat tctggtgatg 2100

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aaatgcctgg aaaagaagca gcagagcgtg 2250

<210> 171
<211> 2250
<212> DNA
<213> Artificial Sequence

<220>
<223> Codon optimized sequence that encodes an MCM polypeptide with the I671V mutation

<400> 171
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gagagttcag ggtcacgtct gatccagcag agactgctcc accagcagca gcccctgcat 120

cccgagtggg ccgccctagc taagaagcag ctgaagggca agaaccccga ggacctgatc 180

tggcacactc ccgaagggat tagcatcaag cccctctaca gcaagagaga caccatggac 240

ctgcccgagg agctccccgg agtgaagcca ttcacaaggg gcccctaccc aaccatgtat 300

accttcagac cctggacaat cagacagtac gcgggctttt ccactgtgga agaatctaac 360

aagttctaca aagacaatat aaaggctggc cagcagggac tgagcgtggc attcgatctt 420

gccacacacc gcggctacga ttctgacaac cccagggtta ggggagacgt gggaatggcc 480

ggcgtggcca tcgacaccgt ggaggacaca aagatcctgt tcgacggaat cccacttgag 540

aagatgtcgg tgtccatgac catgaacggg gccgtcatcc ctgtactggc taacttcatc 600

gtgaccgggg aggagcaggg cgtgcccaag gagaagctga caggcaccat acagaacgac 660

atcctgaagg agtttatggt gagaaacacc tatatcttcc ccccagaacc ctcaatgaag 720

atcatcgctg acatctttga gtataccgct aagcacatgc ctaagttcaa tagcatctcc 780

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gccgccctta aactgatcaa cgaaatagag gagatgggcg gcatggccaa agccgtcgcc 1380

gagggcattc ctaagttgag aatcgaggag tgcgccgcca ggagacaggc taggatcgac 1440

agcggcagcg aggtcatcgt gggtgtgaac aagtaccagc tggaaaagga ggacgccgtg 1500

gaggtgctgg ccatcgacaa cacctctgtt aggaacaggc aaattgagaa gctgaagaag 1560

atcaagtcca gcagagacca ggctctggcc gagagatgtc tggccgcact taccgaatgt 1620

gctgccagcg gggacggcaa catactggcg ctcgccgtgg acgccagccg agctagatgc 1680

accgtgggcg aaattacaga cgctttgaaa aaggtgttcg gcgagcacaa ggccaacgat 1740

aggatggtca gcggagccta ccgccaggag ttcggcgagt ctaaggagat cacctcagcg 1800

attaagaggg tgcacaaatt tatggagaga gagggacgga gacccaggct gctggtggcc 1860

aagatgggac aggacggcca cgatagagga gctaaagtca tcgccacagg attcgccgac 1920

ctaggcttcg atgtcgacat cggacccctg ttccaaaccc cccgggaagt ggcccagcag 1980

gctgtggacg ccgatgtgca cgccgtggga gtgtctacac tggccgccgg gcacaagacc 2040

ctggtccctg aacttatcaa agagctcaac agcctcggca gacccgatat cctggtcatg 2100

tgtggcggcg tcataccacc ccaggactat gagttcctgt ttgaagtggg cgtgagcaac 2160

gtctttggcc ctggaaccag gatcccaaag gctgcagtgc aggtgcttga cgacatcgag 2220

aagtgcctgg agaagaagca gcagagcgtg 2250

<210> 172
<211> 2250
<212> DNA
<213> Artificial Sequence

<220>
<223> Codon optimized sequence that encodes an MCM polypeptide with the I671V mutation

<400> 172
atgctgcgag ccaagaacca gttgttccta ctgagccccc attaccttcg gcaagtcaag 60

gagagcagcg gcagcagact gatccagcag agactcctcc accagcagca gcccctgcac 120

cccgagtggg ctgccctggc caaaaaacag ttaaaaggaa aaaaccctga ggacttgatc 180

tggcacaccc ccgaaggcat tagcatcaaa cccctgtata gcaagagaga cacaatggac 240

ctgcccgagg agctccccgg cgtgaagccc tttaccagag gcccctaccc caccatgtat 300

acgttccggc catggaccat cagacagtac gccggttttt ctacagtgga agagagcaac 360

aagttctaca aagacaatat taaagccggc cagcagggcc tgtcagtcgc cttcgatctg 420

gccacccacc gtggctacga tagcgacaat cctcgagtga gaggagatgt gggaatggct 480

ggagtggcta ttgacaccgt cgaggacacc aaaattctgt tcgacggcat cccactggag 540

aagatgtccg tgtccatgac catgaacggc gccgttattc ccgtactggc taacttcatc 600

gtgacgggcg aggagcaagg ggtgcccaag gagaagctta caggcaccat ccagaatgat 660

atcctgaagg agttcatggt gagaaataca tacatcttcc cccctgagcc cagcatgaag 720

atcattgccg atatcttcga gtacaccgca aagcacatgc ccaaatttaa cagcatctcc 780

atcagcggat accacatgca ggaggccggc gccgatgcta tcctcgagtt ggcttacaca 840

ctcgccgacg gtttggagta cagtcgcacc gggctgcagg ctggtcttac cattgacgag 900

tttgcccctc ggctcagctt cttctggggc atcggcatga atttctacat ggagattgcc 960

aagatgagag caggacgaag actttgggcg cacctcatcg aaaagatgtt ccaacccaag 1020

aatagcaaat ctctcctgct gagggcccat tgtcagacct ccggctggtc tcttaccgag 1080

caggatcctt acaataacat tgtcagaaca gcaattgaag caatggccgc tgtgttcggc 1140

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gtggccgacc cctggggagg cagttatatg atggagtgcc tgaccaatga cgtgtacgac 1320

gccgcactga aactgattaa cgagatagaa gaaatggggg gcatggccaa agccgtggcc 1380

gagggcatcc caaagctgag aatcgaggaa tgcgccgcca ggcggcaggc cagaatcgac 1440

agcggctccg aagtgattgt gggcgtcaac aagtaccagc tggagaagga ggacgccgtg 1500

gaggttctgg ccatcgacaa caccagcgtg aggaacaggc agatcgagaa gctgaaaaag 1560

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gctgcaagcg gcgatgggaa tatcctggca ctggctgtcg acgcttcccg cgcaagatgt 1680

accgtgggcg agatcaccga tgccctgaaa aaggtgttcg gcgagcacaa ggccaacgac 1740

cggatggtga gcggcgccta cagacaggag tttggcgagt ccaaggagat tacaagcgct 1800

attaaaaggg tccacaagtt tatggagcga gagggaagaa ggccaagact gctggtcgct 1860

aaaatgggtc aggacggtca cgataggggg gccaaggtta tcgccaccgg cttcgccgat 1920

ctgggcttcg acgtggacat tggccccctg tttcagaccc ccagagaggt agcccagcag 1980

gccgtggatg ccgacgtgca tgcagtgggc gttagcaccc tggccgcggg ccataaaacc 2040

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tgcggcggcg tgatcccgcc ccaagactac gagtttctgt tcgaggtggg cgtgtctaat 2160

gtgtttgggc ctggcaccag aatccctaag gcagctgtgc aggtgctgga cgacatcgag 2220

aagtgcctgg agaaaaagca gcagtcagtc 2250

<210> 173
<211> 2250
<212> DNA
<213> Artificial Sequence

<220>
<223> Codon optimized sequence that encodes an MCM polypeptide with the I671V mutation

<400> 173
atgcttcgag ccaagaacca gctgtttctt ctgagccccc attatctgag acaggtcaag 60

gagagctcag gcagcagact catccagcag agactgctac accaacagca gccgctccac 120

cccgagtggg ccgccctggc caaaaagcag ctcaagggca agaatcccga ggatctcatt 180

tggcacactc ctgagggtat cagcatcaag ccgctctaca gcaagagaga cacgatggat 240

ctgccggagg agctgcccgg cgtgaagccc tttacgaggg gcccgtaccc caccatgtac 300

acattcagac cctggaccat caggcagtac gccggcttct ccaccgtcga ggagagtaat 360
aaattctaca aagataatat caaggccggc cagcaaggcc tcagcgtcgc cttcgacctg 420
gcaacccatc gcggttacga ttcagataat ccacgtgtga gaggagacgt aggcatggca 480
ggcgtggcca tcgacaccgt ggaggacacc aagatcctgt tcgacggcat tcccctggag 540
aagatgagcg tcagcatgac aatgaatggc gctgtaattc ccgtgctcgc taatttcatc 600
gtgacaggcg aggagcaggg agtgcccaaa gaaaagctga ctggcactat ccagaacgac 660
atcctgaaag aattcatggt gcgtaacaca tacatcttcc ctcccgaacc cagcatgaag 720
atcattgcag acattttcga atacaccgcc aaacatatgc ccaagttcaa cagcatatct 780
attagcggct accatatgca ggaagccggg gcagatgcca tcctggaact ggcatacaca 840
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tttgctccca gactgagctt tttctggggc atcggcatga acttttacat ggagattgcc 960
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caggacccct acaacaacat cgtgaggacc gctattgagg ctatggctgc cgttttcggg 1140
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tctgcccgga tcgctaggaa cactcagatt attatccagg aggagagcgg aattcccaag 1260
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gagggtatcc ctaagctgcg gatcgaagag tgcgctgcta ggagacaggc cagaatagac 1440
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gaagtgctcg ccattgacaa tacctccgtg agaaaccggc agatcgaaaa actaaagaag 1560
atcaagagca gtagggacca ggctctggca gagaggtgcc tggccgcgct gaccgagtgc 1620
gccgcaagcg gcgacgggaa catcctcgca ctggccgtgg acgccagcag agctcggtgt 1680
acagtgggag agatcaccga cgcccttaaa aaggtgtttg gcgagcataa ggcgaacgat 1740
cgcatggtta gcggagctta cagacaggag tttggtgaga gcaaggagat cacgagtgct 1800
atcaagaggg tgcacaaatt catggagcgc gagggcaggc gccctagact cctcgtcgcc 1860
aagatgggtc aggacggtca cgacaggggc gcaaaggtga tcgccaccgg ctttgccgac 1920
ctaggcttcg acgtggacat tggccccctc ttccagacgc ccagagaagt ggcccagcaa 1980
gctgtggacg ccgatgtgca cgcggtggga gtgagcacac tcgccgccgg ccacaagacc 2040
ctggtgcccg agctgattaa ggagctcaac tcactgggga gacccgacat cctggtcatg 2100
tgcggtggag tgatcccccc ccaagactat gagtttctct tcgaggtagg cgtgagtaac 2160
gtgttcgggc ccggcaccag aatccctaag gcggccgtcc aggtgctgga cgatatcgag 2220
aaatgtctgg agaagaagca gcagagcgtt 2250

<210> 174
<211> 2250
<212> DNA
<213> Artificial Sequence

<220>
<223> Codon optimized sequence that encodes an MCM polypeptide with the I671V mutation

<400> 174
atgttaagag ccaaaaacca gctgttcctt ctgagccccc attatctgcg gcaggtgaag 60

gaatccagcg gctccagact catccaacag aggctcctac accagcagca gcccctgcac 120

ccggagtggg cagctctggc aaagaagcag ctcaagggca agaaccccga agatctgatc 180

tggcacaccc ccgaaggaat cagcatcaag cctctctata gcaagagaga taccatggat 240

ctgcccgagg agctgcccgg agtgaagcct tttactcggg gaccttaccc cactatgtac 300

actttccgcc cctggaccat cagacagtac gcgggcttct cgaccgtgga agagagtaat 360

aagttctata aagacaacat caaagccggc cagcagggtc tcagcgtggc gttcgatctg 420

gctacacaca gagggtacga tagcgacaac ccaagggtga ggggggacgt gggcatggcg 480

ggggtggcca tcgataccgt ggaagacacc aagatcctgt tcgacggtat ccccctagag 540

aaaatgtcag tcagcatgac gatgaacggc gcagtaatcc ccgtgctcgc aaatttcatt 600

gtgaccggcg aggagcaggg ggtgcctaag gagaagctga ccggcaccat acagaacgat 660

attctgaagg agttcatggt aaggaataca tacatcttcc ctcctgagcc cagcatgaag 720

atcatcgccg acatcttcga gtacactgcg aagcacatgc ccaaatttaa ttccatatcc 780

atctcgggct accacatgca ggaagccggc gccgatgcaa tactggaact ggcttacacc 840

ctggccgacg ggctggagta cagcaggacc ggcctccagg cgggcctgac cattgacgaa 900

tttgccccca gactcagctt cttctgggga atcgggatga atttttacat ggagatcgcc 960

aaaatgagag caggcaggag actgtgggct cacttgatcg agaaaatgtt tcagcccaag 1020

aacagcaaaa gccttctgct cagagcccac tgccagacta gcggctggtc tctgaccgag 1080

caggacccct ataacaacat cgtgagaacc gccatcgagg ccatggccgc cgtgttcggc 1140

ggaacacagt ctctgcatac caactccttc gacgaggcgc tgggactgcc aacggtcaag 1200

agcgcccgca ttgcaaggaa cacccagata atcatccagg aagagtctgg aattcctaag 1260

gtggcggacc cctggggagg ctcttacatg atggaatgcc tgacaaatga tgtctatgac 1320

gctgcactga aactgatcaa cgagattgag gagatgggtg gcatggccaa ggccgtggcc 1380

gagggcatcc caaaactgag aatcgaagag tgtgccgccc ggagacaagc caggatcgac 1440

tccggaagcg aagtgattgt gggagtcaat aagtaccaat tggaaaagga ggacgccgtg 1500

gaggtgctag ctatcgacaa tacctccgtg cgcaacaggc aaatagagaa gctgaaaaag 1560

atcaagtcat cccgggatca agccctggct gagaggtgtt tggccgccct cacggaatgc 1620

gctgccagcg gcgacggaaa catcctggcc ctggccgtcg acgccagcag agccaggtgc 1680

accgtgggtg aaattaccga cgctctgaag aaggtgttcg gtgaacacaa agccaacgac 1740

agaatggtga gcggtgccta cagacaggag ttcggcgagt ccaaggagat cacttcggcc 1800

atcaagaggg tgcacaagtt tatggagcgg gagggcagga ggcccagact cctagtggca 1860

aaaatggggc aggacggcca tgataggggg gccaaagtga tcgccaccgg attcgcagac 1920

ttgggcttcg acgtggatat cggacccttg tttcagaccc cccgcgaagt cgcacagcag 1980

gcggtggacg cggatgtgca cgctgttggc gttagcacac tggctgccgg ccataaaacc 2040

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tgcggaggcg ttatccctcc ccaggactac gagttcttgt tcgaggtggg cgtgagcaat 2160

gtctttggtc caggaactag gattcccaag gctgccgtgc aggtgctgga cgacatcgaa 2220

aagtgccttg agaagaagca gcagtctgtg 2250

<210> 175
<211> 2250
<212> DNA
<213> Artificial Sequence

<220>
<223> Codon optimized sequence that encodes an MCM polypeptide with the I671V mutation

<400> 175
atgctgaggg ctaaaaacca actgttcctg ctgagccccc actacctgcg ccaggtgaaa 60

gagtctagcg gtagcaggct catccagcag aggctgctgc atcagcagca gcccctccac 120

cccgagtggg ctgccctcgc caagaaacag ttaaagggga agaatcccga ggacctgatt 180

tggcacaccc cggagggcat cagtattaag cctctgtaca gcaagagaga caccatggac 240

ctgcccgagg aactccctgg ggtgaagccc ttcaccaggg gaccctatcc gaccatgtac 300

acattcaggc cttggaccat cagacagtat gcaggcttca gcaccgtgga agagagcaac 360

aagttctaca aggataatat caaggccgga cagcagggac tgagtgtggc cttcgatctt 420

gccacccaca gaggctatga ctctgacaat cccagagttc gtggggacgt tgggatggcc 480

ggagtggcca ttgatacagt ggaggacacc aagatcctgt ttgacgggat cccgctggag 540

aaaatgagcg tgtccatgac tatgaacggg gcagtgatcc cagtgctggc taacttcata 600

gtgactggag aggagcaggg cgtgccgaag gagaagctca caggcaccat ccagaatgac 660

atcctgaaag aattcatggt gcgtaatact tacatattcc ccccagagcc cagcatgaaa 720

atcatcgcgg acatttttga gtacaccgcc aagcacatgc ccaaatttaa ctcaattagc 780

attagtggct atcatatgca ggaggccggt gccgacgcaa tcctggaact ggcttacacc 840

ctggctgacg gccttgagta tagccggaca ggcctgcagg caggcctgac tatcgatgaa 900

tttgccccac gcctgtcttt cttttggggc atcggcatga actttacat ggagattgct 960

aagatgcgcg ctggcagaag actctgggcc cacctgattg agaagatgtt ccagcccaag 1020

aactcaaagt ccctgctgct gagggcccac tgtcagactt ctggatggag cctgaccgag 1080

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tctgcacgta tcgcccggaa cacccagatc atcatccagg aggaatccgg catccccaag 1260

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gagggaatcc caaagctgag gatcgaggag tgcgccgcta gaaggcaggc ccgcatcgat 1440

agcggctcag aggtgatcgt gggcgtgaat aagtatcagc tggagaaaga agacgccgtg 1500

gaagtgctgg cgatcgacaa tacctccgtg cgaaacagac agatcgagaa gctgaagaag 1560

atcaagtcga gccgcgacca ggccctggcc gagagatgtc tggcagccct gaccgagtgc 1620

gcagccagcg gcgacggcaa tatcctggcc ctggccgtgg acgcctcccg cgcgaggtgc 1680

acggtgggcg agattacgga cgctttgaaa aaggtgttcg gcgagcacaa ggccaatgac 1740

aggatggtgt ccggggccta tcgacaagaa ttcggggaga gcaaagaaat cacctccgcc 1800

attaagagag tccacaagtt catggagaga gagggccgga gacccagact tctggtcgcc 1860

aagatgggcc aagacggcca tgataggggc gcaaaggtga tcgccaccgg atttgccgac 1920

ctgggcttcg acgtggatat cggacctctt ttccagactc ccagagaggt ggcccagcag 1980

gccgtagacg ccgacgtgca tgctgtaggt gtgagcacgc tggccgccgg ccataagacc 2040

ctggtccccg aactaatcaa ggagctgaac tccctcggca gacccgacat cctggtgatg 2100

tgtggcggcg tgatcccccc acaggactat gagttcctgt ttgaggtagg cgtgagcaac 2160

gttttcggcc caggaaccag gatccctaag gctgccgtgc aggtgctgga tgacatcgaa 2220

aagtgcctgg agaagaagca gcaatcagtt 2250

<210> 176
<211> 2250
<212> DNA
<213> Artificial Sequence

<220>
<223> Codon optimized sequence that encodes an MCM polypeptide with the I671V mutation

<400> 176
atgcttagag ccaagaatca gctcttcctg ctgagccccc attatcttag acaggtgaag 60

gagagttcgg gctctcggct gatccagcag agactgctgc accagcagca gccattgcac 120

cccgagtggg ccgcgctggc gaagaaacag ctgaagggca agaaccccga ggatctgatc 180

tggcacacac cagaaggcat cagcatcaag cccttgtata gcaagcggga cacaatggat 240

ctccccgagg agctgcccgg cgtaaagccc ttcactcgag gcccctaccc tacgatgtac 300

accttcagac catggactat tcggcagtac gctggattct ccaccgtgga ggaatctaat 360

aaattctata aggataatat caaggccggc cagcagggcc tgagtgtcgc gttcgacctg 420

gccacccata ggggatacga ctcagacaac cccagggttc ggggcgacgt gggcatggcc 480

ggcgtcgcca tcgacaccgt agaggacaca aaaatcctgt tcgacggcat tcccctggag 540

aaaatgagtg tgagcatgac tatgaacggc gcagtgattc ccgtgctggc caatttcata 600

gtgacagggg aggaacaggg ggtccccaaa gagaaactca ccggcaccat tcaaaacgac 660

attctgaagg aattcatggt gcggaacaca tacattttcc cccccgaacc aagcatgaag 720

atcattgctg atatcttcga gtacacagcg aagcacatgc caaagttcaa ctctatttct 780

atctccgggt atcacatgca ggaggcagga gccgatgcca tcctggagct ggcttacacc 840

ctggcagacg gcctcgagta ctcgcgaacc ggactgcagg ccggcctcac catcgatgag 900

tttgcacccc ggctcagctt cttctggggc atcggtatga acttttatat ggagatcgct 960

aagatgcgcg caggtcgtag actttgggcc cacctcatcg aaaaaatgtt tcaacccaag 1020

aattccaaat ccttgctgct tagagcccat tgccagacat ccggctggag tctgaccgag 1080

caggacccct acaacaacat tgtgagaaca gcgatcgagg caatggccgc cgtgttcggc 1140

ggaacccaga gcctccatac caactccttt gacgaggccc tcggactgcc aaccgtcaag 1200

agcgccagga tcgccagaaa cacccagatc atcatccagg aggagagcgg cattccaaaa 1260

gtggccgatc cttggggcgg ctcctacatg atggagtgcc tcactaatga tgtgtacgac 1320

gccgccctga agctgattaa cgagattgag gagatgggcg gaatggctaa ggccgtggct 1380

gaagggatcc ccaaattgag aattgaggaa tgcgccgcta gaaggcaggc tcgcatagac 1440

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gaggtgctgg caattgataa cacctctgtg cggaacagac aaattgaaaa attaaagaaa 1560

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accgtgggcg agataacaga cgccctgaag aaggtgttcg gcgagcacaa ggccaacgat 1740

aggatggtgt ctggagccta tagacaggag tttggcgaaa gcaaagagat cacaagcgct 1800

attaagagag tgcacaagtt tatggagaga gaaggccgca gacccagact cctggtcgcc 1860

aagatgggac aggacggtca cgaccggggt gccaaagtaa tcgctaccgg ctttgccgac 1920

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tgcggagggg tgattccccc acaggattac gaattcctct tcgaggtggg ggtgtcaaat 2160

gtgttcgggc ccggaactag aatccccaag gccgccgtgc aggtgctcga cgacatcgaa 2220

aagtgtttgg agaagaagca gcagagcgtc 2250

<210> 177
<211> 2250
<212> DNA
<213> Artificial Sequence

<220>
<223> Codon optimized sequence that encodes an MCM polypeptide with the I671V mutation

<400> 177
atgctgagag ccaaaaacca actcttcctg ctgagcccac actacctgcg ccaggtcaag 60

gagtcaagcg gcagcagact gatccagcag agactgctcc accagcagca gcccctgcat 120

cctgagtggg ccgctctggc caaaaaacag ctgaagggca agaaccccga ggacctgatc 180

tggcacaccc ccgagggcat cagcatcaaa cccctgtatt caaagcggga cacaatggac 240

ctccctgagg agctgcctgg cgtcaagcca ttcacgaggg gcccataccc caccatgtac 300

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aagttttaca aggacaacat caaggcagga cagcagggcc tgtctgttgc atttgacctc 420

gccacacacc gaggctacga cagcgataac cccagagtca ggggcgatgt gggcatggcc 480

ggcgtggcca tagacacagt ggaggatacc aagatcctgt tcgatgggat cccactggag 540

aagatgtccg tgagcatgac aatgaatggc gccgtcatcc ccgtgctggc taatttcatt 600

gttaccggag aagagcaggg agtgccaaag gagaaactga ccggcaccat ccagaatgat 660

atccttaagg aattcatggt taggaacaca tacattttcc cacccgagcc atctatgaag 720

attattgccg acatcttcga atataccgcc aagcacatgc cgaaattcaa ctctatctca 780

atcagcgggt accatatgca agaggccgga gccgatgcta tcctggaact cgcttacacc 840

ctggccgacg gcctggagta cagcagaact ggcctgcaag ctggactgac tatcgatgag 900

ttcgcgccgc ggctgagctt cttctggggc atcggcatga acttttatat ggagattgcc 960

aaaatgcgcg ccggcaggag actctgggcc cacctgatcg agaaaatgtt ccagcccaaa 1020

aacagcaaaa gcctgcttct gcgtgcccat tgccaaacca gcggctggtc tctgactgaa 1080

caggaccctt acaacaatat cgtgaggacc gccattgagg ccatggccgc cgtgtttggt 1140

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tccgccagaa tcgccagaaa cacacagatc atcatccagg aggagagcgg catccccaaa 1260

gttgctgacc cctggggcgg ctcctacatg atggagtgcc tcaccaacga cgtgtacgac 1320

gcagctttga aacttatcaa cgagattgag gagatgggag gaatggcgaa ggccgtggcc 1380

gagggtattc ccaagctgag gattgaagaa tgcgcagcca gaagacaggc acggatcgat 1440

tccggcagtg aagtgattgt tggagtgaac aagtaccagc tggagaaaga ggacgccgtg 1500

gaagtcctgg ccatcgataa tacaagcgtg agaaacagac agattgaaaa gctgaagaag 1560

atcaagtcta gccgcgatca ggctctggcc gagagatgcc tggccgccct caccgaatgc 1620

gcagccagcg gcgatgggaa catcctcgca ctggctgtcg acgcttccag agctagatgc 1680

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aggatggtga gcggtgcata ccgtcaggaa tttggtgagt ccaaggaaat tacctccgca 1800

atcaagagag tgcacaaatt catggaaagg gaaggtcgaa gacctagact gctggtcgcc 1860

aagatggggc aggacggcca tgataggggc gccaaggtca tagctaccgg gtttgcggac 1920

ctgggcttcg acgtggacat cggccctctc ttccagaccc cccgggaagt ggcccagcaa 1980

gccgtggacg ctgacgtgca cgctgtcgga gtgtccaccc tggctgcagg acacaagacc 2040

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tgcggcggcg tgatcccccc tcaggattac gagttcttgt ttgaagtggg cgtgagcaac 2160

gtgttcggcc ctggcaccag aattcctaaa gccgcagtcc aggtgctcga tgacatcgag 2220

aaatgcctgg agaaaaaaca gcagagcgtc 2250

<210> 178
<211> 2250
<212> DNA
<213> Artificial Sequence

<220>
<223> Codon optimized sequence that encodes an MCM polypeptide with the I671V mutation

<400> 178
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gagagcagtg gatcaaggct gattcagcag aggctgctgc accagcagca gcccctgcac 120

ccagagtggg ccgccctggc taagaagcag ctgaaaggca agaaccccga ggatttgatt 180

tggcacaccc cagagggaat ctctatcaag cctctgtaca gcaaacgcga cacaatggac 240

ctgccagagg agctgccagg cgtgaagcct ttcacacggg ggccttaccc taccatgtac 300

acattcagac cctggaccat cagacagtac gccggcttct ccaccgttga ggagtccaat 360

aagttctaca aggacaacat taaagccgga cagcagggcc tcagcgtggc ctttgacctc 420

gccacccaca ggggctacga cagcgataac ccccgtgtga gaggggacgt gggaatggcc 480

ggggttgcta tcgatactgt ggaggacact aagatcctct ttgatggcat tcccctggaa 540

aagatgagcg tctctatgac catgaacggg gccgtgatcc ccgtgctggc caactttatc 600

gtgactggcg aggagcaggg ggtgccaaaa gagaagctga caggaaccat tcagaacgac 660

atcctgaagg agtttatggt caggaacacc tacattttcc cccctgagcc aagcatgaag 720

atcatcgccg atattttcga gtataccgcg aagcacatgc ctaaattcaa ctctatcagc 780

atcagcggct accacatgca ggaggccggc gcggatgcca ttctggagct ggcctacaca 840

ctggccgacg gcctcgaata cagccggact ggcctgcagg ctggcttgac aatcgacgag 900

ttcgctccaa gactgagctt cttctggggc atcgggatga acttctatat ggagatcgct 960

aagatgagag ccggaagaag actgtgggct cacctgatag agaagatgtt tcagcctaag 1020

aattctaaga gtctgctgct gagggcgcac tgccagacta gcggctggtc cctgaccgag 1080

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gagggcatcc ccaaactgcg gatcgaggag tgcgccgcca gacggcaagc aaggattgac 1440

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gaggtactgg ccatagacaa cacctctgtg cggaaccgcc agatcgagaa gcttaagaag 1560

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cgtatggtga gcggcgctta ccggcaggag ttcggcgaat ccaaggagat caccagtgcc 1800

atcaagagag tccacaagtt tatggaaaga gagggccgca ggcctcggct cctggtggct 1860

aagatggggc aggatggaca cgacaggggc gccaaggtga tcgctactgg cttcgccgac 1920

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gcggtggacg cggacgtgca cgctgtgggc gtgagcacac tggccgccgg ccacaagact 2040

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tgcggcggag tcatcccacc ccaagactat gaattcctgt tcgaagtggg agtgagcaat 2160

gtgttcggcc ctggcaccag aatccccaaa gctgccgtgc aggtcttgga tgacatcgag 2220

aaatgcctgg agaagaagca gcaaagtgtc 2250

<210> 179
<211> 2250
<212> DNA
<213> Artificial Sequence

<220>
<223> Codon optimized sequence that encodes an MCM polypeptide with the I671V mutation

<400> 179
atgctgaggg ccaaaaacca gctgttcctg ctcagccctc attacctaag acaggtcaag 60

gagagctccg gcagcagact gatccagcag cgattactgc accagcagca gccgctgcac 120

cccgagtggg ccgccctcgc caaaaagcag ctgaagggca agaacccaga ggacctcatt 180

tggcataccc ccgagggcat aagcattaag cccctctatt ctaagaggga taccatggac 240

ctgcccgaag agctgcccgg cgtcaaaccc tttaccaggg ggccttaccc gactatgtac 300

acattcagac cctggactat cagacagtac gcagggttct ccacggtcga agagagcaac 360

aagttctaca aggacaacat caaagccggc cagcaagggc tcagcgtcgc attcgacctg 420

gctacccaca ggggctacga ctctgacaac cctagagtga gaggggacgt ggggatggct 480

ggagtcgcca tcgacaccgt ggaggacacc aagatcctct ttgatgggat cccactggag 540

aaaatgtccg tgagcatgac catgaatggg gccgtgatcc ctgtgttagc caactttatc 600

gtgacaggag aggaacaggg ggtgcccaag gaaaagttga ccggcaccat ccagaacgat 660

atcctgaaag agttcatggt taggaatacc tacatcttcc cccccgagcc ctctatgaag 720

atcatcgccg acatatttga atataccgcg aaacacatgc ccaagttcaa cagcatttct 780

atcagcggct accacatgca ggaagccggc gctgatgcca tcctggagct cgcctacaca 840

ctggcggatg gcctggagta cagcagaaca ggcctccagg ctggcctgac catcgatgag 900

ttcgcacccc gcctttcctt cttctgggga attggtatga atttttacat ggaaatcgcg 960

aagatgcgcg ccggcaggag actgtgggca catctgatcg agaagatgtt tcagcctaag 1020

aacagtaaat cgctgctgct gcgggcccat tgccagacgt ccgggtggtc actgaccgaa 1080

caggatccct acaacaacat cgtcagaact gccatcgagg ccatggccgc cgtgttcggg 1140

ggaacccaat ccctgcacac caattctttc gacgaggcac tgggcctgcc caccgtgaag 1200

agcgccagaa ttgcccggaa tacccagatt atcatccagg aagaatccgg catccccaag 1260

gtcgcggacc cctggggcgg ctcttacatg atggaatgct taaccaacga cgtatacgac 1320

gccgccctga aacttatcaa cgaaatcgag gagatgggcg gaatggcaaa ggctgtggcc 1380

gagggaatcc ccaagctgag aatcgaggag tgcgccgcca ggagacaggc cagaatagac 1440

agcgggtcag aggtaatcgt gggggtgaac aagtatcaac tggagaagga ggacgccgtg 1500

gaggtgctcg ctatcgacaa cacatccgtg agaaacagac agatcgagaa actgaagaaa 1560

attaaaagca gcagagacca ggcactggcc gaaagatgcc tggcagcact gaccgagtgc 1620

gctgctagcg gcgacggaaa catcctggcc cttgctgtgg acgcctcaag ggcacgctgc 1680

actgtaggcg agatcaccga cgccctcaag aaggtgttcg gggagcacaa ggcgaatgac 1740

agaatggtga gcggtgccta ccgccaggag tttggagaga gcaaggaaat aaccagcgcc 1800

attaagagag tgcacaagtt tatggagaga gagggcaggc ggcccaggct gctggtggca 1860

aagatgggcc aggacggaca cgaccggggc gctaaagtta tcgcgacagg ctttgctgac 1920

ctgggattcg atgttgacat tggccccctg ttccagacac cccgggaggt tgcccagcag 1980

gccgtggatg ccgacgttca cgccgtgggc gtcagcacac tggccgccgg ccataagacc 2040

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tgcggcggag tgatccctcc ccaggattat gaattcttgt ttgaggtggg agtgagcaac 2160

gtttttggcc ctggcacccg tatccccaag gccgccgttc aggtactgga cgacatcgaa 2220

aaatgcttag agaagaagca gcagtcagtg 2250

<210> 180
<211> 2250
<212> DNA
<213> Artificial Sequence

<220>
<223> Codon optimized sequence that encodes an MCM polypeptide with the I671V mutation

<400> 180
atgctgcgag cgaaaaacca actgtttctg ctgtcccccc attacctgcg ccaggtgaag 60

gagtccagcg gaagccggct catccaacag cggctgctgc accagcagca gcccctgcac 120

cccgagtggg ccgcactggc caagaaacag ctgaaaggca aaaaccccga agacctgatc 180

tggcacacgc ccgaaggcat cagcatcaag cccctctact ccaagcgcga taccatggat 240

ctgcccgagg agctccccgg cgtgaagccc tttaccaggg gcccctatcc caccatgtac 300

accttccggc cctggaccat caggcagtac gccggattca gcacagtgga ggagagcaac 360

aaattttaca aggacaatat caaagccggg cagcaaggcc tgagcgtcgc cttcgacctg 420

gcgacacaca gggggtacga cagcgacaat ccgcgggtca ggggcgacgt cggaatggca 480

ggcgtggcca tcgacaccgt ggaggacacc aaaatcctgt ttgacggcat ccccctcgag 540

aagatgagcg tgtccatgac catgaacggc gcagtgatcc cggtgctggc caacttcatc 600

gtcaccgggg aggagcaggg cgtcccgaag gagaagctga ccggcaccat acaaaacgac 660

atactgaagg aattcatggt gaggaacacg tacatctttc cccccgaacc cagcatgaag 720

atcatcgcag atattttcga gtataccgcc aagcacatgc ccaagttcaa ctccatctcg 780

atcagtgggt accatatgca agaagccggg gccgacgcca tcctggagct cgcctatacc 840

ctggccgacg gcctggagta tagcaggacc ggcctccagg ccgggctgac gatcgatgag 900

tttgccccca ggctgagctt cttctggggg atcgggatga atttttatat ggagatcgcc 960

aagatgaggg ccgggcggag gctgtgggcc cacctgatcg aaaagatgtt ccagcccaag 1020

aactcaaaga gcctgctcct gcgggcccat tgccagacca gcggctggtc cctgaccgag 1080

caggacccct acaacaacat cgtgaggaca gccatcgagg caatggccgc cgtgttcggg 1140

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gaggtgctgg ccattgacaa cacctcggtc cggaacaggc agatcgagaa gctcaagaag 1560

atcaagagca gtcgagacca ggccctggcc gagaggtgcc tggccgccct gacagaatgc 1620

gcagccagcg gcgacggaaa catcctggcg ctggccgtgg acgccagtcg ggccaggtgc 1680

acggtgggcg agatcaccga cgccctgaag aaggtcttcg gggagcacaa ggccaacgac 1740

cggatggtga gcggcgccta ccgacaggag ttcggcgagt caaaggagat aacctccgcc 1800

atcaagaggg tgcacaagtt catggagagg gagggcagga ggcccaggct cctcgtcgcc 1860

aagatgggac aggacggcca tgacaggggc gccaaggtca tcgccaccgg attcgccgac 1920

ctgggcttcg acgtggacat cgggcccctg tttcagaccc cacgggaggt ggcccagcag 1980

gccgtggacg ccgacgtgca cgcggtgggc gtcagcaccc tggccgctgg gcacaagacc 2040

ctcgtgcccg aactgatcaa ggagctgaac tccctgggga ggcccgacat cctcgtgatg 2100

tgcgggggg tgatcccccc ccaggactat gaattcctgt ttgaggtggg ggtgagcaac 2160

gtgttcggcc ccgggactag aatacccaag gccgccgtcc aggtgctgga tgatatcgag 2220

aaatgcctgg agaaaaaaca gcaaagcgtg 2250

<210> 181
<211> 2250
<212> DNA

<213> Artificial Sequence

<220>
<223> Codon optimized sequence that encodes an MCM polypeptide with the I671V mutation

<400> 181
atgctgcggg ccaagaacca gctgttcctg ctgagccccc actacctgcg gcaggtgaag 60

gagagcagcg gcagccggct gatccagcag aggctgctgc accagcagca gccgctgcac 120

ccggagtggg cggcgctggc gaagaagcag ctgaagggga agaacccgga ggacctgatc 180

tggcacacgc cggaggggat cagcatcaag ccgctgtaca gcaagaggga cacgatggac 240

ctgccggagg agctgccggg ggtgaagccg ttcacgaggg ggccgtaccc gacgatgtac 300

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aagttctaca aggacaacat caaggcgggg cagcaggggc tgagcgtggc gttcgacctg 420

gcgacgcaca gggggtacga cagcgacaac ccgagggtga ggggggacgt ggggatggcg 480

ggggtggcga tcgacacggt ggaggacacg aagatcctgt tcgacgggat cccgctggag 540

aagatgagcg tgagcatgac gatgaacggg gcggtgatcc cggtgctggc gaacttcatc 600

gtgacggggg aggagcaggg ggtgccgaag gagaagctga cggggacgat ccagaacgac 660

atcctgaagg agttcatggt gaggaacacg tacatcttcc cgccggagcc gagcatgaag 720

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atcagcgggt accacatgca ggaggcgggg gcggacgcga tcctggagct ggcgtacacg 840

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gaggtgctgg cgatcgacaa cacgagcgtg aggaacaggc agatcgagaa gctgaagaag 1560

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aagatggggc aggacgggca cgacaggggg gcgaaggtga tcgcgacggg gttcgcggac 1920

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gtgttcgggc cggggacgag gatcccgaag gcggcggtgc aggtgctgga cgacatcgag 2220

aagtgcctgg agaagaagca gcagagcgtg 2250

<210> 182
<211> 2250
<212> DNA
<213> Artificial Sequence

<220>
<223> Codon optimized sequence that encodes an MCM polypeptide with the I671V mutation

<400> 182
atgctgcggg ccaagaacca gctgttcctg ctgagccccc actacctgcg gcaggtgaag 60

gagagcagcg gcagccggct gatccagcag cgcctcctcc accagcagca gcccctccac 120

cccgagtggg ccgccctcgc caagaagcag ctcaagggca agaaccccga ggacctcatc 180

tggcacaccc ccgagggcat ctccatcaag cccctctact ccaagcgcga caccatggac 240

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gccacccacc gcggctacga ctccgacaac ccccgcgtcc gcggcgacgt cggcatggcc 480

ggcgtcgcca tcgacaccgt cgaggacacc aagatcctct tcgacggcat ccccctcgag 540

aagatgtccg tctccatgac catgaacggc gccgtcatcc ccgtcctcgc caacttcatc 600

gtcaccggcg aggagcaggg cgtccccaag gagaagctca ccggcaccat ccagaacgac 660

atcctcaagg agttcatggt ccgcaacacc tacatcttcc cccccgagcc ctccatgaag 720

atcatcgccg acatcttcga gtacaccgcc aagcacatgc ccaagttcaa ctccatctcc 780

atctccggct accacatgca ggaggccggc gccgacgcca tcctcgagct cgcctacacc 840

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ttcgcccccc gcctctcctt cttctggggc atcggcatga acttctacat ggagatcgcc 960

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gagggcatcc ccaagctccg catcgaggag tgcgccgccc gccgccaggc ccgcatcgac 1440

tccggctccg aggtcatcgt cggcgtcaac aagtaccagc tcgagaagga ggacgccgtc 1500

gaggtcctcg ccatcgacaa cacctccgtc cgcaaccgcc agatcgagaa gctcaagaag 1560

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gccgcctccg gcgacggcaa catcctcgcc ctcgccgtcg acgcctcccg cgcccgctgc 1680

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gtcttcggcc ccggcacccg catccccaag gccgccgtcc aggtcctcga cgacatcgag 2220

aagtgcctcg agaagaagca gcagtccgtc 2250

<210> 183
<211> 2250
<212> DNA
<213> Artificial Sequence

<220>
<223> Codon optimized sequence that encodes an MCM polypeptide with the I671V mutation

<400> 183
atgctaagag caaagaacca gctttttcta ttgtcccccc attatttgag acaagttaag 60

gaaagttcag gctccagact tatccaacag cgacttctcc accagcagca gccactgcat 120

ccggaatggg ccgccctggc aaagaagcag cttaagggaa agaatcctga ggatttaatc 180

tggcacaccc ctgagggcat tagcatcaag cccttgtact cgaagaggga tactatggac 240

ctgcctgagg agctcccagg cgtgaagccg ttcacccgcg gcccctaccc aaccatgtac 300

actttcaggc cctggaccat ccgacagtac gccggttttt ccacagtgga agaatctaat 360

aaattctata aagataacat aaaggccgga cagcaggggc ttagcgtggc attcgatctg 420

gccacgcatc gcggatacga cagcgataac ccaagagtta gaggtgatgt gggtatggcc 480

ggagttgcca ttgatactgt cgaagacaca aagattctct tcgatggcat ccctctggag 540

aaaatgagtg tgtccatgac tatgaacgga gccgtgattc cagtcctcgc taattttatt 600

gtgacgggag aagaacaggg ggttcccaag gagaaactta cggggaccat tcagaacgat 660

atccttaaag aattcatggt tcgcaacaca tacatcttcc caccagagcc ttctatgaaa 720

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atcaaacgtg tgcacaagtt catggaaaga gagggtcggc ggccacggct ccttgttgcc 1860

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<210> 184
<211> 2250
<212> DNA
<213> Artificial Sequence

<220>
<223> Codon optimized sequence that encodes an MCM polypeptide with the I671V mutation

<400> 184
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cctgagtggg ccgctctcgc taagaagcag ctgaaaggga agaaccccga agaccttata 180

tggcacaccc ctgagggaat cagcatcaag ccgctgtatt ctaaaaggga taccatggac 240

ttgcccgagg agcttcccgg agtgaagcct ttcactaggg gcccctatcc tacgatgtat 300

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aagtgtctgg aaaaaaagca gcagtccgtg 2250

<210> 185
<211> 2250
<212> DNA
<213> Artificial Sequence

<220>
<223> Codon optimized sequence that encodes an MCM polypeptide with the I671V mutation

<400> 185
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ccagagtggg ccgcccttgc aaagaaacag ttaaaaggaa agaaccctga agatctcatc 180

tggcacacac ccgagggcat ctcaataaag ccgctgtact cgaaacgaga caccatggac 240

ctgcctgaag aactgccggg ggtcaagccc tttactagag ggccctaccc aaccatgtac 300

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gctacacata gggggtacga tagtgacaat cctagagtcc gcggtgatgt ggggatggct 480

ggcgtggcaa tagacaccgt tgaggacacg aaaatcctgt tcgatggtat ccctttagag 540

aaaatgtccg tttctatgac gatgaacggg gctgtgatcc ccgtcctagc caatttcatc 600

gtcacgggcg aggaacaggg ggttccaaaa gaaaaattga ccggaactat acaaaatgac 660

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gggactcaaa gtcttcacac aaactctttc gacgaggctc tgggtctacc caccgtgaag 1200

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ctgggcttcg acgtggacat cgggccactc tttcagaccc caagggaagt agcccagcaa 1980

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aagtgccttg agaagaaaca acagtccgtt 2250

<210> 186
<211> 2250
<212> DNA
<213> Artificial Sequence

<220>
<223> Codon optimized sequence that encodes an MCM polypeptide with the I671V mutation

<400> 186
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ccagagtggg ctgctctggc caaaaaacag ctgaagggta aaaacccaga agatctcatc 180

tggcacactc cagagggcat atcaatcaaa ccactctatt caaagcgaga cacaatggac 240

ttgccagaag agctcccagg ggttaaacct ttcaccagag gaccttaccc aacgatgtac 300

accttcaggc cttggaccat ccgccagtac gcgggcttca gcacagtgga ggagagtaac 360

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gccactcaca gagggtatga ctccgacaat ccccgcgtga ggggagacgt gggaatggcg 480

ggggtggcaa ttgacactgt cgaagacacc aagatcctgt ttgacggtat ccctttagaa 540

aaaatgtcag tgtccatgac aatgaacgga gcagtgatac ccgttctcgc caacttcatc 600

gttactggag aggagcaggg ggttccgaag gaaaagctca ccggcacgat ccaaaatgat 660

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gcggtggacg ccgatgtgca cgctgtgggc gtgtctacgc tcgctgccgg acataagaca 2040

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aagtgccttg agaaaaaaca gcagtccgtt 2250

<210> 187
<211> 2250
<212> DNA
<213> Artificial Sequence

<220>
<223> Codon optimized sequence that encodes an MCM polypeptide with the I671V mutation

<400> 187
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cccgagtggg ccgctctggc caaaaagcag ctcaagggca aaaaccccga ggacttaatt 180

tggcacactc ctgagggaat tagcatcaag cctctgtaca gcaagaggga caccatggac 240

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gccacgcaca gggggtatga cagcgataac cccagggtgc ggggcgacgt aggaatggcg 480

ggagtggcca ttgacaccgt ggaggatacc aaaatcctct tcgatggcat tccactcgag 540

aagatgtctg tgagcatgac catgaacggg gccgtgatcc ccgttttggc taacttcatc 600

gtcaccgggg aggagcaggg cgtacccaag gagaagctga caggcaccat acagaacgac 660

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aaatgcctgg agaaaaaaca gcagagcgtg 2250

<210> 188
<211> 2250
<212> DNA
<213> Artificial Sequence

<220>

<223> Codon optimized sequence that encodes an MCM polypeptide with the I671V mutation

<400> 188

atgcttagag ccaaaaatca gctttttctt ctgtcccccc actacctccg gcaggtcaaa 60

gagtctagcg gatcacgtct aatccagcag aggctgctcc accagcagca gcccctccac 120

cctgagtggg cagcgttagc gaaaaagcaa ctgaagggaa agaaccctga agatctgata 180

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ctccccgagg agttacctgg agtgaagccc ttcacaagag gaccatatcc cactatgtac 300

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<211> 2250
<212> DNA
<213> Artificial Sequence

<220>
<223> Codon optimized sequence that encodes an MCM polypeptide with the I671V mutation

<400> 189
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aagtgcctcg agaagaaaca gcaaagtgtg 2250

<210> 190
<211> 2250
<212> DNA
<213> Artificial Sequence

<220>
<223> Codon optimized sequence that encodes an MCM polypeptide with the I671V mutation

<400> 190
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gccacgcatc ggggttatga cagcgataac cctagagtta ggggagatgt tggaatggcc 480

ggtgtggcca ttgacactgt ggaagataca aagatactgt ttgatgggat ccccctcgaa 540

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aaatgtctgg aaaagaaaca gcagagtgtg 2250

<210> 191
<211> 2250
<212> DNA
<213> Artificial Sequence

<220>
<223> Codon optimized sequence that encodes an MCM polypeptide with the I671V mutation

<400> 191
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cccgaatggg cagcgctagc caagaaacag ctaaagggga agaatccaga agatctgata 180

tggcacaccc cagaggggat cagtatcaag cctctatact ccaaaaggga cactatggac 240

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aagtgtctgg agaagaaaca acagtccgtg 2250

<210> 192
<211> 2250
<212> DNA
<213> Artificial Sequence

<220>
<223> Codon optimized sequence that encodes an MCM polypeptide with the I671V mutation

<400> 192
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cctgagtggg ccgccttggc taagaagcaa ctgaaaggga aaaacccaga ggatttgata 180

tggcatacgc ctgagggcat atctataaaa ccactgtact cgaaaagaga cactatggac 240

ttgcccgagg agctccccgg tgttaaacct ttcacccgag ggccataccc gaccatgtac 300

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aagttctaca aggacaacat taaagccggt cagcaggggc tgagcgtagc cttcgaccta 420

gcaacgcacc ggggctatga ctctgataac cctagggtga gaggagacgt aggaatggct 480

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aagatgtctg tttctatgac catgaacggc gccgtgatac cagtactcgc aaatttcata 600

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aaatgcctag agaagaagca gcagagcgtg 2250

<210> 193
<211> 2250
<212> DNA
<213> Artificial Sequence

<220>
<223> Codon optimized sequence that encodes an MCM polypeptide with the I671V mutation

<400> 193
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cccgaatggg cagcgctagc aaagaaacaa ctcaagggaa aaaaccctga ggacttaatt 180

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aagttttaca aggacaacat caaggcaggt cagcagggac tcagcgtcgc attcgactta 420

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<210> 194
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<212> DNA
<213> Artificial Sequence

<220>
<223> Codon optimized sequence that encodes an MCM polypeptide with the I671V mutation

<400> 194
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gtgtttgggc ccgggacccg tatccctaaa gccgcagtgc aagtgcttga tgacattgag 2220

aagtgcttag agaagaaaca gcaatcggtg 2250

<210> 195
<211> 2250
<212> DNA
<213> Artificial Sequence

<220>
<223> Codon optimized sequence that encodes an MCM polypeptide with the I671V mutation

<400> 195
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gagagcagcg gatcaagact catccagcag aggctgctgc accagcagca accgctgcac 120

cccgagtggg ccgcactcgc caagaagcag ctgaaaggca agaacccgga ggacctaatc 180

tggcacaccc ccgaagggat cagcatcaag ccgctatact ccaaaagaga cacaatggac 240

ctacccgagg agctccccgg agtgaaacca ttcacccgcg ggccctaccc cacgatgtac 300

acgttccggc cctggaccat caggcaatac gccggcttct caaccgtgga ggagagtaac 360

aaattctaca aagacaacat caaagcggga cagcagggcc tctcagtggc cttcgacctc 420

gcaacacacc gcggctacga ctcagacaac cccagggtgc gcggggacgt cggaatggcc 480

ggagtcgcca tcgacacagt cgaggacacc aagatcctgt tcgacgggat ccccctggag 540

aaaatgagcg tgagcatgac catgaacggg gccgtgatac cagtgctggc caacttcatc 600

gtaacaggag aggagcaggg ggtgcccaaa gagaagctca cagggacaat ccagaacgac 660

atcctgaagg agttcatggt acgaaacacc tacatcttcc cccccgagcc cagtatgaag 720

ataatcgcgg acatattcga gtacaccgcc aagcacatgc cgaagttcaa ctcgatcagc 780

atctcaggct accacatgca agaggcaggg gcggacgcaa tcctggaact ggcctacaca 840

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ttcgccccac ggctgagctt cttctggggg atcgggatga acttctacat ggaaatcgcc 960

aagatgagag caggcaggcg actgtgggcc cacctaatcg aaaagatgtt ccaaccaaag 1020

aactccaaaa gcctgctcct ccgggcacac tgccaaacaa gtggatggag tctgaccgaa 1080

caggacccat acaacaacat cgtgcggaca gccatagagg ccatggccgc ggtgttcggg 1140

ggcacccaga gcctccacac caacagtttc gacgaagccc tggggctacc aaccgtcaaa 1200

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gagggcatcc cgaagctccg catcgaggag tgcgcagcgc gacggcaggc gaggatcgac 1440

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gaagtgctgg caatcgacaa cacctccgtc cgcaacaggc agatcgagaa actcaaaaag 1560

atcaagagct cacgggacca ggccctcgcc gagagatgcc tcgcggccct aaccgaatgc 1620

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ataaagaggg tccacaagtt catggaacga gaaggccgcc ggccaagact gctggtggcg 1860

aaaatgggcc aggacgggca cgaccgaggc gcaaaggtaa tcgcaacggg gttcgccgac 1920

ctggggttcg acgtcgacat cggacccctg ttccaaaccc ccagggaagt ggcccagcag 1980

gcagtggacg ccgacgtgca cgccgtgggc gtatcgaccc tggccgcggg ccacaaaacg 2040

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tgcggcgggg tgataccccc gcaggactac gagttcctat tcgaggtcgg agtctcgaac 2160

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aagtgcctgg aaaagaaaca gcagtcagtc 2250

<210> 196
<211> 2250
<212> DNA
<213> Artificial Sequence

<220>
<223> Codon optimized sequence that encodes an MCM polypeptide with the I671V mutation

<400> 196
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gagagctctg gttcccggtt aatccagcag agactgctcc atcagcaaca gcccctgcac 120

cccgaatggg cggctctcgc taagaagcaa ttaaagggca agaacccaga agacctgatt 180

tggcatacac cggaaggaat cagtatcaaa cccctctata gcaaaagaga tacgatggat 240

ctccccgagg aactgcccgg agtgaagccc ttcacgcgcg gtccataccc aactatgtat 300

acgtttcggc cctggacgat ccggcagtac gccggctttt ctaccgtcga ggagtctaat 360

aaattttaca aggacaatat caaggctggc caacagggct tgtcggtagc ctttgatctg 420

gccactcacc gtggatatga cagcgataat ccacgggtgc ggggggacgt cggtatggcc 480

ggtgtagcca tcgacaccgt agaagatacc aaaatcctct ttgatgggat ccccctcgag 540

aagatgtccg tgtcaatgac catgaacggt gctgtgatcc ctgtgctcgc caacttcata 600

gttaccgggg aagagcaggg ggtgcctaag gaaaagttaa ccgggacaat ccaaaatgac 660

atcctcaagg agtttatggt gcggaatact tatatattcc cacccgagcc ttcaatgaag 720

atcatcgctg atatcttcga gtacactgct aaacacatgc ccaagtttaa ttctattagt 780

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aaaatgcggg ccgggcgccg gttatgggcc caccttattg agaaaatgtt tcagcccaaa 1020

aattctaagt ctctgctcct aagggcacat tgccaaactt cgggctggtc gcttaccgaa 1080

caggacccat acaacaacat tgtccgcacc gcaatcgagg ccatggctgc tgtgtttggg 1140

ggtactcagt ctctacacac caactccttc gatgaagcac tcggtctgcc gactgtgaaa 1200

agcgccagaa tcgcccggaa tacccaaata ataatccagg aggagtccgg gattcctaaa 1260

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gagggaattc ctaagctgag gattgaagag tgtgcagctc ggcgacaagc gcggatcgac 1440

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gaggtgcttg ctattgataa cacatcggtc cgcaatagac aaatcgagaa gctgaagaaa 1560

attaagagca gtcgcgacca ggcattggcc gagaggtgcc tcgccgccct gacagagtgt 1620

gccgcaagtg gagatggaaa catacttgct ctggccgttg atgcttccag agcccgctgc 1680

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gccgtggacg ccgacgtgca cgcagtgggc gtgtccaccc tggccgcagg ccataagaca 2040

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tgtggcggag ttatcccccc gcaggactac gagttcttgt ttgaagtggg tgtgtccaat 2160

gtgttcgggc ctggtacccg aatcccgaaa gcggccgtac aggttctgga cgatatcgaa 2220

aaatgcttgg aaaaaaagca acagagcgta 2250

<210> 197
<211> 2250
<212> DNA
<213> Artificial Sequence

<220>
<223> Codon optimized sequence that encodes an MCM polypeptide with the I671V mutation

<400> 197
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gaatcttcag gttctcgcct gatacagcaa cgtctgctgc accaacagca gcccctgcat 120

ccagagtggg cagccctggc aaagaaacag ctgaagggaa aaaatcccga ggatcttatc 180

tggcatacac cagaagggat ctcgatcaaa ccactgtaca gtaagcggga taccatggac 240

ttaccggagg agctgcccgg tgtcaagcca tttactcgag gcccgtatcc caccatgtat 300

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aaattttaca aagataacat aaaggctggc cagcaaggcc tctccgtagc tttcgatctg 420

gctacgcata ggggttatga tagtgacaat cctagggtgc ggggggatgt cggtatggct 480

ggcgtggcaa ttgacaccgt tgaggacacc aagatcctct ttgatgggat tcccttggaa 540

aaaatgagtg ttagcatgac aatgaatgga gctgttatcc ccgtgcttgc caattttata 600

gtcaccgggg aggagcaagg ggttcctaaa gagaagctaa cagggaccat tcagaatgac 660

atcttgaaag aatttatggt gaggaataca tacatcttcc ccccagaacc gtccatgaag 720

atcatcgccg atatcttcga atatacagca aaacatatgc cgaaattcaa ttctatttcc 780

atcagcggct atcacatgca ggaggctgga gcagacgcca tcttggagtt ggcctacaca 840

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aaaatgagag cgggaagaag gctttgggcc cacctaatcg agaagatgtt tcagcccaaa 1020

aattctaagt ctctgctgct gcgcgctcac tgtcagacca gtggctggtc cctaacggag 1080

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ttgggatttg acgtggacat tggacctctg ttccagaccc cacgcgaggt cgcgcagcaa 1980

gccgtggatg cggatgtcca cgctgtcggc gtgtccacac tggctgccgg ccataagact 2040

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aagtgtcttg aaaaaaagca gcagtcggtc 2250

<210> 198
<211> 2250
<212> DNA
<213> Artificial Sequence

<220>
<223> Codon optimized sequence that encodes an MCM polypeptide with the I671V mutation

<400> 198
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gagagttctg ggagtagact tatccaacag agactcttac accagcaaca gccccttcat 120

ccagaatggg ctgcactggc taaaaagcag ctgaaaggaa aaaatccgga ggacctcatc 180

tggcacacac ctgaagggat aagcattaag ccactctaca gcaagaggga cacgatggat 240

ctcccagagg agcttccagg ggtaaaaccg tttacacgcg gaccctaccc aaccatgtac 300

acgttccgac catggacaat cagacaatac gccggtttta gcactgtgga ggagtcaaac 360

aagttctata aagataatat caaagccgga caacagggac tttccgtggc ctttgacctg 420

gccacacacc ggggctacga ctctgacaac ccaagagtcc ggggcgacgt tggcatggcc 480

ggtgtggcca tcgacactgt cgaggacacc aagatcctgt tcgatggcat tcccttggaa 540

aaaatgagcg tgtctatgac catgaacggg gcagtaatac ccgtccttgc aaacttcatc 600

gtgaccgggg aagagcaggg cgttcctaag gaaaaactga cggggacaat tcagaacgac 660

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atcagtggct atcacatgca agaggccggg gcagatgcta tcttggaact tgcctacact 840

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aagtgcctcg aaaaaaaaca gcaaagcgtg 2250

<210> 199

<211> 2250
<212> DNA
<213> Artificial Sequence

<220>
<223> Codon optimized sequence that encodes an MCM polypeptide with the I671V mutation

<400> 199
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gagagttccg gctcacgcct gatacaacag agactgctcc atcagcaaca gccgctgcac 120

ccagaatggg cagccctggc caaaaaacaa cttaaaggta agaacccgga ggatttgatc 180

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gtgaccggtg aggaacaggg ggtccctaag gagaaattga cgggcactat tcagaacgac 660

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attagtggct accatatgca ggaggccgga gccgacgcca ttctcgagct ggcatatacc 840

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aagtgtctgg aaaagaaaca acaatcagta 2250

<210> 200
<211> 2250
<212> DNA
<213> Artificial Sequence

<220>
<223> Codon optimized sequence that encodes an MCM polypeptide with the I671V mutation

<400> 200
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ctccccgaag aactaccagg agtgaagccc tttacgcggg gaccctatcc caccatgtat 300

accttccgcc cgtggacgat tcgccagtac gcaggtttct caaccgttga ggaatcaaac 360

aagttttata aagacaatat caaggctggc cagcagggac tctccgtggc atttgacctg 420

gcaacccacc gtgggtacga ttccgataac ccccgcgtac ggggtgatgt tgggatggcc 480

ggcgtcgcta ttgacactgt tgaagacacg aagattctct ttgacggaat cccgctggag 540

aagatgagcg tttcaatgac aatgaatgga gcagtgatcc ccgtcttggc caactttata 600

gtgacggggg aggagcaggg cgtgcctaag gagaaactga caggcacaat ccagaatgac 660

atcttaaaag agttcatggt taggaatacc tacatcttcc cccccgaacc ttcaatgaag 720

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gaagtgctgg ccatcgataa tactagtgtc cggaatcgcc agattgaaaa actgaagaaa 1560

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gccgccagtg gggatggaaa catccttgct ctggcagtgg atgcctcccg cgcccgttgc 1680

actgttggtg agatcacgga tgctctgaag aaggtgttcg gcgaacacaa ggcaaacgac 1740

agaatggtga gcggcgccta ccggcaggag ttcggggaaa gcaaagaaat cacctcagca 1800

attaagagag tgcacaaatt catggaaaga gaaggacgca ggcccagact tttggtggcg 1860

aagatgggac aagatggcca cgaccgtggt gctaaagtaa tcgcaacagg ttttgcagat 1920

ctgggcttcg atgtggatat tggaccgctc ttccagacgc cacgcgaggt cgctcagcaa 1980

gctgttgacg ctgacgttca tgccgtgggg gtctctacgc tggctgccgg ccataaaacc 2040

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tgcggcggag ttataccccc tcaggactac gagtttcttt ttgaagtggg ggtctccaat 2160

gtcttcggcc cgggaactcg gattccaaag gctgccgttc aggtgctcga cgacatagaa 2220

aaatgtctgg agaaaaagca acaatcagta 2250

<210> 201
<211> 2250
<212> DNA
<213> Artificial Sequence

<220>
<223> Codon optimized sequence that encodes an MCM polypeptide with the I671V mutation

<400> 201
atgctgagag caaagaatca gctgtttttg ctgagcccgc actacctgcg gcaagtaaaa 60

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ccagagtggg ccgctcttgc taaaaagcaa ctgaagggca agaacccaga ggatcttatt 180

tggcacaccc cggaggggat ttccatcaag cccctctact ccaaacggga caccatggac 240

ctccccgaag aacttcccgg cgtaaagcca tttacacgag gtccctatcc gacaatgtac 300

acatttcggc cgtggacaat ccgacagtac gctggcttta gcaccgtgga agaatcaaac 360

aaattctaca aagataatat caaagctggg caacaaggac tgtcagtcgc attcgacctt 420

gctacacatc gaggatacga ttccgataac ccgcgcgtca gaggtgacgt aggaatggca 480

ggggtggcga tcgacaccgt cgaggacaca aaaatattgt tcgatgggat tcccctggaa 540

aagatgtccg ttagcatgac aatgaatgga gcagttattc cggtgttggc aaatttcata 600

gtgacgggtg aggagcaggg tgtccctaaa gagaagctaa ctggcacaat tcagaatgat 660

atcctgaaag aattcatggt gcgcaatacc tatatctttc ctccagaacc ttctatgaag 720

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atttctgggt accacatgca agaggccgga gccgacgcca tactggaact cgcctacact 840

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ttcgctccca gacttagctt tttctggggc atcggcatga acttttatat ggaaatcgcc 960

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gagggcattc ctaagctgcg catagaggaa tgcgcagcaa ggaggcaagc acggatcgat 1440

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gaggtcttgg caattgataa caccagcgtt cggaatcgtc agatcgaaaa actgaaaaag 1560

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attaagagag tccacaaatt catggagcgc gaaggaaggc ggccacgttt actcgtagcc 1860

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ctggggtttg acgtggacat tggtccattg tttcagaccc ccagggaggt tgctcagcag 1980

gctgtggacg cggacgtgca tgccgtggga gtgtcgaccc tggctgcagg acacaaaaca 2040

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tgtggtgggg tgattccccc acaggactat gagttcttat tcgaggttgg tgttagtaat 2160

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aaatgcctgg aaaagaagca gcagtcagtg 2250

<210> 202
<211> 2250
<212> DNA
<213> Artificial Sequence

<220>
<223> Codon optimized sequence that encodes an MCM polypeptide with the I671V mutation

<400> 202
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ccagaatggg ctgctttagc aaagaagcag ctgaaaggaa agaacccaga agacctaata 180

tggcacacgc ctgaaggtat ctccattaag cctctgtact caaaacggga cactatggat 240

ctccctgagg agctgccagg cgtcaaaccg tttactcgcg gtccttaccc tactatgtac 300

acattccggc catggaccat acgacagtat gctggattct ctaccgtgga agagagcaat 360

aagttctaca aggataatat taaggcaggc cagcagggac tgagcgtagc gtttgatctt 420

gccacacacc gtgggtatga ctctgataat ccacgagtaa gaggggacgt cggtatggcc 480

ggagttgcaa tcgatactgt agaggataca aaaattctct ttgatgggat accgctcgag 540

aagatgtccg taagcatgac tatgaacggt gccgtgatcc ccgtgctcgc taactttatc 600

gtcaccggcg aagaacaggg cgtgcccaag gagaaattga caggtacaat ccagaacgat 660

attctaaagg agttcatggt gcggaataca tacatttttc cacccgaacc ctctatgaaa 720

atcattgccg acatcttcga gtacaccgcc aagcatatgc ctaagttcaa ctctatttct 780

ataagcggct atcacatgca ggaagcaggt gccgacgcca ttctcgaact ggcttatacc 840

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tttgcgcctc gactgagttt cttttgggga ataggtatga atttctatat ggaaatagcc 960

aagatgcgcg ccggcagaag gctttgggcc catttgatcg agaaaatgtt tcagccaaaa 1020

aacagcaaaa gtctgctctt acgcgcccac tgtcagacct ctggctggtc gttgacagaa 1080

caggatccct ataacaacat cgtacggact gctattgagg caatggcagc agtgtttggc 1140

ggaacccaga gcctgcatac caattcattt gacgaagctc tgggtctgcc aactgtgaaa 1200

tcagcccgca ttgcccgcaa cacccagatt ataatacagg aagaaagtgg cattcccaaa 1260

gtggcggatc cttggggagg aagctacatg atggagtgcc tgactaatga cgtatacgat 1320

gcggcgctga aactgatcaa tgaaatagaa gaaatggggg gaatggccaa ggccgtggcg 1380

gagggcatac ctaaactaag gatcgaggag tgtgcagcca gacgccaggc tcgcatcgac 1440

tccggaagtg aagttatagt tggcgtgaat aaatatcagt tagagaagga ggatgccgtg 1500

gaggtgctgg cgatcgataa taccagcgtc cgcaataggc agatagaaaa gttgaaaaag 1560

attaaatcgt cccgcgacca ggccctggcc gaacgctgtc tggccgcact cactgagtgt 1620

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aaaatggggc aggacggcca tgacaggggc gccaaggtga tagccactgg cttcgcggac 1920

ttggggtttg atgttgatat cggccccctc ttccaaacac cccgcgaggt ggcgcaacag 1980

gcagtggatg ccgatgttca cgcagtgggg gtgagtacac tcgccgcggg ccacaagacc 2040

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tgcggaggag tcattccccc acaagactac gagtttttat ttgaggtggg cgtttctaat 2160

gtcttcgggc ctggaacccg gatcccaaaa gcagccgtac aggtgctgga cgatattgaa 2220

aaatgccttg agaaaaagca gcagtccgtc 2250

<210> 203
<211> 2250
<212> DNA
<213> Artificial Sequence

<220>
<223> Codon optimized sequence that encodes an MCM polypeptide with the I671V mutation

<400> 203
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gagtcaagcg gctcacgcct gatccagcag agactgctgc accaacagca acccctgcac 120

ccagagtggg cagccctggc caagaagcag ctcaagggga gaaccccga agacctgatc 180

tggcacacac cagaagggat atccataaaa ccactataca gcaaaaggga cacgatggac 240

ctcccagaag agctgccagg cgtgaagccc ttcacccgcg ggccataccc aaccatgtac 300

accttcagac catggacaat ccggcagtac gcggggttct caaccgtgga ggagtccaac 360

aaattctaca aggacaacat caaagcaggg cagcagggcc tgagtgtagc attcgacctg 420

gcaacgcaca ggggatacga ctccgacaac cccagggtgc ggggcgacgt gggcatggcc 480

ggggtcgcca tcgacacggt ggaagacaca aagatcctgt tcgacggcat ccccctggag 540

aaaatgtccg tgtcgatgac aatgaacggg gccgtgatcc ccgtgctagc aaacttcatc 600

gtcacagggg aggagcaggg ggtgccaaaa gaaaaactga caggcacaat ccagaacgac 660

atactcaagg agttcatggt caggaacacc tacatcttcc ccccagagcc atcgatgaaa 720

atcatcgccg acatcttcga gtacaccgcc aagcacatgc caaaattcaa ctcgatctcc 780

atatcaggct accacatgca ggaggccggc gccgacgcca tactggagct ggcgtacacg 840

ctggcggacg gcctcgaata cagccggaca ggcctgcaag ccggactgac catcgacgaa 900

ttcgccccaa gactgagttt cttctggggc atcgggatga acttctacat ggaaatcgca 960

aaaatgagag cgggccgacg gctctgggcg cacctgatcg aaaagatgtt ccagccaaag 1020

aactccaagt ccctcctcct cagagcccac tgccagacat caggctggtc cctcaccgag 1080

caggacccct acaacaacat agtgaggacc gccatcgaag cgatggccgc ggtgttcgga 1140

gggacgcagt ccctgcacac caacagcttc gacgaggcac tcggcctgcc cacggtcaaa 1200

tccgcacgca tcgcccggaa cacacagatc atcatacagg aggagagcgg catcccaaag 1260

gtggcagacc catggggcgg ctcatacatg atggagtgcc tcacgaacga cgtgtacgac 1320

gccgcactga aactcatcaa cgaaatcgaa gagatgggag gaatggcaaa ggcggtggcg 1380

gagggcatcc ccaagctgcg catcgaggaa tgcgccgccc ggcggcaagc ccggatcgac 1440

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gaggtcctcg caatcgacaa cacctcagtg cggaaccggc agatcgaaaa gctgaaaaaa 1560

atcaaaagct cacgagacca ggccctggca gagcggtgcc tggcagccct gacagagtgc 1620

gcagccagcg gagacggaaa catcctcgcc ctggcggtgg acgcctcgag agccagatgc 1680

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gtcttcggcc cagggacaag gatccccaag gcagccgtgc aggtgctcga cgacatagag 2220

aaatgcctgg agaagaaaca gcaatcggta 2250

<210> 204
<211> 2250
<212> DNA
<213> Artificial Sequence

<220>
<223> Codon optimized sequence that encodes an MCM polypeptide with the I671V mutation

<400> 204
atgctaagag caaagaacca gctgttcctg ctgtcaccac actacctgag acaagtcaag 60

gaaagttccg gcagcagact gatccagcag cggctgctac accaacagca gcccctgcac 120

ccagagtggg cagccctggc caaaaaacag ctgaagggca aaaacccaga ggacctcatc 180

tggcacacac cagaggggat cagtataaag cccctgtaca gtaaaagaga cacaatggac 240

ctccccgaag agctacccgg agtgaagcca ttcacacgag ggccctaccc aaccatgtac 300

accttccggc cctggaccat caggcagtac gccggcttca gcacagtcga ggagagtaac 360

aaattctaca aagacaacat caaggccggg cagcaggggc tgtcagtggc cttcgacctg 420

gccacacacc gggggtacga ctcggacaac ccgagggtga ggggggacgt gggaatggca 480

ggagtggcca tagacaccgt cgaggacacc aagatcctgt tcgacggaat ccccctggaa 540

aagatgtcgg tctccatgac gatgaacggc gccgtcatcc ccgtgctagc caacttcatc 600

gtcaccgggg aggaacaggg agtgccgaaa gagaaactga ccgggacgat ccagaacgac 660

atcctgaaag agttcatggt aagaaacaca tacatattcc caccggaacc cagtatgaag 720

atcatcgcgg acatattcga atacaccgca aaacacatgc ccaagttcaa ctcgatcagc 780

atatccgggt accacatgca ggaagcaggg gccgacgcca tcctggaact cgcctacacc 840

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ttcgcccccc ggctgagttt cttctgggga atagggatga acttctacat ggagatagcg 960

aagatgcgcg ccggccgccg gctgtgggca cacctgatcg aaaagatgtt ccagcccaag 1020

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caagacccgt acaacaacat cgtccgaaca gcaatcgaag ccatggccgc cgtcttcggc 1140

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tcagccagga tcgcccgaaa cacccagatc ataatccagg aagagtcggg gatcccaaag 1260

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gtgttcggac ccgggaccag aatcccaaag gcagccgtcc aggtcctgga cgacatcgag 2220

aaatgcctgg aaaagaagca gcagagtgta 2250

<210> 205
<211> 2250
<212> DNA
<213> Artificial Sequence

<220>
<223> Codon optimized sequence that encodes an MCM polypeptide with the I671V mutation

<400> 205
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cccgaatggg ccgctcttgc gaagaagcag ctcaagggaa agaaccctga ggacctcatt 180

tggcataccc cagaagggat ttccatcaaa cctctgtatt ccaagagaga taccatggat 240

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gcaactcata ggggttacga ctcggataat ccacgcgtcc ggggggacgt aggtatggct 480

ggggtggcta tcgacaccgt ggaggatacc aagatccttt tcgatggaat tcccctggag 540

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aagtgcctcg agaagaaaca gcagtccgtc 2250

<210> 206
<211> 2250
<212> DNA
<213> Artificial Sequence

<220>
<223> Codon optimized sequence that encodes an MCM polypeptide with the I671V mutation

<400> 206
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gaatcctctg gatcccgtct gatccagcag cgccttctgc accagcaaca gccacttcac 120

cccgagtggg cggcgctggc aaagaagcag ttgaagggga agaaccctga agatctgatt 180

tggcacaccc cggagggtat ctctattaag ccgctttact ccaaacgaga cactatggat 240

ctgccagagg agctgcccgg agtaaagcca tttactcggg gcccatatcc taccatgtac 300

actttccggc catggaccat acgacagtat gctggtttca gcacagtcga ggaaagtaac 360

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gctacccaca ggggctacga ctccgataac cctagagtcc ggggtgacgt cggaatggca 480

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aagatgtcag tttctatgac gatgaatggg gccgttatcc ccgtattggc taacttcatc 600

gtgacaggtg aggagcaggg ggttccgaag gagaagttaa ccggtaccat ccagaatgat 660

atcctgaagg agtttatggt gaggaacacc tacattttcc cccctgagcc ttctatgaag 720

attatcgctg acattttcga gtatactgct aagcacatgc ccaagttcaa ctctatcagc 780

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ctagcggatg gtcttgagta tagtagaacc ggcttgcagg ctggtctgac catcgacgaa 900

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tcagcccgaa ttgcccggaa cacccaaata atcatccagg aagaatccgg aattcctaag 1260

gtggctgatc cttggggcgg gagctatatg atggagtgcc tgaccaacga tgtgtatgac 1320

gctgcgctta aactgattaa tgaaatcgag gagatgggcg gtatggccaa agccgttgcc 1380

gaagggattc ccaaacttag aattgaagaa tgtgcggccc gcagacaagc tcgaattgat 1440

tccggcagcg aagtgattgt gggcgtgaat aagtatcaac tcgagaagga agacgccgtc 1500

gaagtattgg ccatcgacaa tacatccgtg cggaatcgtc agatcgaaaa actgaaaaag 1560

atcaagtcaa gccgcgatca agctctagct gaaaggtgct tagccgcgct gacggagtgt 1620

gccgcttccg gggacggtaa tatcctcgcc ctggctgttg acgcttctag ggcgagatgc 1680

acagtgggcg aaattacaga tgcgttgaaa aaggtattcg gtgagcataa ggctaacgac 1740

cggatggtga gtggcgcgta tcggcaagag ttcggcgagt ctaaagagat tacatccgct 1800

atcaagcggg tgcacaaatt catggagcgg gaggggcgcc gaccgaggtt gttggtagcc 1860

aagatgggac aggacggaca tgatcggggg gctaaggtta ttgccacagg gttcgcagac 1920

ctcggcttcg acgtggatat cgggcccctg ttccagacac cacgcgaggt cgcccaacag 1980

gccgtcgacg cagacgtgca cgcagtgggt gtgagtaccc tggctgccgg acacaaaacc 2040

ctcgtgcccg aacttatcaa ggaattgaac agtcttggca ggccagacat attggttatg 2100

tgtggagggg ttattccccc tcaggactac gagtttttgt tcgaagtggg cgtgagcaat 2160

gtgtttggcc ctgggacacg aatccctaag gccgcggtac aggtgctgga cgatatcgag 2220

aaatgtctgg agaagaaaca gcagtctgtg 2250

<210> 207
<211> 2250
<212> DNA
<213> Artificial Sequence

<220>
<223> Codon optimized sequence that encodes an MCM polypeptide with the I671V mutation

<400> 207
atgctgaggg caaaaaatca actgttcctg cttagcccgc attacctgag gcaggtgaaa 60

gagtctagtg gatctaggct gattcagcaa cgcctcctgc accaacagca accgttacac 120

cccgagtggg ccgccctggc taaaaaacag ctgaagggta aaaatcccga agatcttatt 180

tggcataccc ctgagggaat atcaatcaag ccgctgtatt ccaaacggga caccatggat 240

cttcccgaag agctgcccgg ggtgaaacca ttcactcggg gaccctaccc aactatgtac 300

acgttccggc catggaccat caggcagtac gccggtttct caaccgtgga ggagtccaat 360

aagttttata aggacaatat taaagccggt cagcagggcc tgtccgtggc tttcgatctt 420

gccacgcatc gaggatacga ctcggacaac ccccgggtcc gcggcgatgt gggcatggct 480

ggcgtagcta tcgacactgt tgaggatacc aaaatcttat tcgatggaat accacttgag 540

aaaatgagtg tgagtatgac aatgaatggc gccgttattc cggttctagc caattttatt 600

gtgacaggcg aggaacaagg tgttccgaag gagaagctga ctgggacaat ccaaaacgat 660

attttaaaag agtttatggt gcgtaatacc tacatttttc cacccgaacc ctcaatgaaa 720

attatagcag atatctttga atatacggct aagcacatgc caaagttcaa ctctatcagt 780

atttcaggct accacatgca ggaggctggg gccgacgcta ttcttgagct cgcctataca 840

ctcgctgacg ggttggagta tagccgcacc ggtctccagg caggactgac cattgacgaa 900

ttcgcaccac gactctcttt cttctggggc atcggcatga acttttacat ggaaattgcc 960

aagatgagag ccgggcggcg actttgggcc catctgatcg agaagatgtt ccagccgaaa 1020

aactctaaat ctttgctgtt gcgcgctcat tgccagactt caggttggtc acttactgag 1080

caggatcctt acaacaatat agtgcgtacc gccattgagg ctatggccgc tgtctttggg 1140

gggacccagt cgctgcacac caacagtttt gatgaagctc tggggctacc aaccgttaag 1200

tctgctcgga tcgcacgaaa tacccagatt ataatccagg aagaatccgg gatcccaaaa 1260

gtggccgatc cctggggcgg cagttacatg atggagtgcc tcacaaatga tgtatatgac 1320

gcagccctta agcttataaa cgaaattgaa gaaatgggcg gaatggccaa ggcagttgcg 1380

gagggaatac ctaagcttcg gatcgaagag tgtgctgcac ggcgtcaggc tcgcatagat 1440

tccgggtcag aggtgatcgt tggagtgaac aaatatcaat tggaaaagga agatgcagtg 1500

gaggtattgg ccatcgacaa tacctccgtt cggaacaggc agatagagaa acttaaaaag 1560

attaagagct ctcgtgacca agctctcgca gagaggtgcc tggccgctct gactgagtgc 1620

gccgccagcg gagacgggaa tatactcgcc ttggcagtcg acgcgagccg agcccggtgc 1680

acagtgggag aaatcactga tgccctaaag aaagtgttcg gcgaacacaa ggctaatgac 1740

cgaatggtga gcggagccta ccgtcaggag tttggtgaaa gcaaggaaat cacctctgct 1800

atcaagcggg tgcacaagtt tatggagaga gaaggcagga gacctcgctt gcttgtggcc 1860

aagatgggcc aggacgggca tgacaggggt gccaaggtga tcgcaacagg gttcgccgac 1920

ttgggcttcg acgtcgatat cgggcccctg tttcagactc ctcgagaggt tgcacagcaa 1980

gcggtggatg ctgatgttca tgccgttggt gtaagcactc tggcggccgg acacaaaacc 2040

ctcgtcccag aattaataaa ggagttgaat agcctgggcc ggcccgatat tctcgtaatg 2100

tgcggcggag tgataccgcc gcaggactat gagtttttgt ttgaggtagg cgtcagtaat 2160

gtgttcggac ctggtacccg gattccaaag gcagcggtgc aggtgcttga cgatatcgaa 2220

aagtgcctgg aaaagaaaca gcagtccgtc 2250

<210> 208
<211> 750
<212> PRT
<213> Homo Sapian

<400> 208

Met Leu Arg Ala Lys Asn Gln Leu Phe Leu Leu Ser Pro His Tyr Leu
1 5 10 15

Arg Gln Val Lys Glu Ser Ser Gly Ser Arg Leu Ile Gln Gln Arg Leu
20 25 30

Leu His Gln Gln Gln Pro Leu His Pro Glu Trp Ala Ala Leu Ala Lys
35 40 45

Lys Gln Leu Lys Gly Lys Asn Pro Glu Asp Leu Ile Trp His Thr Pro
50 55 60

Glu Gly Ile Ser Ile Lys Pro Leu Tyr Ser Lys Arg Asp Thr Met Asp
65 70 75 80

Leu Pro Glu Glu Leu Pro Gly Val Lys Pro Phe Thr Arg Gly Pro Tyr
85 90 95

Pro Thr Met Tyr Thr Phe Arg Pro Trp Thr Ile Arg Gln Tyr Ala Gly
100 105 110

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Phe Ser Thr Val Glu Glu Ser Asn Lys Phe Tyr Lys Asp Asn Ile Lys
        115                 120                 125

Ala Gly Gln Gln Gly Leu Ser Val Ala Phe Asp Leu Ala Thr His Arg
    130                 135                 140

Gly Tyr Asp Ser Asp Asn Pro Arg Val Arg Gly Asp Val Gly Met Ala
145                 150                 155                 160

Gly Val Ala Ile Asp Thr Val Glu Asp Thr Lys Ile Leu Phe Asp Gly
                165                 170                 175

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

Ile Pro Val Leu Ala Asn Phe Ile Val Thr Gly Glu Glu Gln Gly Val
        195                 200                 205

Pro Lys Glu Lys Leu Thr Gly Thr Ile Gln Asn Asp Ile Leu Lys Glu
    210                 215                 220

Phe Met Val Arg Asn Thr Tyr Ile Phe Pro Pro Glu Pro Ser Met Lys
225                 230                 235                 240

Ile Ile Ala Asp Ile Phe Glu Tyr Thr Ala Lys His Met Pro Lys Phe
                245                 250                 255

Asn Ser Ile Ser Ile Ser Gly Tyr His Met Gln Glu Ala Gly Ala Asp
            260                 265                 270

Ala Ile Leu Glu Leu Ala Tyr Thr Leu Ala Asp Gly Leu Glu Tyr Ser
        275                 280                 285

Arg Thr Gly Leu Gln Ala Gly Leu Thr Ile Asp Glu Phe Ala Pro Arg
    290                 295                 300

Leu Ser Phe Phe Trp Gly Ile Gly Met Asn Phe Tyr Met Glu Ile Ala
305                 310                 315                 320

Lys Met Arg Ala Gly Arg Arg Leu Trp Ala His Leu Ile Glu Lys Met
                325                 330                 335

Phe Gln Pro Lys Asn Ser Lys Ser Leu Leu Leu Arg Ala His Cys Gln
            340                 345                 350

Thr Ser Gly Trp Ser Leu Thr Glu Gln Asp Pro Tyr Asn Asn Ile Val
        355                 360                 365

Arg Thr Ala Ile Glu Ala Met Ala Ala Val Phe Gly Gly Thr Gln Ser
    370                 375                 380
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Leu His Thr Asn Ser Phe Asp Glu Ala Leu Gly Leu Pro Thr Val Lys
385                 390                 395                 400

Ser Ala Arg Ile Ala Arg Asn Thr Gln Ile Ile Ile Gln Glu Glu Ser
                405                 410                 415

Gly Ile Pro Lys Val Ala Asp Pro Trp Gly Gly Ser Tyr Met Met Glu
            420                 425                 430

Cys Leu Thr Asn Asp Val Tyr Asp Ala Ala Leu Lys Leu Ile Asn Glu
        435                 440                 445

Ile Glu Glu Met Gly Gly Met Ala Lys Ala Val Ala Glu Gly Ile Pro
    450                 455                 460

Lys Leu Arg Ile Glu Glu Cys Ala Ala Arg Arg Gln Ala Arg Ile Asp
465                 470                 475                 480

Ser Gly Ser Glu Val Ile Val Gly Val Asn Lys Tyr Gln Leu Glu Lys
                485                 490                 495

Glu Asp Ala Val Glu Val Leu Ala Ile Asp Asn Thr Ser Val Arg Asn
            500                 505                 510

Arg Gln Ile Glu Lys Leu Lys Lys Ile Lys Ser Ser Arg Asp Gln Ala
        515                 520                 525

Leu Ala Glu Arg Cys Leu Ala Ala Leu Thr Glu Cys Ala Ala Ser Gly
    530                 535                 540

Asp Gly Asn Ile Leu Ala Leu Ala Val Asp Ala Ser Arg Ala Arg Cys
545                 550                 555                 560

Thr Val Gly Glu Ile Thr Asp Ala Leu Lys Lys Val Phe Gly Glu His
                565                 570                 575

Lys Ala Asn Asp Arg Met Val Ser Gly Ala Tyr Arg Gln Glu Phe Gly
            580                 585                 590

Glu Ser Lys Glu Ile Thr Ser Ala Ile Lys Arg Val His Lys Phe Met
        595                 600                 605

Glu Arg Glu Gly Arg Arg Pro Arg Leu Leu Val Ala Lys Met Gly Gln
    610                 615                 620

Asp Gly His Asp Arg Gly Ala Lys Val Ile Ala Thr Gly Phe Ala Asp
625                 630                 635                 640

Leu Gly Phe Asp Val Asp Ile Gly Pro Leu Phe Gln Thr Pro Arg Glu
                645                 650                 655
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Val Ala Gln Gln Ala Val Asp Ala Asp Val His Ala Val Gly Ile Ser
660 665 670

Thr Leu Ala Ala Gly His Lys Thr Leu Val Pro Glu Leu Ile Lys Glu
675 680 685

Leu Asn Ser Leu Gly Arg Pro Asp Ile Leu Val Met Cys Gly Gly Val
690 695 700

Ile Pro Pro Gln Asp Tyr Glu Phe Leu Phe Glu Val Gly Val Ser Asn
705 710 715 720

Val Phe Gly Pro Gly Thr Arg Ile Pro Lys Ala Ala Val Gln Val Leu
725 730 735

Asp Asp Ile Glu Lys Cys Leu Glu Lys Lys Gln Gln Ser Val
740 745 750

<210> 209
<211> 750
<212> PRT
<213> Artificial Sequence

<220>
<223> MCM I69V

<400> 209

Met Leu Arg Ala Lys Asn Gln Leu Phe Leu Leu Ser Pro His Tyr Leu
1 5 10 15

Arg Gln Val Lys Glu Ser Ser Gly Ser Arg Leu Ile Gln Gln Arg Leu
20 25 30

Leu His Gln Gln Gln Pro Leu His Pro Glu Trp Ala Ala Leu Ala Lys
35 40 45

Lys Gln Leu Lys Gly Lys Asn Pro Glu Asp Leu Ile Trp His Thr Pro
50 55 60

Glu Gly Ile Ser Val Lys Pro Leu Tyr Ser Lys Arg Asp Thr Met Asp
65 70 75 80

Leu Pro Glu Glu Leu Pro Gly Val Lys Pro Phe Thr Arg Gly Pro Tyr
85 90 95

Pro Thr Met Tyr Thr Phe Arg Pro Trp Thr Ile Arg Gln Tyr Ala Gly
100 105 110

Phe Ser Thr Val Glu Glu Ser Asn Lys Phe Tyr Lys Asp Asn Ile Lys
115 120 125

Ala Gly Gln Gln Gly Leu Ser Val Ala Phe Asp Leu Ala Thr His Arg

130 135 140

Gly Tyr Asp Ser Asp Asn Pro Arg Val Arg Gly Asp Val Gly Met Ala
145 150 155 160

Gly Val Ala Ile Asp Thr Val Glu Asp Thr Lys Ile Leu Phe Asp Gly
165 170 175

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

Ile Pro Val Leu Ala Asn Phe Ile Val Thr Gly Glu Glu Gln Gly Val
195 200 205

Pro Lys Glu Lys Leu Thr Gly Thr Ile Gln Asn Asp Ile Leu Lys Glu
210 215 220

Phe Met Val Arg Asn Thr Tyr Ile Phe Pro Pro Glu Pro Ser Met Lys
225 230 235 240

Ile Ile Ala Asp Ile Phe Glu Tyr Thr Ala Lys His Met Pro Lys Phe
245 250 255

Asn Ser Ile Ser Ile Ser Gly Tyr His Met Gln Glu Ala Gly Ala Asp
260 265 270

Ala Ile Leu Glu Leu Ala Tyr Thr Leu Ala Asp Gly Leu Glu Tyr Ser
275 280 285

Arg Thr Gly Leu Gln Ala Gly Leu Thr Ile Asp Glu Phe Ala Pro Arg
290 295 300

Leu Ser Phe Phe Trp Gly Ile Gly Met Asn Phe Tyr Met Glu Ile Ala
305 310 315 320

Lys Met Arg Ala Gly Arg Arg Leu Trp Ala His Leu Ile Glu Lys Met
325 330 335

Phe Gln Pro Lys Asn Ser Lys Ser Leu Leu Leu Arg Ala His Cys Gln
340 345 350

Thr Ser Gly Trp Ser Leu Thr Glu Gln Asp Pro Tyr Asn Asn Ile Val
355 360 365

Arg Thr Ala Ile Glu Ala Met Ala Ala Val Phe Gly Gly Thr Gln Ser
370 375 380

Leu His Thr Asn Ser Phe Asp Glu Ala Leu Gly Leu Pro Thr Val Lys
385 390 395 400

Ser Ala Arg Ile Ala Arg Asn Thr Gln Ile Ile Ile Gln Glu Glu Ser

405 410 415

Gly Ile Pro Lys Val Ala Asp Pro Trp Gly Gly Ser Tyr Met Met Glu
420 425 430

Cys Leu Thr Asn Asp Val Tyr Asp Ala Ala Leu Lys Leu Ile Asn Glu
435 440 445

Ile Glu Glu Met Gly Gly Met Ala Lys Ala Val Ala Glu Gly Ile Pro
450 455 460

Lys Leu Arg Ile Glu Glu Cys Ala Ala Arg Arg Gln Ala Arg Ile Asp
465 470 475 480

Ser Gly Ser Glu Val Ile Val Gly Val Asn Lys Tyr Gln Leu Glu Lys
485 490 495

Glu Asp Ala Val Glu Val Leu Ala Ile Asp Asn Thr Ser Val Arg Asn
500 505 510

Arg Gln Ile Glu Lys Leu Lys Lys Ile Lys Ser Ser Arg Asp Gln Ala
515 520 525

Leu Ala Glu Arg Cys Leu Ala Ala Leu Thr Glu Cys Ala Ala Ser Gly
530 535 540

Asp Gly Asn Ile Leu Ala Leu Ala Val Asp Ala Ser Arg Ala Arg Cys
545 550 555 560

Thr Val Gly Glu Ile Thr Asp Ala Leu Lys Lys Val Phe Gly Glu His
565 570 575

Lys Ala Asn Asp Arg Met Val Ser Gly Ala Tyr Arg Gln Glu Phe Gly
580 585 590

Glu Ser Lys Glu Ile Thr Ser Ala Ile Lys Arg Val His Lys Phe Met
595 600 605

Glu Arg Glu Gly Arg Arg Pro Arg Leu Leu Val Ala Lys Met Gly Gln
610 615 620

Asp Gly His Asp Arg Gly Ala Lys Val Ile Ala Thr Gly Phe Ala Asp
625 630 635 640

Leu Gly Phe Asp Val Asp Ile Gly Pro Leu Phe Gln Thr Pro Arg Glu
645 650 655

Val Ala Gln Gln Ala Val Asp Ala Asp Val His Ala Val Gly Ile Ser
660 665 670

Thr Leu Ala Ala Gly His Lys Thr Leu Val Pro Glu Leu Ile Lys Glu

675 680 685

Leu Asn Ser Leu Gly Arg Pro Asp Ile Leu Val Met Cys Gly Gly Val
690 695 700

Ile Pro Pro Gln Asp Tyr Glu Phe Leu Phe Glu Val Gly Val Ser Asn
705 710 715 720

Val Phe Gly Pro Gly Thr Arg Ile Pro Lys Ala Ala Val Gln Val Leu
725 730 735

Asp Asp Ile Glu Lys Cys Leu Glu Lys Lys Gln Gln Ser Val
740 745 750

<210> 210
<211> 750
<212> PRT
<213> Artificial Sequence

<220>
<223> MCM A499T

<400> 210

Met Leu Arg Ala Lys Asn Gln Leu Phe Leu Leu Ser Pro His Tyr Leu
1 5 10 15

Arg Gln Val Lys Glu Ser Ser Gly Ser Arg Leu Ile Gln Gln Arg Leu
20 25 30

Leu His Gln Gln Gln Pro Leu His Pro Glu Trp Ala Ala Leu Ala Lys
35 40 45

Lys Gln Leu Lys Gly Lys Asn Pro Glu Asp Leu Ile Trp His Thr Pro
50 55 60

Glu Gly Ile Ser Ile Lys Pro Leu Tyr Ser Lys Arg Asp Thr Met Asp
65 70 75 80

Leu Pro Glu Glu Leu Pro Gly Val Lys Pro Phe Thr Arg Gly Pro Tyr
85 90 95

Pro Thr Met Tyr Thr Phe Arg Pro Trp Thr Ile Arg Gln Tyr Ala Gly
100 105 110

Phe Ser Thr Val Glu Glu Ser Asn Lys Phe Tyr Lys Asp Asn Ile Lys
115 120 125

Ala Gly Gln Gln Gly Leu Ser Val Ala Phe Asp Leu Ala Thr His Arg
130 135 140

Gly Tyr Asp Ser Asp Asn Pro Arg Val Arg Gly Asp Val Gly Met Ala
145 150 155 160

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Gly Val Ala Ile Asp Thr Val Glu Asp Thr Lys Ile Leu Phe Asp Gly
                165                 170                 175

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

Ile Pro Val Leu Ala Asn Phe Ile Val Thr Gly Glu Glu Gln Gly Val
        195                 200                 205

Pro Lys Glu Lys Leu Thr Gly Thr Ile Gln Asn Asp Ile Leu Lys Glu
    210                 215                 220

Phe Met Val Arg Asn Thr Tyr Ile Phe Pro Pro Glu Pro Ser Met Lys
225                 230                 235                 240

Ile Ile Ala Asp Ile Phe Glu Tyr Thr Ala Lys His Met Pro Lys Phe
                245                 250                 255

Asn Ser Ile Ser Ile Ser Gly Tyr His Met Gln Glu Ala Gly Ala Asp
            260                 265                 270

Ala Ile Leu Glu Leu Ala Tyr Thr Leu Ala Asp Gly Leu Glu Tyr Ser
        275                 280                 285

Arg Thr Gly Leu Gln Ala Gly Leu Thr Ile Asp Glu Phe Ala Pro Arg
    290                 295                 300

Leu Ser Phe Phe Trp Gly Ile Gly Met Asn Phe Tyr Met Glu Ile Ala
305                 310                 315                 320

Lys Met Arg Ala Gly Arg Arg Leu Trp Ala His Leu Ile Glu Lys Met
                325                 330                 335

Phe Gln Pro Lys Asn Ser Lys Ser Leu Leu Leu Arg Ala His Cys Gln
            340                 345                 350

Thr Ser Gly Trp Ser Leu Thr Glu Gln Asp Pro Tyr Asn Asn Ile Val
        355                 360                 365

Arg Thr Ala Ile Glu Ala Met Ala Ala Val Phe Gly Gly Thr Gln Ser
    370                 375                 380

Leu His Thr Asn Ser Phe Asp Glu Ala Leu Gly Leu Pro Thr Val Lys
385                 390                 395                 400

Ser Ala Arg Ile Ala Arg Asn Thr Gln Ile Ile Ile Gln Glu Glu Ser
                405                 410                 415

Gly Ile Pro Lys Val Ala Asp Pro Trp Gly Gly Ser Tyr Met Met Glu
            420                 425                 430
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Cys Leu Thr Asn Asp Val Tyr Asp Ala Ala Leu Lys Leu Ile Asn Glu
        435                 440                 445

Ile Glu Glu Met Gly Gly Met Ala Lys Ala Val Ala Glu Gly Ile Pro
    450                 455                 460

Lys Leu Arg Ile Glu Glu Cys Ala Ala Arg Arg Gln Ala Arg Ile Asp
465                 470                 475                 480

Ser Gly Ser Glu Val Ile Val Gly Val Asn Lys Tyr Gln Leu Glu Lys
                485                 490                 495

Glu Asp Thr Val Glu Val Leu Ala Ile Asp Asn Thr Ser Val Arg Asn
            500                 505                 510

Arg Gln Ile Glu Lys Leu Lys Lys Ile Lys Ser Ser Arg Asp Gln Ala
        515                 520                 525

Leu Ala Glu Arg Cys Leu Ala Ala Leu Thr Glu Cys Ala Ala Ser Gly
    530                 535                 540

Asp Gly Asn Ile Leu Ala Leu Ala Val Asp Ala Ser Arg Ala Arg Cys
545                 550                 555                 560

Thr Val Gly Glu Ile Thr Asp Ala Leu Lys Lys Val Phe Gly Glu His
                565                 570                 575

Lys Ala Asn Asp Arg Met Val Ser Gly Ala Tyr Arg Gln Glu Phe Gly
            580                 585                 590

Glu Ser Lys Glu Ile Thr Ser Ala Ile Lys Arg Val His Lys Phe Met
        595                 600                 605

Glu Arg Glu Gly Arg Arg Pro Arg Leu Leu Val Ala Lys Met Gly Gln
    610                 615                 620

Asp Gly His Asp Arg Gly Ala Lys Val Ile Ala Thr Gly Phe Ala Asp
625                 630                 635                 640

Leu Gly Phe Asp Val Asp Ile Gly Pro Leu Phe Gln Thr Pro Arg Glu
                645                 650                 655

Val Ala Gln Gln Ala Val Asp Ala Asp Val His Ala Val Gly Ile Ser
            660                 665                 670

Thr Leu Ala Ala Gly His Lys Thr Leu Val Pro Glu Leu Ile Lys Glu
        675                 680                 685

Leu Asn Ser Leu Gly Arg Pro Asp Ile Leu Val Met Cys Gly Gly Val
    690                 695                 700
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Ile Pro Pro Gln Asp Tyr Glu Phe Leu Phe Glu Val Gly Val Ser Asn
705 710 715 720

Val Phe Gly Pro Gly Thr Arg Ile Pro Lys Ala Ala Val Gln Val Leu
725 730 735

Asp Asp Ile Glu Lys Cys Leu Glu Lys Lys Gln Gln Ser Val
740 745 750

<210> 211
<211> 750
<212> PRT
<213> Artificial Sequence

<220>
<223> MCM R532H

<400> 211

Met Leu Arg Ala Lys Asn Gln Leu Phe Leu Leu Ser Pro His Tyr Leu
1 5 10 15

Arg Gln Val Lys Glu Ser Ser Gly Ser Arg Leu Ile Gln Gln Arg Leu
20 25 30

Leu His Gln Gln Gln Pro Leu His Pro Glu Trp Ala Ala Leu Ala Lys
35 40 45

Lys Gln Leu Lys Gly Lys Asn Pro Glu Asp Leu Ile Trp His Thr Pro
50 55 60

Glu Gly Ile Ser Ile Lys Pro Leu Tyr Ser Lys Arg Asp Thr Met Asp
65 70 75 80

Leu Pro Glu Glu Leu Pro Gly Val Lys Pro Phe Thr Arg Gly Pro Tyr
85 90 95

Pro Thr Met Tyr Thr Phe Arg Pro Trp Thr Ile Arg Gln Tyr Ala Gly
100 105 110

Phe Ser Thr Val Glu Glu Ser Asn Lys Phe Tyr Lys Asp Asn Ile Lys
115 120 125

Ala Gly Gln Gln Gly Leu Ser Val Ala Phe Asp Leu Ala Thr His Arg
130 135 140

Gly Tyr Asp Ser Asp Asn Pro Arg Val Arg Gly Asp Val Gly Met Ala
145 150 155 160

Gly Val Ala Ile Asp Thr Val Glu Asp Thr Lys Ile Leu Phe Asp Gly
165 170 175

Ile Pro Leu Glu Lys Met Ser Val Ser Met Thr Met Asn Gly Ala Val

180 185 190

Ile Pro Val Leu Ala Asn Phe Ile Val Thr Gly Glu Glu Gln Gly Val
195 200 205

Pro Lys Glu Lys Leu Thr Gly Thr Ile Gln Asn Asp Ile Leu Lys Glu
210 215 220

Phe Met Val Arg Asn Thr Tyr Ile Phe Pro Pro Glu Pro Ser Met Lys
225 230 235 240

Ile Ile Ala Asp Ile Phe Glu Tyr Thr Ala Lys His Met Pro Lys Phe
245 250 255

Asn Ser Ile Ser Ile Ser Gly Tyr His Met Gln Glu Ala Gly Ala Asp
260 265 270

Ala Ile Leu Glu Leu Ala Tyr Thr Leu Ala Asp Gly Leu Glu Tyr Ser
275 280 285

Arg Thr Gly Leu Gln Ala Gly Leu Thr Ile Asp Glu Phe Ala Pro Arg
290 295 300

Leu Ser Phe Phe Trp Gly Ile Gly Met Asn Phe Tyr Met Glu Ile Ala
305 310 315 320

Lys Met Arg Ala Gly Arg Arg Leu Trp Ala His Leu Ile Glu Lys Met
325 330 335

Phe Gln Pro Lys Asn Ser Lys Ser Leu Leu Leu Arg Ala His Cys Gln
340 345 350

Thr Ser Gly Trp Ser Leu Thr Glu Gln Asp Pro Tyr Asn Asn Ile Val
355 360 365

Arg Thr Ala Ile Glu Ala Met Ala Ala Val Phe Gly Gly Thr Gln Ser
370 375 380

Leu His Thr Asn Ser Phe Asp Glu Ala Leu Gly Leu Pro Thr Val Lys
385 390 395 400

Ser Ala Arg Ile Ala Arg Asn Thr Gln Ile Ile Ile Gln Glu Glu Ser
405 410 415

Gly Ile Pro Lys Val Ala Asp Pro Trp Gly Gly Ser Tyr Met Met Glu
420 425 430

Cys Leu Thr Asn Asp Val Tyr Asp Ala Ala Leu Lys Leu Ile Asn Glu
435 440 445

Ile Glu Glu Met Gly Gly Met Ala Lys Ala Val Ala Glu Gly Ile Pro

450 455 460

Lys Leu Arg Ile Glu Glu Cys Ala Ala Arg Arg Gln Ala Arg Ile Asp
465 470 475 480

Ser Gly Ser Glu Val Ile Val Gly Val Asn Lys Tyr Gln Leu Glu Lys
485 490 495

Glu Asp Ala Val Glu Val Leu Ala Ile Asp Asn Thr Ser Val Arg Asn
500 505 510

Arg Gln Ile Glu Lys Leu Lys Lys Ile Lys Ser Ser Arg Asp Gln Ala
515 520 525

Leu Ala Glu His Cys Leu Ala Ala Leu Thr Glu Cys Ala Ala Ser Gly
530 535 540

Asp Gly Asn Ile Leu Ala Leu Ala Val Asp Ala Ser Arg Ala Arg Cys
545 550 555 560

Thr Val Gly Glu Ile Thr Asp Ala Leu Lys Lys Val Phe Gly Glu His
565 570 575

Lys Ala Asn Asp Arg Met Val Ser Gly Ala Tyr Arg Gln Glu Phe Gly
580 585 590

Glu Ser Lys Glu Ile Thr Ser Ala Ile Lys Arg Val His Lys Phe Met
595 600 605

Glu Arg Glu Gly Arg Arg Pro Arg Leu Leu Val Ala Lys Met Gly Gln
610 615 620

Asp Gly His Asp Arg Gly Ala Lys Val Ile Ala Thr Gly Phe Ala Asp
625 630 635 640

Leu Gly Phe Asp Val Asp Ile Gly Pro Leu Phe Gln Thr Pro Arg Glu
645 650 655

Val Ala Gln Gln Ala Val Asp Ala Asp Val His Ala Val Gly Ile Ser
660 665 670

Thr Leu Ala Ala Gly His Lys Thr Leu Val Pro Glu Leu Ile Lys Glu
675 680 685

Leu Asn Ser Leu Gly Arg Pro Asp Ile Leu Val Met Cys Gly Gly Val
690 695 700

Ile Pro Pro Gln Asp Tyr Glu Phe Leu Phe Glu Val Gly Val Ser Asn
705 710 715 720

Val Phe Gly Pro Gly Thr Arg Ile Pro Lys Ala Ala Val Gln Val Leu

725 730 735

Asp Asp Ile Glu Lys Cys Leu Glu Lys Lys Gln Gln Ser Val
740 745 750

<210> 212
<211> 750
<212> PRT
<213> Artificial Sequence

<220>
<223> MCM T598A

<400> 212

Met Leu Arg Ala Lys Asn Gln Leu Phe Leu Leu Ser Pro His Tyr Leu
1 5 10 15

Arg Gln Val Lys Glu Ser Ser Gly Ser Arg Leu Ile Gln Gln Arg Leu
20 25 30

Leu His Gln Gln Gln Pro Leu His Pro Glu Trp Ala Ala Leu Ala Lys
35 40 45

Lys Gln Leu Lys Gly Lys Asn Pro Glu Asp Leu Ile Trp His Thr Pro
50 55 60

Glu Gly Ile Ser Ile Lys Pro Leu Tyr Ser Lys Arg Asp Thr Met Asp
65 70 75 80

Leu Pro Glu Glu Leu Pro Gly Val Lys Pro Phe Thr Arg Gly Pro Tyr
85 90 95

Pro Thr Met Tyr Thr Phe Arg Pro Trp Thr Ile Arg Gln Tyr Ala Gly
100 105 110

Phe Ser Thr Val Glu Glu Ser Asn Lys Phe Tyr Lys Asp Asn Ile Lys
115 120 125

Ala Gly Gln Gln Gly Leu Ser Val Ala Phe Asp Leu Ala Thr His Arg
130 135 140

Gly Tyr Asp Ser Asp Asn Pro Arg Val Arg Gly Asp Val Gly Met Ala
145 150 155 160

Gly Val Ala Ile Asp Thr Val Glu Asp Thr Lys Ile Leu Phe Asp Gly
165 170 175

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

Ile Pro Val Leu Ala Asn Phe Ile Val Thr Gly Glu Glu Gln Gly Val
195 200 205

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Pro Lys Glu Lys Leu Thr Gly Thr Ile Gln Asn Asp Ile Leu Lys Glu
    210                 215                 220

Phe Met Val Arg Asn Thr Tyr Ile Phe Pro Pro Glu Pro Ser Met Lys
225                 230                 235                 240

Ile Ile Ala Asp Ile Phe Glu Tyr Thr Ala Lys His Met Pro Lys Phe
                245                 250                 255

Asn Ser Ile Ser Ile Ser Gly Tyr His Met Gln Glu Ala Gly Ala Asp
            260                 265                 270

Ala Ile Leu Glu Leu Ala Tyr Thr Leu Ala Asp Gly Leu Glu Tyr Ser
        275                 280                 285

Arg Thr Gly Leu Gln Ala Gly Leu Thr Ile Asp Glu Phe Ala Pro Arg
    290                 295                 300

Leu Ser Phe Phe Trp Gly Ile Gly Met Asn Phe Tyr Met Glu Ile Ala
305                 310                 315                 320

Lys Met Arg Ala Gly Arg Arg Leu Trp Ala His Leu Ile Glu Lys Met
                325                 330                 335

Phe Gln Pro Lys Asn Ser Lys Ser Leu Leu Leu Arg Ala His Cys Gln
            340                 345                 350

Thr Ser Gly Trp Ser Leu Thr Glu Gln Asp Pro Tyr Asn Asn Ile Val
        355                 360                 365

Arg Thr Ala Ile Glu Ala Met Ala Ala Val Phe Gly Gly Thr Gln Ser
    370                 375                 380

Leu His Thr Asn Ser Phe Asp Glu Ala Leu Gly Leu Pro Thr Val Lys
385                 390                 395                 400

Ser Ala Arg Ile Ala Arg Asn Thr Gln Ile Ile Ile Gln Glu Glu Ser
                405                 410                 415

Gly Ile Pro Lys Val Ala Asp Pro Trp Gly Gly Ser Tyr Met Met Glu
            420                 425                 430

Cys Leu Thr Asn Asp Val Tyr Asp Ala Ala Leu Lys Leu Ile Asn Glu
        435                 440                 445

Ile Glu Glu Met Gly Gly Met Ala Lys Ala Val Ala Glu Gly Ile Pro
    450                 455                 460

Lys Leu Arg Ile Glu Glu Cys Ala Ala Arg Arg Gln Ala Arg Ile Asp
465                 470                 475                 480
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Ser Gly Ser Glu Val Ile Val Gly Val Asn Lys Tyr Gln Leu Glu Lys
                485                 490                 495

Glu Asp Ala Val Glu Val Leu Ala Ile Asp Asn Thr Ser Val Arg Asn
            500                 505                 510

Arg Gln Ile Glu Lys Leu Lys Lys Ile Lys Ser Ser Arg Asp Gln Ala
        515                 520                 525

Leu Ala Glu Arg Cys Leu Ala Ala Leu Thr Glu Cys Ala Ala Ser Gly
    530                 535                 540

Asp Gly Asn Ile Leu Ala Leu Ala Val Asp Ala Ser Arg Ala Arg Cys
545                 550                 555                 560

Thr Val Gly Glu Ile Thr Asp Ala Leu Lys Lys Val Phe Gly Glu His
                565                 570                 575

Lys Ala Asn Asp Arg Met Val Ser Gly Ala Tyr Arg Gln Glu Phe Gly
            580                 585                 590

Glu Ser Lys Glu Ile Ala Ser Ala Ile Lys Arg Val His Lys Phe Met
        595                 600                 605

Glu Arg Glu Gly Arg Arg Pro Arg Leu Leu Val Ala Lys Met Gly Gln
    610                 615                 620

Asp Gly His Asp Arg Gly Ala Lys Val Ile Ala Thr Gly Phe Ala Asp
625                 630                 635                 640

Leu Gly Phe Asp Val Asp Ile Gly Pro Leu Phe Gln Thr Pro Arg Glu
                645                 650                 655

Val Ala Gln Gln Ala Val Asp Ala Asp Val His Ala Val Gly Ile Ser
            660                 665                 670

Thr Leu Ala Ala Gly His Lys Thr Leu Val Pro Glu Leu Ile Lys Glu
        675                 680                 685

Leu Asn Ser Leu Gly Arg Pro Asp Ile Leu Val Met Cys Gly Gly Val
    690                 695                 700

Ile Pro Pro Gln Asp Tyr Glu Phe Leu Phe Glu Val Gly Val Ser Asn
705                 710                 715                 720

Val Phe Gly Pro Gly Thr Arg Ile Pro Lys Ala Ala Val Gln Val Leu
                725                 730                 735

Asp Asp Ile Glu Lys Cys Leu Glu Lys Lys Gln Gln Ser Val
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<211> 750
<212> PRT
<213> Artificial Sequence

<220>
<223> MCM I671V

<400> 213

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Arg Gln Val Lys Glu Ser Ser Gly Ser Arg Leu Ile Gln Gln Arg Leu
            20                  25                  30

Leu His Gln Gln Gln Pro Leu His Pro Glu Trp Ala Ala Leu Ala Lys
        35                  40                  45

Lys Gln Leu Lys Gly Lys Asn Pro Glu Asp Leu Ile Trp His Thr Pro
    50                  55                  60

Glu Gly Ile Ser Ile Lys Pro Leu Tyr Ser Lys Arg Asp Thr Met Asp
65                  70                  75                  80

Leu Pro Glu Glu Leu Pro Gly Val Lys Pro Phe Thr Arg Gly Pro Tyr
                85                  90                  95

Pro Thr Met Tyr Thr Phe Arg Pro Trp Thr Ile Arg Gln Tyr Ala Gly
            100                 105                 110

Phe Ser Thr Val Glu Glu Ser Asn Lys Phe Tyr Lys Asp Asn Ile Lys
        115                 120                 125

Ala Gly Gln Gln Gly Leu Ser Val Ala Phe Asp Leu Ala Thr His Arg
    130                 135                 140

Gly Tyr Asp Ser Asp Asn Pro Arg Val Arg Gly Asp Val Gly Met Ala
145                 150                 155                 160

Gly Val Ala Ile Asp Thr Val Glu Asp Thr Lys Ile Leu Phe Asp Gly
                165                 170                 175

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

Ile Pro Val Leu Ala Asn Phe Ile Val Thr Gly Glu Glu Gln Gly Val
        195                 200                 205

Pro Lys Glu Lys Leu Thr Gly Thr Ile Gln Asn Asp Ile Leu Lys Glu
    210                 215                 220

Phe Met Val Arg Asn Thr Tyr Ile Phe Pro Pro Glu Pro Ser Met Lys
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225 230 235 240

Ile Ile Ala Asp Ile Phe Glu Tyr Thr Ala Lys His Met Pro Lys Phe
245 250 255

Asn Ser Ile Ser Ile Ser Gly Tyr His Met Gln Glu Ala Gly Ala Asp
260 265 270

Ala Ile Leu Glu Leu Ala Tyr Thr Leu Ala Asp Gly Leu Glu Tyr Ser
275 280 285

Arg Thr Gly Leu Gln Ala Gly Leu Thr Ile Asp Glu Phe Ala Pro Arg
290 295 300

Leu Ser Phe Phe Trp Gly Ile Gly Met Asn Phe Tyr Met Glu Ile Ala
305 310 315 320

Lys Met Arg Ala Gly Arg Arg Leu Trp Ala His Leu Ile Glu Lys Met
325 330 335

Phe Gln Pro Lys Asn Ser Lys Ser Leu Leu Leu Arg Ala His Cys Gln
340 345 350

Thr Ser Gly Trp Ser Leu Thr Glu Gln Asp Pro Tyr Asn Asn Ile Val
355 360 365

Arg Thr Ala Ile Glu Ala Met Ala Ala Val Phe Gly Gly Thr Gln Ser
370 375 380

Leu His Thr Asn Ser Phe Asp Glu Ala Leu Gly Leu Pro Thr Val Lys
385 390 395 400

Ser Ala Arg Ile Ala Arg Asn Thr Gln Ile Ile Ile Gln Glu Glu Ser
405 410 415

Gly Ile Pro Lys Val Ala Asp Pro Trp Gly Gly Ser Tyr Met Met Glu
420 425 430

Cys Leu Thr Asn Asp Val Tyr Asp Ala Ala Leu Lys Leu Ile Asn Glu
435 440 445

Ile Glu Glu Met Gly Gly Met Ala Lys Ala Val Ala Glu Gly Ile Pro
450 455 460

Lys Leu Arg Ile Glu Glu Cys Ala Ala Arg Arg Gln Ala Arg Ile Asp
465 470 475 480

Ser Gly Ser Glu Val Ile Val Gly Val Asn Lys Tyr Gln Leu Glu Lys
485 490 495

Glu Asp Ala Val Glu Val Leu Ala Ile Asp Asn Thr Ser Val Arg Asn

500 505 510

Arg Gln Ile Glu Lys Leu Lys Lys Ile Lys Ser Ser Arg Asp Gln Ala
515 520 525

Leu Ala Glu Arg Cys Leu Ala Ala Leu Thr Glu Cys Ala Ala Ser Gly
530 535 540

Asp Gly Asn Ile Leu Ala Leu Ala Val Asp Ala Ser Arg Ala Arg Cys
545 550 555 560

Thr Val Gly Glu Ile Thr Asp Ala Leu Lys Lys Val Phe Gly Glu His
565 570 575

Lys Ala Asn Asp Arg Met Val Ser Gly Ala Tyr Arg Gln Glu Phe Gly
580 585 590

Glu Ser Lys Glu Ile Thr Ser Ala Ile Lys Arg Val His Lys Phe Met
595 600 605

Glu Arg Glu Gly Arg Arg Pro Arg Leu Leu Val Ala Lys Met Gly Gln
610 615 620

Asp Gly His Asp Arg Gly Ala Lys Val Ile Ala Thr Gly Phe Ala Asp
625 630 635 640

Leu Gly Phe Asp Val Asp Ile Gly Pro Leu Phe Gln Thr Pro Arg Glu
645 650 655

Val Ala Gln Gln Ala Val Asp Ala Asp Val His Ala Val Gly Val Ser
660 665 670

Thr Leu Ala Ala Gly His Lys Thr Leu Val Pro Glu Leu Ile Lys Glu
675 680 685

Leu Asn Ser Leu Gly Arg Pro Asp Ile Leu Val Met Cys Gly Gly Val
690 695 700

Ile Pro Pro Gln Asp Tyr Glu Phe Leu Phe Glu Val Gly Val Ser Asn
705 710 715 720

Val Phe Gly Pro Gly Thr Arg Ile Pro Lys Ala Ala Val Gln Val Leu
725 730 735

Asp Asp Ile Glu Lys Cys Leu Glu Lys Lys Gln Gln Ser Val
740 745 750

<210> 214
<211> 2250
<212> DNA
<213> Homo sapiens

<400> 214

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gaatcatcag gctccaggct catacagcaa cgacttctac accagcaaca gccccttcac 120

ccagaatggg ctgccctggc taaaaagcag ctgaaaggca aaaacccaga agacctaata 180

tggcacaccc cggaagggat ctctataaaa cccttgtatt ccaagagaga tactatggac 240

ttacctgaag aacttccagg agtgaagcca ttcacacgtg gaccatatcc taccatgtat 300

acctttaggc cctggaccat ccgccagtat gctggtttta gtactgtgga agaaagcaat 360

aagttctata aggacaacat taaggctggt cagcagggat tatcagttgc ctttgatctg 420

gcgacacatc gtggctatga ttcagacaac cctcgagttc gtggtgatgt tggaatggct 480

ggagttgcta ttgacactgt ggaagatacc aaaattcttt ttgatggaat tcctttagaa 540

aaaatgtcag tttccatgac tatgaatgga gcagttattc cagttcttgc aaattttata 600

gtaactggag aagaacaagg tgtacctaaa gagaagctta ctggtaccat ccaaaatgat 660

atactaaagg aatttatggt tcgaaataca tacatttttc ctccagaacc atccatgaaa 720

attattgctg acatatttga atatacagca aagcacatgc caaaatttaa ttcaatttca 780

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tttgcaccaa ggttgtcttt cttctgggga attggaatga atttctatat ggaaatagca 960

aagatgagag ctggtagaag actctgggct cacttaatag agaaaatgtt tcagcctaaa 1020

aactcaaaat ctcttcttct aagagcacac tgtcagacat ctggatggtc acttactgag 1080

caggatccct acaataatat tgtccgtact gcaatagaag caatggcagc agtatttgga 1140

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agtgctcgaa ttgccaggaa cacacaaatc atcattcaag aagaatctgg gattcccaaa 1260

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gctgctttaa agctcattaa tgaaattgaa gaaatgggtg gaatggccaa agctgtagct 1380

gagggaatac ctaaacttcg aattgaagaa tgtgctgccc gaagacaagc tagaatagat 1440

tctggttctg aagtaattgt tggagtaaat aagtaccagt tggaaaaaga agacgctgta 1500

gaagttctgg caattgataa tacttcagtg cgaaacaggc agattgaaaa acttaagaag 1560

atcaaatcca gcagggatca agctttggct gaacgttgtc ttgctgcact aaccgaatgt 1620

gctgctagcg gagatggaaa tatcctggct cttgcagtgg atgcatctcg ggcaagatgt 1680

acagtgggag aaatcacaga tgccctgaaa aaggtatttg gtgaacataa agcgaatgat 1740

cgaatggtga gtggagcata tcgccaggaa tttggagaaa gtaaagagat aacatctgct 1800

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aaaatgggac aagatggcca tgacagagga gcaaaagtta ttgctacagg atttgctgat 1920

cttggttttg atgtggacat aggccctctt ttccagactc ctcgtgaagt ggcccagcag 1980

gctgtggatg cggatgtgca tgctgtgggc ataagcaccc tcgctgctgg tcataaaacc 2040

ctagttcctg aactcatcaa agaacttaac tcccttggac ggccagatat tcttgtcatg 2100

tgtggagggg tgataccacc tcaggattat gaatttctgt ttgaagttgg tgtttccaat 2160

gtatttggtc ctgggactcg aattccaaag gctgccgttc aggtgcttga tgatattgag 2220

aagtgtttgg aaaagaagca gcaatctgta 2250

<210> 215
<211> 47
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<220>
<223> 5UTR-001 Upstream UTR

<400> 215
gggaaataag agagaaaaga agagtaagaa gaaatataag agccacc 47

<210> 216
<211> 47
<212> DNA
<213> Artificial Sequence

<220>
<223> 5UTR-002 Upstream UTR

<400> 216
gggagatcag agagaaaaga agagtaagaa gaaatataag agccacc 47

<210> 217
<211> 145
<212> DNA
<213> Artificial Sequence

<220>
<223> 5UTR-003 Upstream UTR

<400> 217
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tacttctatt gcagcaattt aaatcatttc ttttaaagca aaagcaattt tctgaaaatt 120

ttcaccattt acgaacgata gcaac 145

<210> 218
<211> 42
<212> RNA
<213> Artificial Sequence

<220>
<223> 5UTR-004 Upstream UTR

<400> 218
gggagacaag cuuggcauuc cgguacuguu gguaaagcca cc 42

<210> 219
<211> 47
<212> DNA
<213> Artificial Sequence

<220>

<223> 5UTR-005 Upstream UTR

<400> 219
gggagatcag agagaaaaga agagtaagaa gaaatataag agccacc 47

<210> 220
<211> 145
<212> DNA
<213> Artificial Sequence

<220>
<223> 5UTR-006 Upstream UTR

<400> 220
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ttcaccattt acgaacgata gcaac 145

<210> 221
<211> 42
<212> RNA
<213> Artificial Sequence

<220>
<223> 5UTR-007 Upstream UTR

<400> 221
gggagacaag cuuggcauuc cgguacuguu gguaaagcca cc 42

<210> 222
<211> 47
<212> DNA
<213> Artificial Sequence

<220>
<223> 5UTR-008 Upstream UTR

<400> 222
gggaattaac agagaaaaga agagtaagaa gaaatataag agccacc 47

<210> 223
<211> 47
<212> DNA
<213> Artificial Sequence

<220>
<223> 5UTR-009 Upstream UTR

<400> 223
gggaaattag acagaaaaga agagtaagaa gaaatataag agccacc 47

<210> 224
<211> 47
<212> DNA
<213> Artificial Sequence

<220>
<223> 5UTR-010 Upstream UTR

<400> 224
gggaaataag agagtaaaga acagtaagaa gaaatataag agccacc 47

<210> 225
<211> 47
<212> DNA
<213> Artificial Sequence

<220>
<223> 5UTR-011 Upstream UTR

<400> 225
gggaaaaaag agagaaaaga agactaagaa gaaatataag agccacc 47

<210> 226
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<212> DNA
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<220>
<223> 5UTR-012 Upstream UTR

<400> 226
gggaaataag agagaaaaga agagtaagaa gatatataag agccacc 47

<210> 227
<211> 47
<212> DNA
<213> Artificial Sequence

<220>
<223> 5UTR-013 Upstream UTR

<400> 227
gggaaataag agacaaaaca agagtaagaa gaaatataag agccacc 47

<210> 228
<211> 47
<212> DNA
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<220>
<223> 5UTR-014 Upstream UTR

<400> 228
gggaaattag agagtaaaga acagtaagta gaattaaaag agccacc 47

<210> 229
<211> 47
<212> DNA
<213> Artificial Sequence

<220>
<223> 5UTR-015 Upstream UTR

<400> 229
gggaaataag agagaataga agagtaagaa gaaatataag agccacc 47

<210> 230
<211> 47
<212> DNA
<213> Artificial Sequence

<220>

<223> 5UTR-016 Upstream UTR

<400> 230
gggaaataag agagaaaaga agagtaagaa gaaaattaag agccacc 47

<210> 231
<211> 47
<212> DNA
<213> Artificial Sequence

<220>
<223> 5UTR-017 Upstream UTR

<400> 231
gggaaataag agagaaaaga agagtaagaa gaaatttaag agccacc 47

<210> 232
<211> 371
<212> DNA
<213> Artificial Sequence

<220>
<223> 3UTR-001 Creatine Kinase

<400> 232
gcgcctgccc acctgccacc gactgctgga acccagccag tgggagggcc tggcccacca 60

gagtcctgct ccctcactcc tcgccccgcc ccctgtccca gagtcccacc tgggggctct 120

ctccaccctt ctcagagttc cagtttcaac cagagttcca accaatgggc tccatcctct 180

ggattctggc caatgaaata tctccctggc agggtcctct tcttttccca gagctccacc 240

ccaaccagga gctctagtta atggagagct cccagcacac tcggagcttg tgctttgtct 300

ccacgcaaag cgataaataa aagcattggt ggcctttggt ctttgaataa agcctgagta 360

ggaagtctag a 371

<210> 233
<211> 568
<212> DNA
<213> Artificial Sequence

<220>
<223> 3UTR-002 Myoglobin

<400> 233
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atctcgtgta gccatataga gtttgcttct gagtgtctgc tttgtttagt agaggtgggc 120

aggaggagct gaggggctgg ggctggggtg ttgaagttgg ctttgcatgc ccagcgatgc 180

gcctccctgt gggatgtcat caccctggga accgggagtg gcccttggct cactgtgttc 240

tgcatggttt ggatctgaat taattgtcct ttcttctaaa tcccaaccga acttcttcca 300

acctccaaac tggctgtaac cccaaatcca agccattaac tacacctgac agtagcaatt 360

gtctgattaa tcactggccc cttgaagaca gcagaatgtc cctttgcaat gaggaggaga 420

tctgggctgg gcgggccagc tggggaagca tttgactatc tggaacttgt gtgtgcctcc 480

tcaggtatgg cagtgactca cctggtttta ataaaacaac ctgcaacatc tcatggtctt 540

tgaataaagc ctgagtagga agtctaga 568

<210> 234
<211> 289
<212> DNA
<213> Artificial Sequence

<220>
<223> 3UTR-003 alpha-actin

<400> 234
acacactcca cctccagcac gcgacttctc aggacgacga atcttctcaa tgggggggcg 60

gctgagctcc agccaccccg cagtcacttt ctttgtaaca acttccgttg ctgccatcgt 120

aaactgacac agtgtttata acgtgtacat acattaactt attacctcat tttgttattt 180

ttcgaaacaa agccctgtgg aagaaaatgg aaaacttgaa gaagcattaa agtcattctg 240

ttaagctgcg taaatggtct ttgaataaag cctgagtagg aagtctaga 289

<210> 235
<211> 379
<212> DNA
<213> Artificial Sequence

<220>
<223> 3UTR-004 Albumin

<400> 235
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aagcttattc atctgttttt ctttttcgtt ggtgtaaagc caacaccctg tctaaaaaac 120

ataaatttct ttaatcattt tgcctctttt ctctgtgctt caattaataa aaaatggaaa 180

gaatctaata gagtggtaca gcactgttat ttttcaaaga tgtgttgcta tcctgaaaat 240

tctgtaggtt ctgtggaagt tccagtgttc tctcttattc cacttcggta gaggatttct 300

agtttcttgt gggctaatta ataaaatcat taatactctt ctaatggtct ttgaataaag 360

cctgagtagg aagtctaga 379

<210> 236
<211> 118
<212> DNA
<213> Artificial Sequence

<220>
<223> 3UTR-005 alpha-globin

<400> 236
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ctcttggtct ttgaataaag cctgagtagg aaggcggccg ctcgagcatg catctaga 118

<210> 237
<211> 908
<212> DNA
<213> Artificial Sequence

<220>

<223> 3UTR-006 G-CSF

<400> 237
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catatttaaa gacagggaag agcagaacgg agccccaggc ctctgtgtcc ttccctgcat 120

ttctgagttt cattctcctg cctgtagcag tgagaaaaag ctcctgtcct cccatcccct 180

ggactgggag gtagataggt aaataccaag tatttattac tatgactgct ccccagccct 240

ggctctgcaa tgggcactgg gatgagccgc tgtgagcccc tggtcctgag ggtccccacc 300

tgggaccctt gagagtatca ggtctcccac gtgggagaca agaaatccct gtttaatatt 360

taaacagcag tgttccccat ctgggtcctt gcacccctca ctctggcctc agccgactgc 420

acagcggccc ctgcatcccc ttggctgtga ggcccctgga caagcagagg tggccagagc 480

tgggaggcat ggccctgggg tcccacgaat ttgctgggga atctcgtttt tcttcttaag 540

acttttggga catggtttga ctcccgaaca tcaccgacgc gtctcctgtt tttctgggtg 600

gcctcgggac acctgccctg cccccacgag ggtcaggact gtgactcttt ttagggccag 660

gcaggtgcct ggacatttgc cttgctggac ggggactggg gatgtgggag ggagcagaca 720

ggaggaatca tgtcaggcct gtgtgtgaaa ggaagctcca ctgtcaccct ccacctcttc 780

acccccccact caccagtgtc ccctccactg tcacattgta actgaacttc aggataataa 840

agtgtttgcc tccatggtct ttgaataaag cctgagtagg aaggcggccg ctcgagcatg 900

catctaga 908

<210> 238
<211> 835
<212> DNA
<213> Artificial Sequence

<220>
<223> 3UTR-007 Col1a2; collagen, type I, alpha 2

<400> 238
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tcttcttttt taactgaaag ctgaatcctt ccatttcttc tgcacatcta cttgcttaaa 120

ttgtgggcaa aagagaaaaa gaaggattga tcagagcatt gtgcaataca gtttcattaa 180

ctccttcccc cgctccccca aaaatttgaa ttttttttc aacactctta cacctgttat 240

ggaaaatgtc aacctttgta agaaaaccaa aataaaaatt gaaaaataaa aaccataaac 300

atttgcacca cttgtggctt ttgaatatct tccacagagg gaagtttaaa acccaaactt 360

ccaaaggttt aaactacctc aaaacacttt cccatgagtg tgatccacat tgttaggtgc 420

tgacctagac agagatgaac tgaggtcctt gttttgtttt gttcataata caaaggtgct 480

aattaatagt atttcagata cttgaagaat gttgatggtg ctagaagaat ttgagaagaa 540

atactcctgt attgagttgt atcgtgtggt gtatttttta aaaaatttga tttagcattc 600

atattttcca tcttattccc aattaaaagt atgcagatta tttgcccaaa tcttcttcag 660

attcagcatt tgttctttgc cagtctcatt ttcatcttct tccatggttc cacagaagct 720

ttgtttcttg ggcaagcaga aaaattaaat tgtacctatt ttgtatatgt gagatgttta 780

aataaattgt gaaaaaaatg aaataaagca tgtttggttt tccaaaagaa catat 835

<210> 239
<211> 297
<212> DNA
<213> Artificial Sequence

<220>
<223> 3UTR-008 Col6a2; collagen, type VI, alpha 2

<400> 239
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gggcccgggt cccacacggc cagcaccgct gctcactcgg acgacgccct gggcctgcac 120

ctctccagct cctcccacgg ggtccccgta gccccggccc ccgcccagcc ccaggtctcc 180

ccaggccctc cgcaggctgc ccggcctccc tccccctgca gccatcccaa ggctcctgac 240

ctacctggcc cctgagctct ggagcaagcc ctgacccaat aaaggctttg aacccat 297

<210> 240
<211> 602
<212> DNA
<213> Artificial Sequence

<220>
<223> 3UTR-009 RPN1; ribophorin I

<400> 240
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ggtggttttg ttttgctttg tttaaagccg tgggaaaatg gcacaacttt acctctgtgg 120

gagatgcaac actgagagcc aaggggtggg agttgggata atttttatat aaaagaagtt 180

tttccacttt gaattgctaa aagtggcatt tttcctatgt gcagtcactc ctctcatttc 240

taaaataggg acgtggccag gcacggtggc tcatgcctgt aatcccagca ctttgggagg 300

ccgaggcagg cggctcacga ggtcaggaga tcgagactat cctggctaac acggtaaaac 360

cctgtctcta ctaaaagtac aaaaaattag ctgggcgtgg tggtgggcac ctgtagtccc 420

agctactcgg gaggctgagg caggagaaag gcatgaatcc aagaggcaga gcttgcagtg 480

agctgagatc acgccattgc actccagcct gggcaacagt gttaagactc tgtctcaaat 540

ataaataaat aaataaataa ataaataaat aaataaaaat aaagcgagat gttgccctca 600

aa 602

<210> 241
<211> 785
<212> DNA
<213> Artificial Sequence

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aagcgctggg tttgcccact gtgaaaagtg cccggattgc tcggaacaca cagatcatca 1320

ttcaggaaga atctgggatc cccaaagtgg cggatccttg gggagggtcg tacatgatgg 1380

agtcgctcac aaatgacgtt tatgaggctg ctctgaagtt gatatatgaa gttgaagaaa 1440

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ctgcccgaag acaagctaga atagattctg gttctgaggt aattgttgga gtaaataagt 1560

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agaagcagat tgaaaaactc aagaagatta aatccagcag ggatcaagct ttggctgagc 1680

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cagtggatgc agctcgtgca agatgtacag ttggagaaat cacggatgcc ttgaaaaaag 1800

tatttggtga gcataaagct aatgatcgta tggtgagtgg agcatatcgg caggagtttg 1860

gagaaagtaa agagatcaca tctgccatca agagagttaa taaattcatg gaacgtgaag 1920

gtcgcagacc tcgtcttctt gtggcaaaaa tgggacaaga tggccatgac aggggagcca 1980

aggtcattgc tacaggattt gctgatcttg gttttgatgt ggacataggc cctcttttc 2040

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ctgtccaagt gcttgatgat attgagaagt gtttggcaga gaagcagcag tctgtgtgat 2340

aataggctgg agcctcggtg gccatgcttc ttgccccttg ggcctccccc cagcccctcc 2400

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<210> 251
<211> 25
<212> PRT
<213> Artificial Sequence

<220>
<223> mitochondrial targeting peptides

<400> 251

Met Leu Ser Leu Arg Gln Ser Ile Arg Phe Phe Lys Pro Ala Thr Arg
1 5 10 15

Thr Leu Cys Ser Ser Arg Tyr Leu Leu
20 25

<210> 252
<211> 16
<212> PRT
<213> Artificial Sequence

<220>
<223> mitochondrial targeting peptides

<400> 252

Met Ala Leu Leu Arg Gly Val Phe Val Val Ala Ala Lys Arg Thr Pro
1 5 10 15

<210> 253
<211> 23
<212> PRT

<213> Artificial Sequence

<220>
<223> mitochondrial targeting peptides

<400> 253

Met Leu Arg Ile Pro Val Arg Lys Ala Leu Val Gly Leu Ser Lys Ser
1 5 10 15

Ser Lys Gly Cys Val Arg Thr
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<210> 254
<211> 31
<212> PRT
<213> Artificial Sequence

<220>
<223> mitochondrial targeting peptide

<400> 254

Met Arg Gln Pro Ala Val Arg Leu Val Arg Leu Gly Arg Val Pro Tyr
1 5 10 15

Ala Glu Leu Leu Gly Leu Gln Asp Arg Trp Leu Arg Arg Leu Gln
20 25 30

<210> 255
<211> 11
<212> PRT
<213> Artificial Sequence

<220>
<223> mitochondrial targeting peptides

<400> 255

Met Glu Thr Trp Arg Lys Gly Ser Phe Arg Asn
1 5 10

<210> 256
<211> 28
<212> PRT
<213> Artificial Sequence

<220>
<223> mitochondrial targeting peptides

<400> 256

Met Ala Ala Leu Arg Arg Met Leu His Leu Pro Ser Leu Met Met Gly
1 5 10 15

Thr Cys Arg Pro Phe Ala Gly Ser Leu Ala Asp Ser
20 25

<210> 257
<211> 33
<212> PRT

<213> Artificial Sequence

<220>
<223> mitochondrial targeting peptides

<400> 257

Met Leu Leu Trp Pro Leu Arg Gly Trp Ala Ala Arg Ala Leu Arg Cys
1 5 10 15

Phe Gly Pro Gly Ser Arg Gly Ser Pro Ala Ser Gly Pro Gly Pro Arg
20 25 30

Arg

<210> 258
<211> 34
<212> PRT
<213> Artificial Sequence

<220>
<223> mitochondrial targeting peptides

<400> 258

Met Arg Cys Leu Thr Thr Pro Met Leu Leu Arg Ala Leu Ala Gln Ala
1 5 10 15

Ala Arg Ala Gly Pro Pro Gly Gly Arg Ser Leu His Ser Ser Ala Val
20 25 30

Ala Ala

<210> 259
<211> 53
<212> PRT
<213> Artificial Sequence

<220>
<223> mitochondrial targeting peptides

<400> 259

Met Ala Ala Ser Trp Arg Leu Gly Cys Asp Pro Arg Leu Leu Arg Tyr
1 5 10 15

Leu Val Gly Phe Pro Gly Arg Arg Ser Val Gly Leu Val Lys Gly Ala
20 25 30

Leu Gly Trp Ser Val Ser Arg Gly Ala Asn Trp Arg Trp Phe His Ser
35 40 45

Thr Gln Trp Leu Arg
50

<210> 260

<211> 41
<212> PRT
<213> Artificial Sequence

<220>
<223> mitochondrial targeting peptides

<400> 260

Met Ser Ala Leu Cys Trp Gly Arg Gly Ala Ala Gly Leu Lys Arg Ala
1 5 10 15

Leu Arg Pro Cys Gly Arg Pro Gly Leu Pro Gly Lys Glu Gly Thr Ala
20 25 30

Gly Gly Val Cys Gly Pro Arg Arg Ser
35 40

<210> 261
<211> 33
<212> PRT
<213> Artificial Sequence

<220>
<223> mitochondrial targeting peptides

<400> 261

Met Gly Gly Leu Phe Trp Arg Ser Ala Leu Arg Gly Leu Arg Cys Gly
1 5 10 15

Pro Arg Ala Pro Gly Pro Ser Leu Leu Val Arg His Gly Ser Gly Gly
20 25 30

Pro

<210> 262
<211> 56
<212> PRT
<213> Artificial Sequence

<220>
<223> mitochondrial targeting peptides

<400> 262

Met Ala Val Leu Trp Arg Leu Ser Ala Val Cys Gly Ala Leu Gly Gly
1 5 10 15

Arg Ala Leu Leu Leu Arg Thr Pro Val Val Arg Pro Ala His Ile Ser
20 25 30

Ala Phe Leu Gln Asp Arg Pro Ile Pro Glu Trp Cys Gly Val Gln His
35 40 45

Ile His Leu Ser Pro Ser His His
50 55

<210> 263
<211> 55
<212> PRT
<213> Artificial Sequence

<220>
<223> mitochondrial targeting peptides

<400> 263

Met Tyr Tyr Lys Phe Ser Gly Phe Thr Gln Lys Leu Ala Gly Ala Trp
1 5 10 15

Ala Ser Glu Ala Tyr Ser Pro Gln Gly Leu Lys Pro Val Val Ser Thr
20 25 30

Glu Ala Pro Pro Ile Ile Phe Ala Thr Pro Thr Lys Leu Thr Ser Asp
35 40 45

Ser Thr Val Tyr Asp Tyr Ala
50 55

<210> 264
<211> 30
<212> PRT
<213> Artificial Sequence

<220>
<223> Mouse methylmalonyl-CoA mutase

<400> 264

Met Leu Arg Ala Lys Asn Gln Leu Phe Leu Leu Ser Pro His Tyr Leu
1 5 10 15

Lys Gln Leu Asn Ile Pro Ser Ala Ser Arg Trp Lys Arg Leu
20 25 30

<210> 265
<211> 32
<212> PRT
<213> Artificial Sequence

<220>
<223> Human methylmalonyl-CoA mutase

<400> 265

Met Leu Arg Ala Lys Asn Gln Leu Phe Leu Leu Ser Pro His Tyr Leu
1 5 10 15

Arg Gln Val Lys Glu Ser Ser Gly Ser Arg Leu Ile Gln Gln Arg Leu
20 25 30

<210> 266
<211> 92
<212> DNA
<213> Artificial Sequence

<220>
<223> 5UTR-018 Upstream UTR

<400> 266
tcaagctttt ggaccctcgt acagaagcta atacgactca ctatagggaa ataagagaga 60

aaagaagagt aagaagaaat ataagagcca cc 92

<210> 267
<211> 119
<212> DNA
<213> Artificial Sequence

<220>
<223> 3UTR-018

<400> 267
tgataatagg ctggagcctc ggtggccatg cttcttgccc cttgggcctc cccccagccc 60

ctcctcccct tcctgcaccc gtacccccgt ggtctttgaa taaagtctga gtgggcggc 119

<210> 268
<211> 748
<212> PRT
<213> Artificial Sequence

<220>
<223> mouse MCM

<400> 268

Met Leu Arg Ala Lys Asn Gln Leu Phe Leu Leu Ser Pro His Tyr Leu
1 5 10 15

Lys Gln Leu Asn Ile Pro Ser Ala Ser Arg Trp Lys Arg Leu Leu His
20 25 30

Gln Gln Gln Pro Leu His Pro Glu Trp Ala Val Leu Ala Lys Lys Gln
35 40 45

Leu Lys Gly Lys Asn Pro Glu Asp Leu Ile Trp His Thr Pro Glu Gly
50 55 60

Ile Ser Ile Lys Pro Leu Tyr Ser Arg Ala Asp Thr Leu Asp Leu Pro
65 70 75 80

Glu Glu Leu Pro Gly Val Lys Pro Phe Thr Arg Gly Pro Tyr Pro Thr
85 90 95

Met Tyr Thr Tyr Arg Pro Trp Thr Ile Arg Gln Tyr Ala Gly Phe Ser
100 105 110

Thr Val Glu Glu Ser Asn Lys Phe Tyr Lys Asp Asn Ile Lys Ala Gly
115 120 125

Gln Gln Gly Leu Ser Val Ala Phe Asp Leu Ala Thr His Arg Gly Tyr
130 135 140

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Asp Ser Asp Asn Pro Arg Val Arg Gly Asp Val Gly Met Ala Gly Val
145                 150                 155                 160

Ala Ile Asp Thr Val Glu Asp Thr Lys Ile Leu Phe Asp Gly Ile Pro
                165                 170                 175

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

Val Leu Ala Thr Phe Ile Val Thr Gly Glu Glu Gln Gly Val Pro Lys
        195                 200                 205

Glu Lys Leu Thr Gly Thr Ile Gln Asn Asp Ile Leu Lys Glu Phe Met
    210                 215                 220

Val Arg Asn Thr Tyr Ile Phe Pro Pro Glu Pro Ser Met Lys Ile Ile
225                 230                 235                 240

Ala Asp Ile Phe Gln Tyr Thr Ala Gln His Met Pro Lys Phe Asn Ser
                245                 250                 255

Ile Ser Ile Ser Gly Tyr His Met Gln Glu Ala Gly Ala Asp Ala Ile
            260                 265                 270

Leu Glu Leu Ala Tyr Thr Ile Ala Asp Gly Leu Glu Tyr Cys Arg Thr
        275                 280                 285

Gly Leu Gln Ala Gly Leu Thr Ile Asp Glu Phe Ala Pro Arg Leu Ser
    290                 295                 300

Phe Phe Trp Gly Ile Gly Met Asn Phe Tyr Met Glu Ile Ala Lys Met
305                 310                 315                 320

Arg Ala Gly Arg Arg Leu Trp Ala His Leu Ile Glu Lys Met Phe Gln
                325                 330                 335

Pro Lys Asn Ser Lys Ser Leu Leu Leu Arg Ala His Cys Gln Thr Ser
            340                 345                 350

Gly Trp Ser Leu Thr Glu Gln Asp Pro Tyr Asn Asn Ile Val Arg Thr
        355                 360                 365

Ala Ile Glu Ala Met Ala Ala Val Phe Gly Gly Thr Gln Ser Leu His
    370                 375                 380

Thr Asn Ser Phe Asp Glu Ala Leu Gly Leu Pro Thr Val Lys Ser Ala
385                 390                 395                 400

Arg Ile Ala Arg Asn Thr Gln Ile Ile Ile Gln Glu Glu Ser Gly Ile
                405                 410                 415
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Pro Lys Val Ala Asp Pro Trp Gly Gly Ser Tyr Met Met Glu Ser Leu
            420                 425                 430

Thr Asn Asp Val Tyr Glu Ala Ala Leu Lys Leu Ile Tyr Glu Val Glu
        435                 440                 445

Glu Met Gly Gly Met Ala Lys Ala Val Ala Glu Gly Ile Pro Lys Leu
    450                 455                 460

Arg Ile Glu Glu Cys Ala Ala Arg Arg Gln Ala Arg Ile Asp Ser Gly
465                 470                 475                 480

Ser Glu Val Ile Val Gly Val Asn Lys Tyr Gln Leu Glu Lys Glu Asp
                485                 490                 495

Ser Val Glu Val Leu Ala Ile Asp Asn Thr Ser Val Arg Lys Lys Gln
            500                 505                 510

Ile Glu Lys Leu Lys Lys Ile Lys Ser Ser Arg Asp Gln Ala Leu Ala
        515                 520                 525

Glu Gln Cys Leu Ser Ala Leu Thr Gln Cys Ala Ala Ser Gly Asp Gly
    530                 535                 540

Asn Ile Leu Ala Leu Ala Val Asp Ala Ala Arg Ala Arg Cys Thr Val
545                 550                 555                 560

Gly Glu Ile Thr Asp Ala Leu Lys Lys Val Phe Gly Glu His Lys Ala
                565                 570                 575

Asn Asp Arg Met Val Ser Gly Ala Tyr Arg Gln Glu Phe Gly Glu Ser
            580                 585                 590

Lys Glu Ile Thr Ser Ala Ile Lys Arg Val Asn Lys Phe Met Glu Arg
        595                 600                 605

Glu Gly Arg Arg Pro Arg Leu Leu Val Ala Lys Met Gly Gln Asp Gly
    610                 615                 620

His Asp Arg Gly Ala Lys Val Ile Ala Thr Gly Phe Ala Asp Leu Gly
625                 630                 635                 640

Phe Asp Val Asp Ile Gly Pro Leu Phe Gln Thr Pro Arg Glu Val Ala
                645                 650                 655

Gln Gln Ala Val Asp Ala Asp Val His Ala Val Gly Val Ser Thr Leu
            660                 665                 670

Ala Ala Gly His Lys Thr Leu Val Pro Glu Leu Ile Lys Glu Leu Thr
        675                 680                 685
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Ala Leu Gly Arg Pro Asp Ile Leu Val Met Cys Gly Gly Val Ile Pro
690 695 700

Pro Gln Asp Tyr Glu Phe Leu Tyr Glu Val Gly Val Ser Asn Val Phe
705 710 715 720

Gly Pro Gly Thr Arg Ile Pro Arg Ala Ala Val Gln Val Leu Asp Asp
725 730 735

Ile Glu Lys Cys Leu Ala Glu Lys Gln Gln Ser Val
740 745

<210> 269
<211> 239
<212> PRT
<213> Artificial Sequence

<220>
<223> GFP sequence

<400> 269

Met Val Ser Lys Gly Glu Glu Leu Phe Thr Gly Val Val Pro Ile Leu
1 5 10 15

Val Glu Leu Asp Gly Asp Val Asn Gly His Lys Phe Ser Val Ser Gly
20 25 30

Glu Gly Glu Gly Asp Ala Thr Tyr Gly Lys Leu Thr Leu Lys Phe Ile
35 40 45

Cys Thr Thr Gly Lys Leu Pro Val Pro Trp Pro Thr Leu Val Thr Thr
50 55 60

Leu Thr Tyr Gly Val Gln Cys Phe Ser Arg Tyr Pro Asp His Met Lys
65 70 75 80

Gln His Asp Phe Phe Lys Ser Ala Met Pro Glu Gly Tyr Val Gln Glu
85 90 95

Arg Thr Ile Phe Phe Lys Asp Asp Gly Asn Tyr Lys Thr Arg Ala Glu
100 105 110

Val Lys Phe Glu Gly Asp Thr Leu Val Asn Arg Ile Glu Leu Lys Gly
115 120 125

Ile Asp Phe Lys Glu Asp Gly Asn Ile Leu Gly His Lys Leu Glu Tyr
130 135 140

Asn Tyr Asn Ser His Asn Val Tyr Ile Met Ala Asp Lys Gln Lys Asn
145 150 155 160

Gly Ile Lys Val Asn Phe Lys Ile Arg His Asn Ile Glu Asp Gly Ser

165 170 175

Val Gln Leu Ala Asp His Tyr Gln Gln Asn Thr Pro Ile Gly Asp Gly
180 185 190

Pro Val Leu Leu Pro Asp Asn His Tyr Leu Ser Thr Gln Ser Ala Leu
195 200 205

Ser Lys Asp Pro Asn Glu Lys Arg Asp His Met Val Leu Leu Glu Phe
210 215 220

Val Thr Ala Ala Gly Ile Thr Leu Gly Met Asp Glu Leu Tyr Lys
225 230 235

<210> 270
<211> 68
<212> PRT
<213> Artificial Sequence

<220>
<223> O14561 mitochondrial targeting peptide

<400> 270

Met Ala Ser Arg Val Leu Ser Ala Tyr Val Ser Arg Leu Pro Ala Ala
1 5 10 15

Phe Ala Pro Leu Pro Arg Val Arg Met Leu Ala Val Ala Arg Pro Leu
20 25 30

Ser Thr Ala Leu Cys Ser Ala Gly Thr Gln Thr Arg Leu Gly Thr Leu
35 40 45

Gln Pro Ala Leu Val Leu Ala Gln Val Pro Gly Arg Val Thr Gln Leu
50 55 60

Cys Arg Gln Tyr
65

<210> 271
<211> 30
<212> PRT
<213> Artificial Sequence

<220>
<223> O14874 mitochondrial targeting peptide

<400> 271

Met Ile Leu Ala Ser Val Leu Arg Ser Gly Pro Gly Gly Gly Leu Pro
1 5 10 15

Leu Arg Pro Leu Leu Gly Pro Ala Leu Ala Leu Arg Ala Arg
20 25 30

<210> 272

<211> 45
<212> PRT
<213> Artificial Sequence

<220>
<223> O15091mitochondrial targeting peptide

<400> 272

Met Thr Phe Tyr Leu Phe Gly Ile Arg Ser Phe Pro Lys Leu Trp Lys
1 5 10 15

Ser Pro Tyr Leu Gly Leu Gly Pro Gly His Ser Tyr Val Ser Leu Phe
20 25 30

Leu Ala Asp Arg Cys Gly Ile Arg Asn Gln Gln Arg Leu
35 40 45

<210> 273
<211> 29
<212> PRT
<213> Artificial Sequence

<220>
<223> O15235 mitochondrial targeting peptide

<400> 273

Met Ser Trp Ser Gly Leu Leu His Gly Leu Asn Thr Ser Leu Thr Cys
1 5 10 15

Gly Pro Ala Leu Val Pro Arg Leu Trp Ala Thr Cys Ser
20 25

<210> 274
<211> 27
<212> PRT
<213> Artificial Sequence

<220>
<223> O15382 mitochondrial targeting peptide

<400> 274

Met Ala Ala Ala Ala Leu Gly Gln Ile Trp Ala Arg Lys Leu Leu Ser
1 5 10 15

Val Pro Trp Leu Leu Cys Gly Pro Arg Arg Tyr
20 25

<210> 275
<211> 42
<212> PRT
<213> Artificial Sequence

<220>
<223> O43181 mitochondrial targeting peptide

<400> 275

Met Ala Ala Val Ser Met Ser Val Val Leu Arg Gln Thr Leu Trp Arg

1 5 10 15

Arg Arg Ala Val Ala Val Ala Ala Leu Ser Val Ser Arg Val Pro Thr
20 25 30

Arg Ser Leu Arg Thr Ser Thr Trp Arg Leu
35 40

<210> 276
<211> 31
<212> PRT
<213> Artificial Sequence

<220>
<223> O43464 mitochondrial targeting peptide

<400> 276

Met Ala Ala Pro Arg Ala Gly Arg Gly Ala Gly Trp Ser Leu Arg Ala
1 5 10 15

Trp Arg Ala Leu Gly Gly Ile Arg Trp Gly Arg Arg Pro Arg Leu
20 25 30

<210> 277
<211> 28
<212> PRT
<213> Artificial Sequence

<220>
<223> O43572 mitochondrial targeting peptide

<400> 277

Met Arg Gly Ala Gly Pro Ser Pro Arg Gln Ser Pro Arg Thr Leu Arg
1 5 10 15

Pro Asp Pro Gly Pro Ala Met Ser Phe Phe Arg Arg
20 25

<210> 278
<211> 46
<212> PRT
<213> Artificial Sequence

<220>
<223> O43674 mitochondrial targeting peptide

<400> 278

Met Ala Ala Met Ser Leu Leu Arg Arg Val Ser Val Thr Ala Val Ala
1 5 10 15

Ala Leu Ser Gly Arg Pro Leu Gly Thr Arg Leu Gly Phe Gly Gly Phe
20 25 30

Leu Thr Arg Gly Phe Pro Lys Ala Ala Ala Pro Val Arg His
35 40 45

<210> 279
<211> 27
<212> PRT
<213> Artificial Sequence

<220>
<223> O43677 mitochondrial targeting peptide

<400> 279

Met Ala Pro Ser Ala Leu Leu Arg Pro Leu Ser Arg Leu Leu Ala Pro
1 5 10 15

Ala Arg Leu Pro Ser Gly Pro Ser Val Arg Ser
20 25

<210> 280
<211> 27
<212> PRT
<213> Artificial Sequence

<220>
<223> O43766 mitochondrial targeting peptide

<400> 280

Met Ser Leu Arg Cys Gly Asp Ala Ala Arg Thr Leu Gly Pro Arg Val
1 5 10 15

Phe Gly Arg Tyr Phe Cys Ser Pro Val Arg Pro
20 25

<210> 281
<211> 41
<212> PRT
<213> Artificial Sequence

<220>
<223> O43819 mitochondrial targeting peptide

<400> 281

Met Leu Leu Leu Thr Arg Ser Pro Thr Ala Trp His Arg Leu Ser Gln
1 5 10 15

Leu Lys Pro Arg Val Leu Pro Gly Thr Leu Gly Gly Gln Ala Leu His
20 25 30

Leu Arg Ser Trp Leu Leu Ser Arg Gln
35 40

<210> 282
<211> 34
<212> PRT
<213> Artificial Sequence

<220>
<223> O43837 mitochondrial targeting peptide

<400> 282

Met Ala Ala Leu Ser Gly Val Arg Trp Leu Thr Arg Ala Leu Val Ser
1 5 10 15

Ala Gly Asn Pro Gly Ala Trp Arg Gly Leu Ser Thr Ser Ala Ala Ala
20 25 30

His Ala

<210> 283
<211> 87
<212> PRT
<213> Artificial Sequence

<220>
<223> O60313 mitochondrial targeting peptide

<400> 283

Met Trp Arg Leu Arg Arg Ala Ala Val Ala Cys Glu Val Cys Gln Ser
1 5 10 15

Leu Val Lys His Ser Ser Gly Ile Lys Gly Ser Leu Pro Leu Gln Lys
20 25 30

Leu His Leu Val Ser Arg Ser Ile Tyr His Ser His His Pro Thr Leu
35 40 45

Lys Leu Gln Arg Pro Gln Leu Arg Thr Ser Phe Gln Gln Phe Ser Ser
50 55 60

Leu Thr Asn Leu Pro Leu Arg Lys Leu Lys Phe Ser Pro Ile Lys Tyr
65 70 75 80

Gly Tyr Gln Pro Arg Arg Asn
85

<210> 284
<211> 23
<212> PRT
<213> Artificial Sequence

<220>
<223> O60397 mitochondrial targeting peptide

<400> 284

Met Leu Trp Asn Leu Leu Ala Leu His Gln Ile Gly Gln Arg Thr Ile
1 5 10 15

Ser Thr Ala Ser His Arg His
20

<210> 285
<211> 22
<212> PRT

<213> Artificial Sequence

<220>
<223> O75027 mitochondrial targeting peptide

<400> 285

Met Ala Leu Leu Ala Met His Ser Trp Arg Trp Ala Ala Ala Ala Ala
1 5 10 15

Ala Phe Glu Lys Arg Arg
20

<210> 286
<211> 44
<212> PRT
<213> Artificial Sequence

<220>
<223> O75208 mitochondrial targeting peptide

<400> 286

Met Ala Ala Ala Ala Val Ser Gly Ala Leu Gly Arg Ala Gly Trp Arg
1 5 10 15

Leu Leu Gln Leu Arg Cys Leu Pro Val Ala Arg Cys Arg Gln Ala Leu
20 25 30

Val Pro Arg Ala Phe His Ala Ser Ala Val Gly Leu
35 40

<210> 287
<211> 38
<212> PRT
<213> Artificial Sequence

<220>
<223> O75251 mitochondrial targeting peptide

<400> 287

Met Ala Val Leu Ser Ala Pro Gly Leu Arg Gly Phe Arg Ile Leu Gly
1 5 10 15

Leu Arg Ser Ser Val Gly Pro Ala Val Gln Ala Arg Gly Val His Gln
20 25 30

Ser Val Ala Thr Asp Gly
35

<210> 288
<211> 33
<212> PRT
<213> Artificial Sequence

<220>
<223> O75306 mitochondrial targeting peptide

<400> 288

Met Ala Ala Leu Arg Ala Leu Cys Gly Phe Arg Gly Val Ala Ala Gln
1 5 10 15

Val Leu Arg Pro Gly Ala Gly Val Arg Leu Pro Ile Gln Pro Ser Arg
20 25 30

Gly

<210> 289
<211> 28
<212> PRT
<213> Artificial Sequence

<220>
<223> O75380 mitochondrial targeting peptide

<400> 289

Met Ala Ala Ala Met Thr Phe Cys Arg Leu Leu Asn Arg Cys Gly Glu
1 5 10 15

Ala Ala Arg Ser Leu Pro Leu Gly Ala Arg Cys Phe
20 25

<210> 290
<211> 27
<212> PRT
<213> Artificial Sequence

<220>
<223> O75390 mitochondrial targeting peptide

<400> 290

Met Ala Leu Leu Thr Ala Ala Ala Arg Leu Leu Gly Thr Lys Asn Ala
1 5 10 15

Ser Cys Leu Val Leu Ala Ala Arg His Ala Ser
20 25

<210> 291
<211> 45
<212> PRT
<213> Artificial Sequence

<220>
<223> O75439 mitochondrial targeting peptide

<400> 291

Met Ala Ala Ala Ala Ala Arg Val Val Leu Ser Ser Ala Ala Arg Arg
1 5 10 15

Arg Leu Trp Gly Phe Ser Glu Ser Leu Leu Ile Arg Gly Ala Ala Gly
20 25 30

Arg Ser Leu Tyr Phe Gly Glu Asn Arg Leu Arg Ser Thr

35 40 45

<210> 292
<211> 36
<212> PRT
<213> Artificial Sequence

<220>
<223> O75489 mitochondrial targeting peptide

<400> 292

Met Ala Ala Ala Ala Val Ala Arg Leu Trp Trp Arg Gly Ile Leu Gly
1 5 10 15

Ala Ser Ala Leu Thr Arg Gly Thr Gly Arg Pro Ser Val Leu Leu Leu
20 25 30

Pro Val Arg Arg
35

<210> 293
<211> 38
<212> PRT
<213> Artificial Sequence

<220>
<223> O75521 mitochondrial targeting peptide

<400> 293

Met Ala Met Ala Tyr Leu Ala Trp Arg Leu Ala Arg Arg Ser Cys Pro
1 5 10 15

Ser Ser Leu Gln Val Thr Ser Phe Pro Val Val Gln Leu His Met Asn
20 25 30

Arg Thr Ala Met Arg Ala
35

<210> 294
<211> 21
<212> PRT
<213> Artificial Sequence

<220>
<223> O75600 mitochondrial targeting peptide

<400> 294

Met Trp Pro Gly Asn Ala Trp Arg Ala Ala Leu Phe Trp Val Pro Arg
1 5 10 15

Gly Arg Arg Ala Gln
20

<210> 295
<211> 43
<212> PRT

<213> Artificial Sequence

<220>
<223> O75616 mitochondrial targeting peptide

<400> 295

Met Ala Ala Pro Ser Trp Arg Gly Ala Arg Leu Val Gln Ser Val Leu
1 5 10 15

Arg Val Trp Gln Val Gly Pro His Val Ala Arg Glu Arg Val Ile Pro
20 25 30

Phe Ser Ser Leu Leu Gly Phe Gln Arg Arg Cys
35 40

<210> 296
<211> 30
<212> PRT
<213> Artificial Sequence

<220>
<223> O75879 mitochondrial targeting peptide

<400> 296

Met Ala Ala Pro Met Leu Arg Trp Gly Cys Arg Gly Arg Arg Trp Ala
1 5 10 15

Phe Ala Arg Val Asp Gly Gly Ser Cys His Arg Arg Gly Ala
20 25 30

<210> 297
<211> 56
<212> PRT
<213> Artificial Sequence

<220>
<223> O76031 mitochondrial targeting peptide

<400> 297

Met Pro Ser Cys Gly Ala Cys Thr Cys Gly Ala Ala Ala Val Arg Leu
1 5 10 15

Ile Thr Ser Ser Leu Ala Ser Ala Gln Arg Gly Ile Ser Gly Gly Arg
20 25 30

Ile His Met Ser Val Leu Gly Arg Leu Gly Thr Phe Glu Thr Gln Ile
35 40 45

Leu Gln Arg Ala Pro Leu Arg Ser
50 55

<210> 298
<211> 16
<212> PRT
<213> Artificial Sequence

<220>
<223> O94925 mitochondrial targeting peptide

<400> 298

Met Met Arg Leu Arg Gly Ser Gly Met Leu Arg Asp Leu Leu Leu Arg
1 5 10 15

<210> 299
<211> 28
<212> PRT
<213> Artificial Sequence

<220>
<223> O95169 mitochondrial targeting peptide

<400> 299

Met Ala Val Ala Arg Ala Gly Val Leu Gly Val Gln Trp Leu Gln Arg
1 5 10 15

Ala Ser Arg Asn Val Met Pro Leu Gly Ala Arg Thr
20 25

<210> 300
<211> 33
<212> PRT
<213> Artificial Sequence

<220>
<223> O95178 mitochondrial targeting peptide

<400> 300

Met Ser Ala Leu Thr Arg Leu Ala Ser Phe Ala Arg Val Gly Gly Arg
1 5 10 15

Leu Phe Arg Ser Gly Cys Ala Arg Thr Ala Gly Asp Gly Gly Val Arg
20 25 30

His

<210> 301
<211> 115
<212> PRT
<213> Artificial Sequence

<220>
<223> O95202 mitochondrial targeting peptide

<400> 301

Met Ala Ser Ile Leu Leu Arg Ser Cys Arg Gly Arg Ala Pro Ala Arg
1 5 10 15

Leu Pro Pro Pro Pro Arg Tyr Thr Val Pro Arg Gly Ser Pro Gly Asp
20 25 30

Pro Ala His Leu Ser Cys Ala Ser Thr Leu Gly Leu Arg Asn Cys Leu

35 40 45

Asn Val Pro Phe Gly Cys Cys Thr Pro Ile His Pro Val Tyr Thr Ser
50 55 60

Ser Arg Gly Asp His Leu Gly Cys Trp Ala Leu Arg Pro Glu Cys Leu
65 70 75 80

Arg Ile Val Ser Arg Ala Pro Trp Thr Ser Thr Ser Val Gly Phe Val
85 90 95

Ala Val Gly Pro Gln Cys Leu Pro Val Arg Gly Trp His Ser Ser Arg
100 105 110

Pro Val Arg
115

<210> 302
<211> 35
<212> PRT
<213> Artificial Sequence

<220>
<223> O95299 mitochondrial targeting peptide

<400> 302

Met Ala Leu Arg Leu Leu Lys Leu Ala Ala Thr Ser Ala Ser Ala Arg
1 5 10 15

Val Val Ala Ala Gly Ala Gln Arg Val Arg Gly Ile His Ser Ser Val
20 25 30

Gln Cys Lys
35

<210> 303
<211> 7
<212> PRT
<213> Artificial Sequence

<220>
<223> O95571 mitochondrial targeting peptide

<400> 303

Met Ala Glu Ala Val Leu Arg
1 5

<210> 304
<211> 39
<212> PRT
<213> Artificial Sequence

<220>
<223> O95822 mitochondrial targeting peptide

<400> 304

Met Arg Gly Phe Gly Pro Gly Leu Thr Ala Arg Arg Leu Leu Pro Leu
1 5 10 15

Arg Leu Pro Pro Arg Pro Pro Gly Pro Arg Leu Ala Ser Gly Gln Ala
20 25 30

Ala Gly Ala Leu Glu Arg Ala
35

<210> 305
<211> 54
<212> PRT
<213> Artificial Sequence

<220>
<223> O95831 mitochondrial targeting peptide

<400> 305

Met Phe Arg Cys Gly Gly Leu Ala Ala Gly Ala Leu Lys Gln Lys Leu
1 5 10 15

Val Pro Leu Val Arg Thr Val Cys Val Arg Ser Pro Arg Gln Arg Asn
20 25 30

Arg Leu Pro Gly Asn Leu Phe Gln Arg Trp His Val Pro Leu Glu Leu
35 40 45

Gln Met Thr Arg Gln Met
50

<210> 306
<211> 53
<212> PRT
<213> Artificial Sequence

<220>
<223> P00367 mitochondrial targeting peptide

<400> 306

Met Tyr Arg Tyr Leu Gly Glu Ala Leu Leu Leu Ser Arg Ala Gly Pro
1 5 10 15

Ala Ala Leu Gly Ser Ala Ser Ala Asp Ser Ala Ala Leu Leu Gly Trp
20 25 30

Ala Arg Gly Gln Pro Ala Ala Ala Pro Gln Pro Gly Leu Ala Leu Ala
35 40 45

Ala Arg Arg His Tyr
50

<210> 307
<211> 43
<212> PRT

<213> Artificial Sequence

<220>
<223> P00390 mitochondrial targeting peptide

<400> 307

Met Ala Leu Leu Pro Arg Ala Leu Ser Ala Gly Ala Gly Pro Ser Trp
1 5 10 15

Arg Arg Ala Ala Arg Ala Phe Arg Gly Phe Leu Leu Leu Leu Pro Glu
20 25 30

Pro Ala Ala Leu Thr Arg Ala Leu Ser Arg Ala
35 40

<210> 308
<211> 32
<212> PRT
<213> Artificial Sequence

<220>
<223> P00480 mitochondrial targeting peptide

<400> 308

Met Leu Phe Asn Leu Arg Ile Leu Leu Asn Asn Ala Ala Phe Arg Asn
1 5 10 15

Gly His Asn Phe Met Val Arg Asn Phe Arg Cys Gly Gln Pro Leu Gln
20 25 30

<210> 309
<211> 29
<212> PRT
<213> Artificial Sequence

<220>
<223> P00505 mitochondrial targeting peptide

<400> 309

Met Ala Leu Leu His Ser Gly Arg Val Leu Pro Gly Ile Ala Ala Ala
1 5 10 15

Phe His Pro Gly Leu Ala Ala Ala Ala Ser Ala Arg Ala
20 25

<210> 310
<211> 24
<212> PRT
<213> Artificial Sequence

<220>
<223> P04179 mitochondrial targeting peptide

<400> 310

Met Leu Ser Arg Ala Val Cys Gly Thr Ser Arg Gln Leu Ala Pro Ala
1 5 10 15

Leu Gly Tyr Leu Gly Ser Arg Gln
            20

<210> 311
<211> 35
<212> PRT
<213> Artificial Sequence

<220>
<223> P04181 (25) mitochondrial targeting peptide

<400> 311

Met Phe Ser Lys Leu Ala His Leu Gln Arg Phe Ala Val Leu Ser Arg
1   5   10   15

Gly Val His Ser Ser Val Ala Ser Ala Thr Ser Val Ala Thr Lys Lys
            20   25   30

Thr Val Gln
        35

<210> 312
<211> 25
<212> PRT
<213> Artificial Sequence

<220>
<223> P04181 (35) mitochondrial targeting peptide

<400> 312

Met Phe Ser Lys Leu Ala His Leu Gln Arg Phe Ala Val Leu Ser Arg
1   5   10   15

Gly Val His Ser Ser Val Ala Ser Ala
            20   25

<210> 313
<211> 17
<212> PRT
<213> Artificial Sequence

<220>
<223> P05091 mitochondrial targeting peptide

<400> 313

Met Leu Arg Ala Ala Ala Arg Phe Gly Pro Arg Leu Gly Arg Arg Leu
1   5   10   15

Leu

<210> 314
<211> 39
<212> PRT
<213> Artificial Sequence

<220>
<223> P05108 mitochondrial targeting peptide

<400> 314

Met Leu Ala Lys Gly Leu Pro Pro Arg Ser Val Leu Val Lys Gly Cys
1 5 10 15

Gln Thr Phe Leu Ser Ala Pro Arg Glu Gly Leu Gly Arg Leu Arg Val
20 25 30

Pro Thr Gly Glu Gly Ala Gly
35

<210> 315
<211> 52
<212> PRT
<213> Artificial Sequence

<220>
<223> P05165 mitochondrial targeting peptide

<400> 315

Met Ala Gly Phe Trp Val Gly Thr Ala Pro Leu Val Ala Ala Gly Arg
1 5 10 15

Arg Gly Arg Trp Pro Pro Gln Gln Leu Met Leu Ser Ala Ala Leu Arg
20 25 30

Thr Leu Lys His Val Leu Tyr Tyr Ser Arg Gln Cys Leu Met Val Ser
35 40 45

Arg Asn Leu Gly
50

<210> 316
<211> 28
<212> PRT
<213> Artificial Sequence

<220>
<223> P05166 mitochondrial targeting peptide

<400> 316

Met Ala Ala Ala Leu Arg Val Ala Ala Val Gly Ala Arg Leu Ser Val
1 5 10 15

Leu Ala Ser Gly Leu Arg Ala Ala Val Arg Ser Leu
20 25

<210> 317
<211> 61
<212> PRT
<213> Artificial Sequence

<220>
<223> P05496 mitochondrial targeting peptide

<400> 317

Met Gln Thr Ala Gly Ala Leu Phe Ile Ser Pro Ala Leu Ile Arg Cys
1 5 10 15

Cys Thr Arg Gly Leu Ile Arg Pro Val Ser Ala Ser Phe Leu Asn Ser
20 25 30

Pro Val Asn Ser Ser Lys Gln Pro Ser Tyr Ser Asn Phe Pro Leu Gln
35 40 45

Val Ala Arg Arg Glu Phe Gln Thr Ser Val Val Ser Arg
50 55 60

<210> 318
<211> 47
<212> PRT
<213> Artificial Sequence

<220>
<223> P06576 mitochondrial targeting peptide

<400> 318

Met Leu Gly Phe Val Gly Arg Val Ala Ala Ala Pro Ala Ser Gly Ala
1 5 10 15

Leu Arg Arg Leu Thr Pro Ser Ala Ser Leu Pro Pro Ala Gln Leu Leu
20 25 30

Leu Arg Ala Ala Pro Thr Ala Val His Pro Val Arg Asp Tyr Ala
35 40 45

<210> 319
<211> 13
<212> PRT
<213> Artificial Sequence

<220>
<223> P07919 mitochondrial targeting peptide

<400> 319

Met Gly Leu Glu Asp Glu Gln Lys Met Leu Thr Glu Ser
1 5 10

<210> 320
<211> 44
<212> PRT
<213> Artificial Sequence

<220>
<223> P07954 mitochondrial targeting peptide

<400> 320

Met Tyr Arg Ala Leu Arg Leu Leu Ala Arg Ser Arg Pro Leu Val Arg
1 5 10 15

Ala Pro Ala Ala Ala Leu Ala Ser Ala Pro Gly Leu Gly Gly Ala Ala
20 25 30

Val Pro Ser Phe Trp Pro Pro Asn Ala Ala Arg Met
35 40

<210> 321
<211> 30
<212> PRT
<213> Artificial Sequence

<220>
<223> P08559 mitochondrial targeting peptide

<400> 321

Met Arg Lys Met Leu Ala Ala Val Ser Arg Val Leu Ser Gly Ala Ser
1 5 10 15

Gln Lys Pro Ala Ser Arg Val Leu Val Ala Ser Arg Asn Phe
20 25 30

<210> 322
<211> 84
<212> PRT
<213> Artificial Sequence

<220>
<223> P08574 mitochondrial targeting peptide

<400> 322

Met Ala Ala Ala Ala Ala Ser Leu Arg Gly Val Val Leu Gly Pro Arg
1 5 10 15

Gly Ala Gly Leu Pro Gly Ala Arg Ala Arg Gly Leu Leu Cys Ser Ala
20 25 30

Arg Pro Gly Gln Leu Pro Leu Arg Thr Pro Gln Ala Val Ala Leu Ser
35 40 45

Ser Lys Ser Gly Leu Ser Arg Gly Arg Lys Val Met Leu Ser Ala Leu
50 55 60

Gly Met Leu Ala Ala Gly Gly Ala Gly Leu Ala Met Ala Leu His Ser
65 70 75 80

Ala Val Ser Ala

<210> 323
<211> 35
<212> PRT
<213> Artificial Sequence

<220>
<223> P09622 mitochondrial targeting peptide

<400> 323

Met Gln Ser Trp Ser Arg Val Tyr Cys Ser Leu Ala Lys Arg Gly His
1 5 10 15

Phe Asn Arg Ile Ser His Gly Leu Gln Gly Leu Ser Ala Val Pro Leu
20 25 30

Arg Thr Tyr
35

<210> 324
<211> 22
<212> PRT
<213> Artificial Sequence

<220>
<223> P0C7M7 mitochondrial targeting peptide

<400> 324

Met Lys Ile Phe Phe Arg Tyr Gln Thr Phe Arg Phe Ile Trp Leu Thr
1 5 10 15

Lys Pro Pro Gly Arg Arg
20

<210> 325
<211> 14
<212> PRT
<213> Artificial Sequence

<220>
<223> P0C7P0 mitochondrial targeting peptide

<400> 325

Met Arg Gly Ala Gly Ala Ile Leu Arg Pro Ala Ala Arg Gly
1 5 10

<210> 326
<211> 60
<212> PRT
<213> Artificial Sequence

<220>
<223> P10109 mitochondrial targeting peptide

<400> 326

Met Ala Ala Ala Gly Gly Ala Arg Leu Leu Arg Ala Ala Ser Ala Val
1 5 10 15

Leu Gly Gly Pro Ala Gly Arg Trp Leu His His Ala Gly Ser Arg Ala
20 25 30

Gly Ser Ser Gly Leu Leu Arg Asn Arg Gly Pro Gly Gly Ser Ala Glu
35 40 45

Ala Ser Arg Ser Leu Ser Val Ser Ala Arg Ala Arg
50 55 60

<210> 327
<211> 25
<212> PRT
<213> Artificial Sequence

<220>
<223> P10176 mitochondrial targeting peptide

<400> 327

Met Ser Val Leu Thr Pro Leu Leu Leu Arg Gly Leu Thr Gly Ser Ala
1 5 10 15

Arg Arg Leu Pro Val Pro Arg Ala Lys
20 25

<210> 328
<211> 86
<212> PRT
<213> Artificial Sequence

<220>
<223> P10515 mitochondrial targeting peptide

<400> 328

Met Trp Arg Val Cys Ala Arg Arg Ala Gln Asn Val Ala Pro Trp Ala
1 5 10 15

Gly Leu Glu Ala Arg Trp Thr Ala Leu Gln Glu Val Pro Gly Thr Pro
20 25 30

Arg Val Thr Ser Arg Ser Gly Pro Ala Pro Ala Arg Arg Asn Ser Val
35 40 45

Thr Thr Gly Tyr Gly Gly Val Arg Ala Leu Cys Gly Trp Thr Pro Ser
50 55 60

Ser Gly Ala Thr Pro Arg Asn Arg Leu Leu Leu Gln Leu Leu Gly Ser
65 70 75 80

Pro Gly Arg Arg Tyr Tyr
85

<210> 329
<211> 31
<212> PRT
<213> Artificial Sequence

<220>
<223> P10606 mitochondrial targeting peptide

<400> 329

Met Ala Ser Arg Leu Leu Arg Gly Ala Gly Thr Leu Ala Ala Gln Ala

1 5 10 15

Leu Arg Ala Arg Gly Pro Ser Gly Ala Ala Ala Met Arg Ser Met
20 25 30

<210> 330
<211> 26
<212> PRT
<213> Artificial Sequence

<220>
<223> P10809 mitochondrial targeting peptide

<400> 330

Met Leu Arg Leu Pro Thr Val Phe Arg Gln Met Arg Pro Val Ser Arg
1 5 10 15

Val Leu Ala Pro His Leu Thr Arg Ala Tyr
20 25

<210> 331
<211> 30
<212> PRT
<213> Artificial Sequence

<220>
<223> P11177 mitochondrial targeting peptide

<400> 331

Met Ala Ala Val Ser Gly Leu Val Arg Arg Pro Leu Arg Glu Val Ser
1 5 10 15

Gly Leu Leu Lys Arg Arg Phe His Trp Thr Ala Pro Ala Ala
20 25 30

<210> 332
<211> 61
<212> PRT
<213> Artificial Sequence

<220>
<223> P11182 mitochondrial targeting peptide

<400> 332

Met Ala Ala Val Arg Met Leu Arg Thr Trp Ser Arg Asn Ala Gly Lys
1 5 10 15

Leu Ile Cys Val Arg Tyr Phe Gln Thr Cys Gly Asn Val His Val Leu
20 25 30

Lys Pro Asn Tyr Val Cys Phe Phe Gly Tyr Pro Ser Phe Lys Tyr Ser
35 40 45

His Pro His His Phe Leu Lys Thr Thr Ala Ala Leu Arg
50 55 60

<210> 333
<211> 25
<212> PRT
<213> Artificial Sequence

<220>
<223> P11310 mitochondrial targeting peptide

<400> 333

Met Ala Ala Gly Phe Gly Arg Cys Cys Arg Val Leu Arg Ser Ile Ser
1 5 10 15

Arg Phe His Trp Arg Ser Gln His Thr
20 25

<210> 334
<211> 20
<212> PRT
<213> Artificial Sequence

<220>
<223> P11498 mitochondrial targeting peptide

<400> 334

Met Leu Lys Phe Arg Thr Val His Gly Gly Leu Arg Leu Leu Gly Ile
1 5 10 15

Arg Arg Thr Ser
20

<210> 335
<211> 24
<212> PRT
<213> Artificial Sequence

<220>
<223> P12074 mitochondrial targeting peptide

<400> 335

Met Ala Val Val Gly Val Ser Ser Val Ser Arg Leu Leu Gly Arg Ser
1 5 10 15

Arg Pro Gln Leu Gly Arg Pro Met
20

<210> 336
<211> 39
<212> PRT
<213> Artificial Sequence

<220>
<223> P12532 mitochondrial targeting peptide

<400> 336

Met Ala Gly Pro Phe Ser Arg Leu Leu Ser Ala Arg Pro Gly Leu Arg
1 5 10 15

Leu Leu Ala Leu Ala Gly Ala Gly Ser Leu Ala Ala Gly Phe Leu Leu
20 25 30

Arg Pro Glu Pro Val Arg Ala
35

<210> 337
<211> 45
<212> PRT
<213> Artificial Sequence

<220>
<223> P12694 mitochondrial targeting peptide

<400> 337

Met Ala Val Ala Ile Ala Ala Ala Arg Val Trp Arg Leu Asn Arg Gly
1 5 10 15

Leu Ser Gln Ala Ala Leu Leu Leu Leu Arg Gln Pro Gly Ala Arg Gly
20 25 30

Leu Ala Arg Ser His Pro Pro Arg Gln Gln Gln Gln Phe
35 40 45

<210> 338
<211> 22
<212> PRT
<213> Artificial Sequence

<220>
<223> P13073 mitochondrial targeting peptide

<400> 338

Met Leu Ala Thr Arg Val Phe Ser Leu Val Gly Lys Arg Ala Ile Ser
1 5 10 15

Thr Ser Val Cys Val Arg
20

<210> 339
<211> 56
<212> PRT
<213> Artificial Sequence

<220>
<223> P13196 mitochondrial targeting peptide

<400> 339

Met Glu Ser Val Val Arg Arg Cys Pro Phe Leu Ser Arg Val Pro Gln
1 5 10 15

Ala Phe Leu Gln Lys Ala Gly Lys Ser Leu Leu Phe Tyr Ala Gln Asn
20 25 30

Cys Pro Lys Met Met Glu Val Gly Ala Lys Pro Ala Pro Arg Ala Leu

35 40 45

Ser Thr Ala Ala Val His Tyr Gln
50 55

<210> 340
<211> 19
<212> PRT
<213> Artificial Sequence

<220>
<223> P13804 mitochondrial targeting peptide

<400> 340

Met Phe Arg Ala Ala Ala Pro Gly Gln Leu Arg Arg Ala Ala Ser Leu
1 5 10 15

Leu Arg Phe

<210> 341
<211> 35
<212> PRT
<213> Artificial Sequence

<220>
<223> P13995 mitochondrial targeting peptide

<400> 341

Met Ala Ala Thr Ser Leu Met Ser Ala Leu Ala Ala Arg Leu Leu Gln
1 5 10 15

Pro Ala His Ser Cys Ser Leu Arg Leu Arg Pro Phe His Leu Ala Ala
20 25 30

Val Arg Asn
35

<210> 342
<211> 23
<212> PRT
<213> Artificial Sequence

<220>
<223> P14406 mitochondrial targeting peptide

<400> 342

Met Leu Arg Asn Leu Leu Ala Leu Arg Gln Ile Gly Gln Arg Thr Ile
1 5 10 15

Ser Thr Ala Ser Arg Arg His
20

<210> 343
<211> 24
<212> PRT

<213> Artificial Sequence

<220>
<223> P15538 mitochondrial targeting peptide

<400> 343

Met Ala Leu Arg Ala Lys Ala Glu Val Cys Met Ala Val Pro Trp Leu
1 5 10 15

Ser Leu Gln Arg Ala Gln Ala Leu
20

<210> 344
<211> 16
<212> PRT
<213> Artificial Sequence

<220>
<223> P15954 mitochondrial targeting peptide

<400> 344

Met Leu Gly Gln Ser Ile Arg Arg Phe Thr Thr Ser Val Val Arg Arg
1 5 10 15

<210> 345
<211> 24
<212> PRT
<213> Artificial Sequence

<220>
<223> P16219 mitochondrial targeting peptide

<400> 345

Met Ala Ala Ala Leu Leu Ala Arg Ala Ser Gly Pro Ala Arg Arg Ala
1 5 10 15

Leu Cys Pro Arg Ala Trp Arg Gln
20

<210> 346
<211> 39
<212> PRT
<213> Artificial Sequence

<220>
<223> P17540 mitochondrial targeting peptide

<400> 346

Met Ala Ser Ile Phe Ser Lys Leu Leu Thr Gly Arg Asn Ala Ser Leu
1 5 10 15

Leu Phe Ala Thr Met Gly Thr Ser Val Leu Thr Thr Gly Tyr Leu Leu
20 25 30

Asn Arg Gln Lys Val Cys Ala
35

<210> 347
<211> 32
<212> PRT
<213> Artificial Sequence

<220>
<223> P18859 mitochondrial targeting peptide

<400> 347

Met Ile Leu Gln Arg Leu Phe Arg Phe Ser Ser Val Ile Arg Ser Ala
1 5 10 15

Val Ser Val His Leu Arg Arg Asn Ile Gly Val Thr Ala Val Ala Phe
20 25 30

<210> 348
<211> 24
<212> PRT
<213> Artificial Sequence

<220>
<223> P19099 mitochondrial targeting peptide

<400> 348

Met Ala Leu Arg Ala Lys Ala Glu Val Cys Val Ala Ala Pro Trp Leu
1 5 10 15

Ser Leu Gln Arg Ala Arg Ala Leu
20

<210> 349
<211> 32
<212> PRT
<213> Artificial Sequence

<220>
<223> P19404 mitochondrial targeting peptide

<400> 349

Met Phe Phe Ser Ala Ala Leu Arg Ala Arg Ala Ala Gly Leu Thr Ala
1 5 10 15

His Trp Gly Arg His Val Arg Asn Leu His Lys Thr Val Met Gln Asn
20 25 30

<210> 350
<211> 41
<212> PRT
<213> Artificial Sequence

<220>
<223> P20674 mitochondrial targeting peptide

<400> 350

Met Leu Gly Ala Ala Leu Arg Arg Cys Ala Val Ala Ala Thr Thr Arg
1 5 10 15

Ala Asp Pro Arg Gly Leu Leu His Ser Ala Arg Thr Pro Gly Pro Ala
20 25 30

Val Ala Ile Gln Ser Val Arg Cys Tyr
35 40

<210> 351
<211> 28
<212> PRT
<213> Artificial Sequence

<220>
<223> P21912 mitochondrial targeting peptide

<400> 351

Met Ala Ala Val Val Ala Leu Ser Leu Arg Arg Arg Leu Pro Ala Thr
1 5 10 15

Thr Leu Gly Gly Ala Cys Leu Gln Ala Ser Arg Gly
20 25

<210> 352
<211> 50
<212> PRT
<213> Artificial Sequence

<220>
<223> P21953 mitochondrial targeting peptide

<400> 352

Met Ala Val Val Ala Ala Ala Ala Gly Trp Leu Leu Arg Leu Arg Ala
1 5 10 15

Ala Gly Ala Glu Gly His Trp Arg Arg Leu Pro Gly Ala Gly Leu Ala
20 25 30

Arg Gly Phe Leu His Pro Ala Ala Thr Val Glu Asp Ala Ala Gln Arg
35 40 45

Arg Gln
50

<210> 353
<211> 32
<212> PRT
<213> Artificial Sequence

<220>
<223> P22033 mitochondrial targeting peptide

<400> 353

Met Leu Arg Ala Lys Asn Gln Leu Phe Leu Leu Ser Pro His Tyr Leu
1 5 10 15

Arg Gln Val Lys Glu Ser Ser Gly Ser Arg Leu Ile Gln Gln Arg Leu

20 25 30

<210> 354
<211> 49
<212> PRT
<213> Artificial Sequence

<220>
<223> P22557 mitochondrial targeting peptide

<400> 354

Met Val Thr Ala Ala Met Leu Leu Gln Cys Cys Pro Val Leu Ala Arg
1 5 10 15

Gly Pro Thr Ser Leu Leu Gly Lys Val Val Lys Thr His Gln Phe Leu
20 25 30

Phe Gly Ile Gly Arg Cys Pro Ile Leu Ala Thr Gln Gly Pro Asn Cys
35 40 45

Ser

<210> 355
<211> 32
<212> PRT
<213> Artificial Sequence

<220>
<223> P22570 mitochondrial targeting peptide

<400> 355

Met Ala Ser Arg Cys Trp Arg Trp Trp Gly Trp Ser Ala Trp Pro Arg
1 5 10 15

Thr Arg Leu Pro Pro Ala Gly Ser Thr Pro Ser Phe Cys His His Phe
20 25 30

<210> 356
<211> 14
<212> PRT
<213> Artificial Sequence

<220>
<223> P22695 mitochondrial targeting peptide

<400> 356

Met Lys Leu Leu Thr Arg Ala Gly Ser Phe Ser Arg Phe Tyr
1 5 10

<210> 357
<211> 54
<212> PRT
<213> Artificial Sequence

<220>
<223> P22830 mitochondrial targeting peptide

<400> 357

Met Arg Ser Leu Gly Ala Asn Met Ala Ala Ala Leu Arg Ala Ala Gly
1 5 10 15

Val Leu Leu Arg Asp Pro Leu Ala Ser Ser Ser Trp Arg Val Cys Gln
20 25 30

Pro Trp Arg Trp Lys Ser Gly Ala Ala Ala Ala Ala Val Thr Thr Glu
35 40 45

Thr Ala Gln His Ala Gln
50

<210> 358
<211> 18
<212> PRT
<213> Artificial Sequence

<220>
<223> P23368 mitochondrial targeting peptide

<400> 358

Met Leu Ser Arg Leu Arg Val Val Ser Thr Thr Cys Thr Leu Ala Cys
1 5 10 15

Arg His

<210> 359
<211> 35
<212> PRT
<213> Artificial Sequence

<220>
<223> P23378 mitochondrial targeting peptide

<400> 359

Met Gln Ser Cys Ala Arg Ala Trp Gly Leu Arg Leu Gly Arg Gly Val
1 5 10 15

Gly Gly Gly Arg Arg Leu Ala Gly Gly Ser Gly Pro Cys Trp Ala Pro
20 25 30

Arg Ser Arg
35

<210> 360
<211> 48
<212> PRT
<213> Artificial Sequence

<220>
<223> P23434 mitochondrial targeting peptide

<400> 360

Met Ala Leu Arg Val Val Arg Ser Val Arg Ala Leu Leu Cys Thr Leu
1 5 10 15

Arg Ala Val Pro Ser Pro Ala Ala Pro Cys Pro Pro Arg Pro Trp Gln
20 25 30

Leu Gly Val Gly Ala Val Arg Thr Leu Arg Thr Gly Pro Ala Leu Leu
35 40 45

<210> 361
<211> 25
<212> PRT
<213> Artificial Sequence

<220>
<223> P23786 mitochondrial targeting peptide

<400> 361

Met Val Pro Arg Leu Leu Leu Arg Ala Trp Pro Arg Gly Pro Ala Val
1 5 10 15

Gly Pro Gly Ala Pro Ser Arg Pro Leu
20 25

<210> 362
<211> 21
<212> PRT
<213> Artificial Sequence

<220>
<223> P24310 mitochondrial targeting peptide

<400> 362

Met Gln Ala Leu Arg Val Ser Gln Ala Leu Ile Arg Ser Phe Ser Ser
1 5 10 15

Thr Ala Arg Asn Arg
20

<210> 363
<211> 24
<212> PRT
<213> Artificial Sequence

<220>
<223> P24311 mitochondrial targeting peptide

<400> 363

Met Phe Pro Leu Val Lys Ser Ala Leu Asn Arg Leu Gln Val Arg Ser
1 5 10 15

Ile Gln Gln Thr Met Ala Arg Gln
20

<210> 364

<211> 42
<212> PRT
<213> Artificial Sequence

<220>
<223> P24539 mitochondrial targeting peptide

<400> 364

Met Leu Ser Arg Val Val Leu Ser Ala Ala Ala Thr Ala Ala Pro Ser
1 5 10 15

Leu Lys Asn Ala Ala Phe Leu Gly Pro Gly Val Leu Gln Ala Thr Arg
20 25 30

Thr Phe His Thr Gly Gln Pro His Leu Val
35 40

<210> 365
<211> 33
<212> PRT
<213> Artificial Sequence

<220>
<223> P24752 mitochondrial targeting peptide

<400> 365

Met Ala Val Leu Ala Ala Leu Leu Arg Ser Gly Ala Arg Ser Arg Ser
1 5 10 15

Pro Leu Leu Arg Arg Leu Val Gln Glu Ile Arg Tyr Val Glu Arg Ser
20 25 30

Tyr

<210> 366
<211> 43
<212> PRT
<213> Artificial Sequence

<220>
<223> P25705 mitochondrial targeting peptide

<400> 366

Met Leu Ser Val Arg Val Ala Ala Ala Val Val Arg Ala Leu Pro Arg
1 5 10 15

Arg Ala Gly Leu Val Ser Arg Asn Ala Leu Gly Ser Ser Phe Ile Ala
20 25 30

Ala Arg Asn Phe His Ala Ser Asn Thr His Leu
35 40

<210> 367
<211> 29
<212> PRT

<213> Artificial Sequence

<220>
<223> P26440 mitochondrial targeting peptide

<400> 367

Met Ala Thr Ala Thr Arg Leu Leu Gly Trp Arg Val Ala Ser Trp Arg
1 5 10 15

Leu Arg Pro Pro Leu Ala Gly Phe Val Ser Gln Arg Ala
20 25

<210> 368
<211> 30
<212> PRT
<213> Artificial Sequence

<220>
<223> P28330 mitochondrial targeting peptide

<400> 368

Met Ala Ala Arg Leu Leu Arg Gly Ser Leu Arg Val Leu Gly Gly His
1 5 10 15

Arg Ala Pro Arg Gln Leu Pro Ala Ala Arg Cys Ser His Ser
20 25 30

<210> 369
<211> 23
<212> PRT
<213> Artificial Sequence

<220>
<223> P28331 mitochondrial targeting peptide

<400> 369

Met Leu Arg Ile Pro Val Arg Lys Ala Leu Val Gly Leu Ser Lys Ser
1 5 10 15

Pro Lys Gly Cys Val Arg Thr
20

<210> 370
<211> 17
<212> PRT
<213> Artificial Sequence

<220>
<223> P29372 mitochondrial targeting peptide

<400> 370

Met Val Thr Pro Ala Leu Gln Met Lys Lys Pro Lys Gln Phe Cys Arg
1 5 10 15

Arg

<210> 371
<211> 27
<212> PRT
<213> Artificial Sequence

<220>
<223> P29803 mitochondrial targeting peptide

<400> 371

Met Leu Ala Ala Phe Ile Ser Arg Val Leu Arg Arg Val Ala Gln Lys
1 5 10 15

Ser Ala Arg Arg Val Leu Val Ala Ser Arg Asn
20 25

<210> 372
<211> 24
<212> PRT
<213> Artificial Sequence

<220>
<223> P30038 mitochondrial targeting peptide

<400> 372

Met Leu Leu Pro Ala Pro Ala Leu Arg Arg Ala Leu Leu Ser Arg Pro
1 5 10 15

Trp Thr Gly Ala Gly Leu Arg Trp
20

<210> 373
<211> 41
<212> PRT
<213> Artificial Sequence

<220>
<223> P30042 mitochondrial targeting peptide

<400> 373

Met Ala Ala Val Arg Val Leu Val Ala Ser Arg Leu Ala Ala Ala Ser
1 5 10 15

Ala Phe Thr Ser Leu Ser Pro Gly Gly Arg Thr Pro Ser Gln Arg Ala
20 25 30

Ala Leu His Leu Ser Val Pro Arg Pro
35 40

<210> 374
<211> 52
<212> PRT
<213> Artificial Sequence

<220>
<223> P30044 mitochondrial targeting peptide

<400> 374

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Met Gly Leu Ala Gly Val Cys Ala Leu Arg Arg Ser Ala Gly Tyr Ile
1               5                   10                  15

Leu Val Gly Gly Ala Gly Gly Gln Ser Ala Ala Ala Ala Ala Arg Arg
            20                  25                  30

Tyr Ser Glu Gly Glu Trp Ala Ser Gly Gly Val Arg Ser Phe Ser Arg
        35                  40                  45

Ala Ala Ala Ala
    50
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<210> 375
<211> 62
<212> PRT
<213> Artificial Sequence

<220>
<223> P30048 mitochondrial targeting peptide

<400> 375

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Met Ala Ala Ala Val Gly Arg Leu Leu Arg Ala Ser Val Ala Arg His
1               5                   10                  15

Val Ser Ala Ile Pro Trp Gly Ile Ser Ala Thr Ala Ala Leu Arg Pro
            20                  25                  30

Ala Ala Cys Gly Arg Thr Ser Leu Thr Asn Leu Leu Cys Ser Gly Ser
        35                  40                  45

Ser Gln Ala Lys Leu Phe Ser Thr Ser Ser Ser Cys His Ala
    50                  55                  60
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<210> 376
<211> 22
<212> PRT
<213> Artificial Sequence

<220>
<223> P30049 mitochondrial targeting peptide

<400> 376

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Met Leu Pro Ala Ala Leu Leu Arg Arg Pro Gly Leu Gly Arg Leu Val
1               5                   10                  15

Arg His Ala Arg Ala Tyr
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<210> 377
<211> 27
<212> PRT
<213> Artificial Sequence

<220>
<223> P30084 mitochondrial targeting peptide

<400> 377

Met Ala Ala Leu Arg Val Leu Leu Ser Cys Val Arg Gly Pro Leu Arg
1 5 10 15

Pro Pro Val Arg Cys Pro Ala Trp Arg Pro Phe
20 25

<210> 378
<211> 29
<212> PRT
<213> Artificial Sequence

<220>
<223> P30405 mitochondrial targeting peptide

<400> 378

Met Leu Ala Leu Arg Cys Gly Ser Arg Trp Leu Gly Leu Leu Ser Val
1 5 10 15

Pro Arg Ser Val Pro Leu Arg Leu Pro Ala Ala Arg Ala
20 25

<210> 379
<211> 17
<212> PRT
<213> Artificial Sequence

<220>
<223> P30837 mitochondrial targeting peptide

<400> 379

Met Leu Arg Phe Leu Ala Pro Arg Leu Leu Ser Leu Gln Gly Arg Thr
1 5 10 15

Ala

<210> 380
<211> 43
<212> PRT
<213> Artificial Sequence

<220>
<223> P31040 mitochondrial targeting peptide

<400> 380

Met Ser Gly Val Arg Gly Leu Ser Arg Leu Leu Ser Ala Arg Arg Leu
1 5 10 15

Ala Leu Ala Lys Ala Trp Pro Thr Val Leu Gln Thr Gly Thr Arg Gly
20 25 30

Phe His Phe Thr Val Asp Gly Asn Lys Arg Ala
35 40

<210> 381
<211> 38
<212> PRT
<213> Artificial Sequence

<220>
<223> P31327 mitochondrial targeting peptide

<400> 381

Met Thr Arg Ile Leu Thr Ala Phe Lys Val Val Arg Thr Leu Lys Thr
1 5 10 15

Gly Phe Gly Phe Thr Asn Val Thr Ala His Gln Lys Trp Lys Phe Ser
20 25 30

Arg Pro Gly Ile Arg Leu
35

<210> 382
<211> 34
<212> PRT
<213> Artificial Sequence

<220>
<223> P31930 mitochondrial targeting peptide

<400> 382

Met Ala Ala Ser Val Val Cys Arg Ala Ala Thr Ala Gly Ala Gln Val
1 5 10 15

Leu Leu Arg Ala Arg Arg Ser Pro Ala Leu Leu Arg Thr Pro Ala Leu
20 25 30

Arg Ser

<210> 383
<211> 36
<212> PRT
<213> Artificial Sequence

<220>
<223> P31937 mitochondrial targeting peptide

<400> 383

Met Ala Ala Ser Leu Arg Leu Leu Gly Ala Ala Ser Gly Leu Arg Tyr
1 5 10 15

Trp Ser Arg Arg Leu Arg Pro Ala Ala Gly Ser Phe Ala Ala Val Cys
20 25 30

Ser Arg Ser Val
35

<210> 384

<211> 69
<212> PRT
<213> Artificial Sequence

<220>
<223> P33316 mitochondrial targeting peptide

<400> 384

Met Thr Pro Leu Cys Pro Arg Pro Ala Leu Cys Tyr His Phe Leu Thr
1 5 10 15

Ser Leu Leu Arg Ser Ala Met Gln Asn Ala Arg Gly Ala Arg Gln Arg
20 25 30

Ala Glu Ala Ala Val Leu Ser Gly Pro Gly Pro Pro Leu Gly Arg Ala
35 40 45

Ala Gln His Gly Ile Pro Arg Pro Leu Ser Ser Ala Gly Arg Leu Ser
50 55 60

Gln Gly Cys Arg Gly
65

<210> 385
<211> 29
<212> PRT
<213> Artificial Sequence

<220>
<223> P34897 mitochondrial targeting peptide

<400> 385

Met Leu Tyr Phe Ser Leu Phe Trp Ala Ala Arg Pro Leu Gln Arg Cys
1 5 10 15

Gly Gln Leu Val Arg Met Ala Ile Arg Ala Gln His Ser
20 25

<210> 386
<211> 38
<212> PRT
<213> Artificial Sequence

<220>
<223> P35218 mitochondrial targeting peptide

<400> 386

Met Leu Gly Arg Asn Thr Trp Lys Thr Ser Ala Phe Ser Phe Leu Val
1 5 10 15

Glu Gln Met Trp Ala Pro Leu Trp Ser Arg Ser Met Arg Pro Gly Arg
20 25 30

Trp Cys Ser Gln Arg Ser
35

<210> 387
<211> 27
<212> PRT
<213> Artificial Sequence

<220>
<223> P35914 mitochondrial targeting peptide

<400> 387

Met Ala Ala Met Arg Lys Ala Leu Pro Arg Arg Leu Val Gly Leu Ala
1 5 10 15

Ser Leu Arg Ala Val Ser Thr Ser Ser Met Gly
20 25

<210> 388
<211> 25
<212> PRT
<213> Artificial Sequence

<220>
<223> P36542 mitochondrial targeting peptide

<400> 388

Met Phe Ser Arg Ala Gly Val Ala Gly Leu Ser Ala Trp Thr Leu Gln
1 5 10 15

Pro Gln Trp Ile Gln Val Arg Asn Met
20 25

<210> 389
<211> 110
<212> PRT
<213> Artificial Sequence

<220>
<223> P36551 mitochondrial targeting peptide

<400> 389

Met Ala Leu Gln Leu Gly Arg Leu Ser Ser Gly Pro Cys Trp Leu Val
1 5 10 15

Ala Arg Gly Gly Cys Gly Gly Pro Arg Ala Trp Ser Gln Cys Gly Gly
20 25 30

Gly Gly Leu Arg Ala Trp Ser Gln Arg Ser Ala Ala Gly Arg Val Cys
35 40 45

Arg Pro Pro Gly Pro Ala Gly Thr Glu Gln Ser Arg Gly Leu Gly His
50 55 60

Gly Ser Thr Ser Arg Gly Gly Pro Trp Val Gly Thr Gly Leu Ala Ala
65 70 75 80

Ala Leu Ala Gly Leu Val Gly Leu Ala Thr Ala Ala Phe Gly His Val

85 90 95

Gln Arg Ala Glu Met Leu Pro Lys Thr Ser Gly Thr Arg Ala
100 105 110

<210> 390
<211> 18
<212> PRT
<213> Artificial Sequence

<220>
<223> P36639 mitochondrial targeting peptide

<400> 390

Met Tyr Trp Ser Asn Gln Ile Thr Arg Arg Leu Gly Glu Arg Val Gln
1 5 10 15

Gly Phe

<210> 391
<211> 67
<212> PRT
<213> Artificial Sequence

<220>
<223> P36776 mitochondrial targeting peptide

<400> 391

Met Ala Ala Ser Thr Gly Tyr Val Arg Leu Trp Gly Ala Ala Arg Cys
1 5 10 15

Trp Val Leu Arg Arg Pro Met Leu Ala Ala Ala Gly Gly Arg Val Pro
20 25 30

Thr Ala Ala Gly Ala Trp Leu Leu Arg Gly Gln Arg Thr Cys Asp Ala
35 40 45

Ser Pro Pro Trp Ala Leu Trp Gly Arg Gly Pro Ala Ile Gly Gly Gln
50 55 60

Trp Arg Gly
65

<210> 392
<211> 67
<212> PRT
<213> Artificial Sequence

<220>
<223> P36957 mitochondrial targeting peptide

<400> 392

Met Leu Ser Arg Ser Arg Cys Val Ser Arg Ala Phe Ser Arg Ser Leu
1 5 10 15

Ser Ala Phe Gln Lys Gly Asn Cys Pro Leu Gly Arg Arg Ser Leu Pro
20 25 30

Gly Val Ser Leu Cys Gln Gly Pro Gly Tyr Pro Asn Ser Arg Lys Val
35 40 45

Val Ile Asn Asn Ser Val Phe Ser Val Arg Phe Phe Arg Thr Thr Ala
50 55 60

Val Cys Lys
65

<210> 393
<211> 46
<212> PRT
<213> Artificial Sequence

<220>
<223> P38646 mitochondrial targeting peptide

<400> 393

Met Ile Ser Ala Ser Arg Ala Ala Ala Ala Arg Leu Val Gly Ala Ala
1 5 10 15

Ala Ser Arg Gly Pro Thr Ala Ala Arg His Gln Asp Ser Trp Asn Gly
20 25 30

Leu Ser His Glu Ala Phe Arg Leu Val Ser Arg Arg Asp Tyr
35 40 45

<210> 394
<211> 33
<212> PRT
<213> Artificial Sequence

<220>
<223> P40305 mitochondrial targeting peptide

<400> 394

Met Glu Ala Ser Ala Leu Thr Ser Ser Ala Val Thr Ser Val Ala Lys
1 5 10 15

Val Val Arg Val Ala Ser Gly Ser Ala Val Val Leu Pro Leu Ala Arg
20 25 30

Ile

<210> 395
<211> 24
<212> PRT
<213> Artificial Sequence

<220>
<223> P40926 mitochondrial targeting peptide

<400> 395

Met Leu Ser Ala Leu Ala Arg Pro Ala Ser Ala Ala Leu Arg Arg Ser
1 5 10 15

Phe Ser Thr Ser Ala Gln Asn Asn
20

<210> 396
<211> 36
<212> PRT
<213> Artificial Sequence

<220>
<223> P40939 mitochondrial targeting peptide

<400> 396

Met Val Ala Cys Arg Ala Ile Gly Ile Leu Ser Arg Phe Ser Ala Phe
1 5 10 15

Arg Ile Leu Arg Ser Arg Gly Tyr Ile Cys Arg Asn Phe Thr Gly Ser
20 25 30

Ser Ala Leu Leu
35

<210> 397
<211> 41
<212> PRT
<213> Artificial Sequence

<220>
<223> P42126 mitochondrial targeting peptide

<400> 397

Met Ala Leu Val Ala Ser Val Arg Val Pro Ala Arg Val Leu Leu Arg
1 5 10 15

Ala Gly Ala Arg Leu Pro Gly Ala Ala Leu Gly Arg Thr Glu Arg Ala
20 25 30

Ala Gly Gly Gly Asp Gly Ala Arg Arg
35 40

<210> 398
<211> 59
<212> PRT
<213> Artificial Sequence

<220>
<223> P42704 mitochondrial targeting peptide

<400> 398

Met Ala Ala Leu Leu Arg Ser Ala Arg Trp Leu Leu Arg Ala Gly Ala
1 5 10 15

Ala Pro Arg Leu Pro Leu Ser Leu Arg Leu Leu Pro Gly Gly Pro Gly
20 25 30

Arg Leu His Ala Ala Ser Tyr Leu Pro Ala Ala Arg Ala Gly Pro Val
35 40 45

Ala Gly Gly Leu Leu Ser Pro Ala Arg Leu Tyr
50 55

<210> 399
<211> 16
<212> PRT
<213> Artificial Sequence

<220>
<223> P42765 mitochondrial targeting peptide

<400> 399

Met Ala Leu Leu Arg Gly Val Phe Val Val Ala Ala Lys Arg Thr Pro
1 5 10 15

<210> 400
<211> 42
<212> PRT
<213> Artificial Sequence

<220>
<223> P43304 mitochondrial targeting peptide

<400> 400

Met Ala Phe Gln Lys Ala Val Lys Gly Thr Ile Leu Val Gly Gly Gly
1 5 10 15

Ala Leu Ala Thr Val Leu Gly Leu Ser Gln Phe Ala His Tyr Arg Arg
20 25 30

Lys Gln Met Asn Leu Ala Tyr Val Lys Ala
35 40

<210> 401
<211> 45
<212> PRT
<213> Artificial Sequence

<220>
<223> P43897 mitochondrial targeting peptide

<400> 401

Met Ser Leu Leu Arg Ser Leu Arg Val Phe Leu Val Ala Arg Thr Gly
1 5 10 15

Ser Tyr Pro Ala Gly Ser Leu Leu Arg Gln Ser Pro Gln Pro Arg His
20 25 30

Thr Phe Tyr Ala Gly Pro Arg Leu Ser Ala Ser Ala Ser

35 40 45

<210> 402
<211> 33
<212> PRT
<213> Artificial Sequence

<220>
<223> P45954 mitochondrial targeting peptide

<400> 402

Met Glu Gly Leu Ala Val Arg Leu Leu Arg Gly Ser Arg Leu Leu Arg
1 5 10 15

Arg Asn Phe Leu Thr Cys Leu Ser Ser Trp Lys Ile Pro Pro His Val
20 25 30

Ser

<210> 403
<211> 29
<212> PRT
<213> Artificial Sequence

<220>
<223> P46199 mitochondrial targeting peptide

<400> 403

Met Asn Gln Lys Leu Leu Lys Leu Glu Asn Leu Leu Arg Phe His Thr
1 5 10 15

Ile Tyr Arg Gln Leu His Ser Leu Cys Gln Arg Arg Ala
20 25

<210> 404
<211> 78
<212> PRT
<213> Artificial Sequence

<220>
<223> P47985 mitochondrial targeting peptide

<400> 404

Met Leu Ser Val Ala Ser Arg Ser Gly Pro Phe Ala Pro Val Leu Ser
1 5 10 15

Ala Thr Ser Arg Gly Val Ala Gly Ala Leu Arg Pro Leu Val Gln Ala
20 25 30

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

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

Val Ala Ser Val Gly Leu Asn Val Pro Ala Ser Val Cys Tyr
65 70 75

<210> 405
<211> 23
<212> PRT
<213> Artificial Sequence

<220>
<223> P48047 mitochondrial targeting peptide

<400> 405

Met Ala Ala Pro Ala Val Ser Gly Leu Ser Arg Gln Val Arg Cys Phe
1 5 10 15

Ser Thr Ser Val Val Arg Pro
20

<210> 406
<211> 67
<212> PRT
<213> Artificial Sequence

<220>
<223> P48201 mitochondrial targeting peptide

<400> 406

Met Phe Ala Cys Ala Lys Leu Ala Cys Thr Pro Ser Leu Ile Arg Ala
1 5 10 15

Gly Ser Arg Val Ala Tyr Arg Pro Ile Ser Ala Ser Val Leu Ser Arg
20 25 30

Pro Glu Ala Ser Arg Thr Gly Glu Gly Ser Thr Val Phe Asn Gly Ala
35 40 45

Gln Asn Gly Val Ser Gln Leu Ile Gln Arg Glu Phe Gln Thr Ser Ala
50 55 60

Ile Ser Arg
65

<210> 407
<211> 28
<212> PRT
<213> Artificial Sequence

<220>
<223> P48728 mitochondrial targeting peptide

<400> 407

Met Gln Arg Ala Val Ser Val Val Ala Arg Leu Gly Phe Arg Leu Gln
1 5 10 15

Ala Phe Pro Pro Ala Leu Cys Arg Pro Leu Ser Cys

20 25

<210> 408
<211> 39
<212> PRT
<213> Artificial Sequence

<220>
<223> P48735 mitochondrial targeting peptide

<400> 408

Met Ala Gly Tyr Leu Arg Val Val Arg Ser Leu Cys Arg Ala Ser Gly
1 5 10 15

Ser Arg Pro Ala Trp Ala Pro Ala Ala Leu Thr Ala Pro Thr Ser Gln
20 25 30

Glu Gln Pro Arg Arg His Tyr
35

<210> 409
<211> 43
<212> PRT
<213> Artificial Sequence

<220>
<223> P49411 mitochondrial targeting peptide

<400> 409

Met Ala Ala Ala Thr Leu Leu Arg Ala Thr Pro His Phe Ser Gly Leu
1 5 10 15

Ala Ala Gly Arg Thr Phe Leu Leu Gln Gly Leu Leu Arg Leu Leu Lys
20 25 30

Ala Pro Ala Leu Pro Leu Leu Cys Arg Gly Leu
35 40

<210> 410
<211> 26
<212> PRT
<213> Artificial Sequence

<220>
<223> P49419 mitochondrial targeting peptide

<400> 410

Met Trp Arg Leu Pro Arg Ala Leu Cys Val His Ala Ala Lys Thr Ser
1 5 10 15

Lys Leu Ser Gly Pro Trp Ser Arg Pro Ala
20 25

<210> 411
<211> 53
<212> PRT

<213> Artificial Sequence

<220>
<223> P49448 mitochondrial targeting peptide

<400> 411

Met Tyr Arg Tyr Leu Ala Lys Ala Leu Leu Pro Ser Arg Ala Gly Pro
1 5 10 15

Ala Ala Leu Gly Ser Ala Ala Asn His Ser Ala Ala Leu Leu Gly Arg
20 25 30

Gly Arg Gly Gln Pro Ala Ala Ala Ser Gln Pro Gly Leu Ala Leu Ala
35 40 45

Ala Arg Arg His Tyr
50

<210> 412
<211> 33
<212> PRT
<213> Artificial Sequence

<220>
<223> P49590 mitochondrial targeting peptide

<400> 412

Met Pro Leu Leu Gly Leu Leu Pro Arg Arg Ala Trp Ala Ser Leu Leu
1 5 10 15

Ser Gln Leu Leu Arg Pro Pro Cys Ala Ser Cys Thr Gly Ala Val Arg
20 25 30

Cys

<210> 413
<211> 63
<212> PRT
<213> Artificial Sequence

<220>
<223> P49675 mitochondrial targeting peptide

<400> 413

Met Leu Leu Ala Thr Phe Lys Leu Cys Ala Gly Ser Ser Tyr Arg His
1 5 10 15

Met Arg Asn Met Lys Gly Leu Arg Gln Gln Ala Val Met Ala Ile Ser
20 25 30

Gln Glu Leu Asn Arg Arg Ala Leu Gly Gly Pro Thr Pro Ser Thr Trp
35 40 45

Ile Asn Gln Val Arg Arg Arg Ser Ser Leu Leu Gly Ser Arg Leu

50 55 60

<210> 414
<211> 40
<212> PRT
<213> Artificial Sequence

<220>
<223> P49748 mitochondrial targeting peptide

<400> 414

Met Gln Ala Ala Arg Met Ala Ala Ser Leu Gly Arg Gln Leu Leu Arg
1 5 10 15

Leu Gly Gly Gly Ser Ser Arg Leu Thr Ala Leu Leu Gly Gln Pro Arg
20 25 30

Pro Gly Pro Ala Arg Arg Pro Tyr
35 40

<210> 415
<211> 20
<212> PRT
<213> Artificial Sequence

<220>
<223> P49821 mitochondrial targeting peptide

<400> 415

Met Leu Ala Thr Arg Arg Leu Leu Gly Trp Ser Leu Pro Ala Arg Val
1 5 10 15

Ser Val Arg Phe
20

<210> 416
<211> 42
<212> PRT
<213> Artificial Sequence

<220>
<223> P49916 mitochondrial targeting peptide

<400> 416

Met Ser Leu Ala Phe Lys Ile Phe Phe Pro Gln Thr Leu Arg Ala Leu
1 5 10 15

Ser Arg Lys Glu Leu Cys Leu Phe Arg Lys His His Trp Arg Asp Val
20 25 30

Arg Gln Phe Ser Gln Trp Ser Glu Thr Asp
35 40

<210> 417
<211> 27
<212> PRT

<213> Artificial Sequence

<220>
<223> P50213 mitochondrial targeting peptide

<400> 417

Met Ala Gly Pro Ala Trp Ile Ser Lys Val Ser Arg Leu Leu Gly Ala
1 5 10 15

Phe His Asn Pro Lys Gln Val Thr Arg Gly Phe
20 25

<210> 418
<211> 37
<212> PRT
<213> Artificial Sequence

<220>
<223> P50440 mitochondrial targeting peptide

<400> 418

Met Leu Arg Val Arg Cys Leu Arg Gly Gly Ser Arg Gly Ala Glu Ala
1 5 10 15

Val His Tyr Ile Gly Ser Arg Leu Gly Arg Thr Leu Thr Gly Trp Val
20 25 30

Gln Arg Thr Phe Gln
35

<210> 419
<211> 18
<212> PRT
<213> Artificial Sequence

<220>
<223> P51398 mitochondrial targeting peptide

<400> 419

Met Met Leu Lys Gly Ile Thr Arg Leu Ile Ser Arg Ile His Lys Leu
1 5 10 15

Asp Pro

<210> 420
<211> 39
<212> PRT
<213> Artificial Sequence

<220>
<223> P51553 mitochondrial targeting peptide

<400> 420

Met Ala Leu Lys Val Ala Thr Val Ala Gly Ser Ala Ala Lys Ala Val
1 5 10 15

Leu Gly Pro Ala Leu Leu Cys Arg Pro Trp Glu Val Leu Gly Ala His
20 25 30

Glu Val Pro Ser Arg Asn Ile
35

<210> 421
<211> 47
<212> PRT
<213> Artificial Sequence

<220>
<223> P51649 mitochondrial targeting peptide

<400> 421

Met Ala Thr Cys Ile Trp Leu Arg Ser Cys Gly Ala Arg Arg Leu Gly
1 5 10 15

Ser Thr Phe Pro Gly Cys Arg Leu Arg Pro Arg Ala Gly Gly Leu Val
20 25 30

Pro Ala Ser Gly Pro Ala Pro Gly Pro Ala Gln Leu Arg Cys Tyr
35 40 45

<210> 422
<211> 79
<212> PRT
<213> Artificial Sequence

<220>
<223> P51687 mitochondrial targeting peptide

<400> 422

Met Leu Leu Leu His Arg Ala Val Val Leu Arg Leu Gln Gln Ala Cys
1 5 10 15

Arg Leu Lys Ser Ile Pro Ser Arg Ile Cys Ile Gln Ala Cys Ser Thr
20 25 30

Asn Asp Ser Phe Gln Pro Gln Arg Pro Ser Leu Thr Phe Ser Gly Asp
35 40 45

Asn Ser Ser Thr Gln Gly Trp Arg Val Met Gly Thr Leu Leu Gly Leu
50 55 60

Gly Ala Val Leu Ala Tyr Gln Asp His Arg Cys Arg Ala Ala Gln
65 70 75

<210> 423
<211> 45
<212> PRT
<213> Artificial Sequence

<220>
<223> P52815 mitochondrial targeting peptide

<400> 423

Met Leu Pro Ala Ala Ala Arg Pro Leu Trp Gly Pro Cys Leu Gly Leu
1 5 10 15

Arg Ala Ala Ala Phe Arg Leu Ala Arg Arg Gln Val Pro Cys Val Cys
20 25 30

Ala Val Arg His Met Arg Ser Ser Gly His Gln Arg Cys
35 40 45

<210> 424
<211> 13
<212> PRT
<213> Artificial Sequence

<220>
<223> P53007 mitochondrial targeting peptide

<400> 424

Met Pro Ala Pro Arg Ala Pro Arg Ala Leu Ala Ala Ala
1 5 10

<210> 425
<211> 40
<212> PRT
<213> Artificial Sequence

<220>
<223> P53597 mitochondrial targeting peptide

<400> 425

Met Thr Ala Thr Leu Ala Ala Ala Ala Asp Ile Ala Thr Met Val Ser
1 5 10 15

Gly Ser Ser Gly Leu Ala Ala Ala Arg Leu Leu Ser Arg Ser Phe Leu
20 25 30

Leu Pro Gln Asn Gly Ile Arg His
35 40

<210> 426
<211> 37
<212> PRT
<213> Artificial Sequence

<220>
<223> P54868 mitochondrial targeting peptide

<400> 426

Met Gln Arg Leu Leu Thr Pro Val Lys Arg Ile Leu Gln Leu Thr Arg
1 5 10 15

Ala Val Gln Glu Thr Ser Leu Thr Pro Ala Arg Leu Leu Pro Val Ala
20 25 30

His Gln Arg Phe Ser
35

<210> 427
<211> 33
<212> PRT
<213> Artificial Sequence

<220>
<223> P55084 mitochondrial targeting peptide

<400> 427

Met Thr Ile Leu Thr Tyr Pro Phe Lys Asn Leu Pro Thr Ala Ser Lys
1 5 10 15

Trp Ala Leu Arg Phe Ser Ile Arg Pro Leu Ser Cys Ser Ser Gln Leu
20 25 30

Arg

<210> 428
<211> 39
<212> PRT
<213> Artificial Sequence

<220>
<223> P55809 mitochondrial targeting peptide

<400> 428

Met Ala Ala Leu Lys Leu Leu Ser Ser Gly Leu Arg Leu Cys Ala Ser
1 5 10 15

Ala Arg Gly Ser Gly Ala Thr Trp Tyr Lys Gly Cys Val Cys Ser Phe
20 25 30

Ser Thr Ser Ala His Arg His
35

<210> 429
<211> 34
<212> PRT
<213> Artificial Sequence

<220>
<223> P56181 mitochondrial targeting peptide

<400> 429

Met Ala Ala Pro Cys Leu Leu Arg Gln Gly Arg Ala Gly Ala Leu Lys
1 5 10 15

Thr Met Leu Gln Glu Ala Gln Val Phe Arg Gly Leu Ala Ser Thr Val
20 25 30

Ser Leu

<210> 430
<211> 24
<212> PRT
<213> Artificial Sequence

<220>
<223> P59942 mitochondrial targeting peptide

<400> 430

Met Val Leu Pro Leu Pro Trp Leu Ser Arg Tyr His Phe Leu Arg Leu
1 5 10 15

Leu Leu Pro Ser Trp Ser Leu Ala
20

<210> 431
<211> 22
<212> PRT
<213> Artificial Sequence

<220>
<223> P78540 mitochondrial targeting peptide

<400> 431

Met Ser Leu Arg Gly Ser Leu Ser Arg Leu Leu Gln Thr Arg Val His
1 5 10 15

Ser Ile Leu Lys Lys Ser
20

<210> 432
<211> 30
<212> PRT
<213> Artificial Sequence

<220>
<223> P78549 mitochondrial targeting peptide

<400> 432

Met Cys Ser Pro Gln Glu Ser Gly Met Thr Ala Leu Ser Ala Arg Met
1 5 10 15

Leu Thr Arg Ser Arg Ser Leu Gly Pro Gly Ala Gly Pro Arg
20 25 30

<210> 433
<211> 28
<212> PRT
<213> Artificial Sequence

<220>
<223> P80404 mitochondrial targeting peptide

<400> 433

Met Ala Ser Met Leu Leu Ala Gln Arg Leu Ala Cys Ser Phe Gln His

1 5 10 15

Ser Tyr Arg Leu Leu Val Pro Gly Ser Arg His Ile
20 25

<210> 434
<211> 57
<212> PRT
<213> Artificial Sequence

<220>
<223> P82914 mitochondrial targeting peptide

<400> 434

Met Leu Arg Val Ala Trp Arg Thr Leu Ser Leu Ile Arg Thr Arg Ala
1 5 10 15

Val Thr Gln Val Leu Val Pro Gly Leu Pro Gly Gly Gly Ser Ala Lys
20 25 30

Phe Pro Phe Asn Gln Trp Gly Leu Gln Pro Arg Ser Leu Leu Leu Gln
35 40 45

Ala Ala Arg Gly Tyr Val Val Arg Lys
50 55

<210> 435
<211> 115
<212> PRT
<213> Artificial Sequence

<220>
<223> P83111 mitochondrial targeting peptide

<400> 435

Met Tyr Arg Leu Met Ser Ala Val Thr Ala Arg Ala Ala Ala Pro Gly
1 5 10 15

Gly Leu Ala Ser Ser Cys Gly Arg Arg Gly Val His Gln Arg Ala Gly
20 25 30

Leu Pro Pro Leu Gly His Gly Trp Val Gly Gly Leu Gly Leu Gly Leu
35 40 45

Gly Leu Ala Leu Gly Val Lys Leu Ala Gly Gly Leu Arg Gly Ala Ala
50 55 60

Pro Ala Gln Ser Pro Ala Ala Pro Asp Pro Glu Ala Ser Pro Leu Ala
65 70 75 80

Glu Pro Pro Gln Glu Gln Ser Leu Ala Pro Trp Ser Pro Gln Thr Pro
85 90 95

Ala Pro Pro Cys Ser Arg Cys Phe Ala Arg Ala Ile Glu Ser Ser Arg

100 105 110

Asp Leu Leu
115

<210> 436
<211> 42
<212> PRT
<213> Artificial Sequence

<220>
<223> Q00059 mitochondrial targeting peptide

<400> 436

Met Ala Phe Leu Arg Ser Met Trp Gly Val Leu Ser Ala Leu Gly Arg
1 5 10 15

Ser Gly Ala Glu Leu Cys Thr Gly Cys Gly Ser Arg Leu Arg Ser Pro
20 25 30

Phe Ser Phe Val Tyr Leu Pro Arg Trp Phe
35 40

<210> 437
<211> 49
<212> PRT
<213> Artificial Sequence

<220>
<223> Q00325 mitochondrial targeting peptide

<400> 437

Met Phe Ser Ser Val Ala His Leu Ala Arg Ala Asn Pro Phe Asn Thr
1 5 10 15

Pro His Leu Gln Leu Val His Asp Gly Leu Gly Asp Leu Arg Ser Ser
20 25 30

Ser Pro Gly Pro Thr Gly Gln Pro Arg Arg Pro Arg Asn Leu Ala Ala
35 40 45

Ala

<210> 438
<211> 10
<212> PRT
<213> Artificial Sequence

<220>
<223> Q02127 mitochondrial targeting peptide

<400> 438

Met Ala Trp Arg His Leu Lys Lys Arg Ala
1 5 10

<210> 439
<211> 40
<212> PRT
<213> Artificial Sequence

<220>
<223> Q02218 mitochondrial targeting peptide

<400> 439

Met Phe His Leu Arg Thr Cys Ala Ala Lys Leu Arg Pro Leu Thr Ala
1 5 10 15

Ser Gln Thr Val Lys Thr Phe Ser Gln Asn Arg Pro Ala Ala Ala Arg
20 25 30

Thr Phe Gln Gln Ile Arg Cys Tyr
35 40

<210> 440
<211> 12
<212> PRT
<213> Artificial Sequence

<220>
<223> Q02221 mitochondrial targeting peptide

<400> 440

Met Ala Leu Pro Leu Arg Pro Leu Thr Arg Gly Leu
1 5 10

<210> 441
<211> 33
<212> PRT
<213> Artificial Sequence

<220>
<223> Q02252 mitochondrial targeting peptide

<400> 441

Met Ala Ala Leu Leu Ala Ala Ala Ala Val Arg Ala Arg Ile Leu Gln
1 5 10 15

Val Ser Ser Lys Val Lys Ser Ser Pro Thr Trp Tyr Ser Ala Ser Ser
20 25 30

Phe

<210> 442
<211> 33
<212> PRT
<213> Artificial Sequence

<220>
<223> Q02318 mitochondrial targeting peptide

<400> 442

Met Ala Ala Leu Gly Cys Ala Arg Leu Arg Trp Ala Leu Arg Gly Ala
1 5 10 15

Gly Arg Gly Leu Cys Pro His Gly Ala Arg Ala Lys Ala Ala Ile Pro
20 25 30

Ala

<210> 443
<211> 46
<212> PRT
<213> Artificial Sequence

<220>
<223> Q02338 mitochondrial targeting peptide

<400> 443

Met Leu Ala Thr Arg Leu Ser Arg Pro Leu Ser Arg Leu Pro Gly Lys
1 5 10 15

Thr Leu Ser Ala Cys Asp Arg Glu Asn Gly Ala Arg Arg Pro Leu Leu
20 25 30

Leu Gly Ser Thr Ser Phe Ile Pro Ile Gly Arg Arg Thr Tyr
35 40 45

<210> 444
<211> 16
<212> PRT
<213> Artificial Sequence

<220>
<223> Q04837 mitochondrial targeting peptide

<400> 444

Met Phe Arg Arg Pro Val Leu Gln Val Leu Arg Gln Phe Val Arg His
1 5 10 15

<210> 445
<211> 42
<212> PRT
<213> Artificial Sequence

<220>
<223> Q05932 mitochondrial targeting peptide

<400> 445

Met Ser Arg Ala Arg Ser His Leu Arg Ala Ala Leu Phe Leu Ala Ala
1 5 10 15

Ala Ser Ala Arg Gly Ile Thr Thr Gln Val Ala Ala Arg Arg Gly Leu
20 25 30

Ser Ala Trp Pro Val Pro Gln Glu Pro Ser

35 40

<210> 446
<211> 66
<212> PRT
<213> Artificial Sequence

<220>
<223> Q06055 mitochondrial targeting peptide

<400> 446

Met Phe Ala Cys Ser Lys Phe Val Ser Thr Pro Ser Leu Val Lys Ser
1 5 10 15

Thr Ser Gln Leu Leu Ser Arg Pro Leu Ser Ala Val Val Leu Lys Arg
20 25 30

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

Pro Leu Thr Ser Leu Val Ser Ser Arg Ser Phe Gln Thr Ser Ala Ile
50 55 60

Ser Arg
65

<210> 447
<211> 73
<212> PRT
<213> Artificial Sequence

<220>
<223> Q07021 mitochondrial targeting peptide

<400> 447

Met Leu Pro Leu Leu Arg Cys Val Pro Arg Val Leu Gly Ser Ser Val
1 5 10 15

Ala Gly Leu Arg Ala Ala Ala Pro Ala Ser Pro Phe Arg Gln Leu Leu
20 25 30

Gln Pro Ala Pro Arg Leu Cys Thr Arg Pro Phe Gly Leu Leu Ser Val
35 40 45

Arg Ala Gly Ser Glu Arg Arg Pro Gly Leu Leu Arg Pro Arg Gly Pro
50 55 60

Cys Ala Cys Gly Cys Gly Cys Gly Ser
65 70

<210> 448
<211> 35
<212> PRT
<213> Artificial Sequence

<220>
<223> Q07973 mitochondrial targeting peptide

<400> 448

Met Ser Ser Pro Ile Ser Lys Ser Arg Ser Leu Ala Ala Phe Leu Gln
1 5 10 15

Gln Leu Arg Ser Pro Arg Gln Pro Pro Arg Leu Val Thr Ser Thr Ala
20 25 30

Tyr Thr Ser
35

<210> 449
<211> 31
<212> PRT
<213> Artificial Sequence

<220>
<223> Q08AH1 mitochondrial targeting peptide

<400> 449

Met Gln Trp Leu Met Arg Phe Arg Thr Leu Trp Gly Ile His Lys Ser
1 5 10 15

Phe His Asn Ile His Pro Ala Pro Ser Gln Leu Arg Cys Arg Ser
20 25 30

<210> 450
<211> 46
<212> PRT
<213> Artificial Sequence

<220>
<223> Q08AH3 mitochondrial targeting peptide

<400> 450

Met His Trp Leu Arg Lys Val Gln Gly Leu Cys Thr Leu Trp Gly Thr
1 5 10 15

Gln Met Ser Ser Arg Thr Leu Tyr Ile Asn Ser Arg Gln Leu Val Ser
20 25 30

Leu Gln Trp Gly His Gln Glu Val Pro Ala Lys Phe Asn Phe
35 40 45

<210> 451
<211> 33
<212> PRT
<213> Artificial Sequence

<220>
<223> Q10713 mitochondrial targeting peptide

<400> 451

Met Ala Ala Val Val Leu Ala Ala Thr Arg Leu Leu Arg Gly Ser Gly

1 5 10 15

Ser Trp Gly Cys Ser Arg Leu Arg Phe Gly Pro Pro Ala Tyr Arg Arg
20 25 30

Phe

<210> 452
<211> 117
<212> PRT
<213> Artificial Sequence

<220>
<223> Q12849 mitochondrial targeting peptide

<400> 452

Met Ala Gly Thr Arg Trp Val Leu Gly Ala Leu Leu Arg Gly Cys Gly
1 5 10 15

Cys Asn Cys Ser Ser Cys Arg Arg Thr Gly Ala Ala Cys Leu Pro Phe
20 25 30

Tyr Ser Ala Ala Gly Ser Ile Pro Ser Gly Val Ser Gly Arg Arg Arg
35 40 45

Leu Leu Leu Leu Leu Gly Ala Ala Ala Ala Ala Ala Ser Gln Thr Arg
50 55 60

Gly Leu Gln Thr Gly Pro Val Pro Pro Gly Arg Leu Ala Gly Pro Pro
65 70 75 80

Ala Val Ala Thr Ser Ala Ala Ala Ala Ala Ala Ala Ser Tyr Ser Ala
85 90 95

Leu Arg Ala Ser Leu Leu Pro Gln Ser Leu Ala Ala Ala Ala Ala Val
100 105 110

Pro Thr Arg Ser Tyr
115

<210> 453
<211> 59
<212> PRT
<213> Artificial Sequence

<220>
<223> Q12931 mitochondrial targeting peptide

<400> 453

Met Ala Arg Glu Leu Arg Ala Leu Leu Leu Trp Gly Arg Arg Leu Arg
1 5 10 15

Pro Leu Leu Arg Ala Pro Ala Leu Ala Ala Val Pro Gly Gly Lys Pro

20 25 30

Ile Leu Cys Pro Arg Arg Thr Thr Ala Gln Leu Gly Pro Arg Arg Asn
35 40 45

Pro Ala Trp Ser Leu Gln Ala Gly Arg Leu Phe
50 55

<210> 454
<211> 33
<212> PRT
<213> Artificial Sequence

<220>
<223> Q13011 mitochondrial targeting peptide

<400> 454

Met Ala Ala Gly Ile Val Ala Ser Arg Arg Leu Arg Asp Leu Leu Thr
1 5 10 15

Arg Arg Leu Thr Gly Ser Asn Tyr Pro Gly Leu Ser Ile Ser Leu Arg
20 25 30

Leu

<210> 455
<211> 55
<212> PRT
<213> Artificial Sequence

<220>
<223> Q13084 mitochondrial targeting peptide

<400> 455

Met Pro Leu His Lys Tyr Pro Val Trp Leu Trp Lys Arg Leu Gln Leu
1 5 10 15

Arg Glu Gly Ile Cys Ser Arg Leu Pro Gly His Tyr Leu Arg Ser Leu
20 25 30

Glu Glu Glu Arg Thr Pro Thr Pro Val His Tyr Arg Pro His Gly Ala
35 40 45

Lys Phe Lys Ile Asn Pro Lys
50 55

<210> 456
<211> 23
<212> PRT
<213> Artificial Sequence

<220>
<223> Q13268 mitochondrial targeting peptide

<400> 456

Met Leu Ser Ala Val Ala Arg Gly Tyr Gln Gly Trp Phe His Pro Cys
1 5 10 15

Ala Arg Leu Ser Val Arg Met
20

<210> 457
<211> 43
<212> PRT
<213> Artificial Sequence

<220>
<223> Q13423 mitochondrial targeting peptide

<400> 457

Met Ala Asn Leu Leu Lys Thr Val Val Thr Gly Cys Ser Cys Pro Leu
1 5 10 15

Leu Ser Asn Leu Gly Ser Cys Lys Gly Leu Arg Val Lys Lys Asp Phe
20 25 30

Leu Arg Thr Phe Tyr Thr His Gln Glu Leu Trp
35 40

<210> 458
<211> 67
<212> PRT
<213> Artificial Sequence

<220>
<223> Q13825 mitochondrial targeting peptide

<400> 458

Met Ala Ala Ala Val Ala Ala Ala Pro Gly Ala Leu Gly Ser Leu His
1 5 10 15

Ala Gly Gly Ala Arg Leu Val Ala Ala Cys Ser Ala Trp Leu Cys Pro
20 25 30

Gly Leu Arg Leu Pro Gly Ser Leu Ala Gly Arg Arg Ala Gly Pro Ala
35 40 45

Ile Trp Ala Gln Gly Trp Val Pro Ala Ala Gly Gly Pro Ala Pro Lys
50 55 60

Arg Gly Tyr
65

<210> 459
<211> 101
<212> PRT
<213> Artificial Sequence

<220>
<223> Q14154 mitochondrial targeting peptide

<400> 459

Met Trp Arg Leu Pro Gly Leu Leu Gly Arg Ala Leu Pro Arg Thr Leu
1 5 10 15

Gly Pro Ser Leu Trp Arg Val Thr Pro Lys Ser Thr Ser Pro Asp Gly
20 25 30

Pro Gln Thr Thr Ser Ser Thr Leu Leu Val Pro Val Pro Asn Leu Asp
35 40 45

Arg Ser Gly Pro His Gly Pro Gly Thr Ser Gly Gly Pro Arg Ser His
50 55 60

Gly Trp Lys Asp Ala Phe Gln Trp Met Ser Ser Arg Val Ser Pro Asn
65 70 75 80

Thr Leu Trp Asp Ala Ile Ser Trp Gly Thr Leu Ala Val Leu Ala Leu
85 90 95

Gln Leu Ala Arg Gln
100

<210> 460
<211> 29
<212> PRT
<213> Artificial Sequence

<220>
<223> Q14197 mitochondrial targeting peptide

<400> 460

Met Ala Ala Thr Arg Cys Leu Arg Trp Gly Leu Ser Arg Ala Gly Val
1 5 10 15

Trp Leu Leu Pro Pro Pro Ala Arg Cys Pro Arg Arg Ala
20 25

<210> 461
<211> 48
<212> PRT
<213> Artificial Sequence

<220>
<223> Q14249 mitochondrial targeting peptide

<400> 461

Met Arg Ala Leu Arg Ala Gly Leu Thr Leu Ala Ser Gly Ala Gly Leu
1 5 10 15

Gly Ala Val Val Glu Gly Trp Arg Arg Arg Arg Glu Asp Ala Arg Ala
20 25 30

Ala Pro Gly Leu Leu Gly Arg Leu Pro Val Leu Pro Val Ala Ala Ala

35 40 45

<210> 462
<211> 28
<212> PRT
<213> Artificial Sequence

<220>
<223> Q15118 mitochondrial targeting peptide

<400> 462

Met Arg Leu Ala Arg Leu Leu Arg Gly Ala Ala Leu Ala Gly Pro Gly
1 5 10 15

Pro Gly Leu Arg Ala Ala Gly Phe Ser Arg Ser Phe
20 25

<210> 463
<211> 48
<212> PRT
<213> Artificial Sequence

<220>
<223> Q15390 mitochondrial targeting peptide

<400> 463

Met Leu Gly Trp Ile Lys Arg Leu Ile Arg Met Val Phe Gln Gln Val
1 5 10 15

Gly Val Ser Met Gln Ser Val Leu Trp Ser Arg Lys Pro Tyr Gly Ser
20 25 30

Ser Arg Ser Ile Val Arg Lys Ile Gly Thr Asn Leu Ser Leu Ile Gln
35 40 45

<210> 464
<211> 33
<212> PRT
<213> Artificial Sequence

<220>
<223> Q16134 mitochondrial targeting peptide

<400> 464

Met Leu Val Pro Leu Ala Lys Leu Ser Cys Leu Ala Tyr Gln Cys Phe
1 5 10 15

His Ala Leu Lys Ile Lys Lys Asn Tyr Leu Pro Leu Cys Ala Thr Arg
20 25 30

Trp

<210> 465
<211> 41
<212> PRT

<213> Artificial Sequence

<220>
<223> Q16595 mitochondrial targeting peptide

<400> 465

Met Trp Thr Leu Gly Arg Arg Ala Val Ala Gly Leu Leu Ala Ser Pro
1 5 10 15

Ser Pro Ala Gln Ala Gln Thr Leu Thr Arg Val Pro Arg Pro Ala Glu
20 25 30

Leu Ala Pro Leu Cys Gly Arg Arg Gly
35 40

<210> 466
<211> 34
<212> PRT
<213> Artificial Sequence

<220>
<223> Q16698 mitochondrial targeting peptide

<400> 466

Met Lys Leu Pro Ala Arg Val Phe Phe Thr Leu Gly Ser Arg Leu Pro
1 5 10 15

Cys Gly Leu Ala Pro Arg Arg Phe Phe Ser Tyr Gly Thr Lys Ile Leu
20 25 30

Tyr Gln

<210> 467
<211> 56
<212> PRT
<213> Artificial Sequence

<220>
<223> Q16740 mitochondrial targeting peptide

<400> 467

Met Trp Pro Gly Ile Leu Val Gly Gly Ala Arg Val Ala Ser Cys Arg
1 5 10 15

Tyr Pro Ala Leu Gly Pro Arg Leu Ala Ala His Phe Pro Ala Gln Arg
20 25 30

Pro Pro Gln Arg Thr Leu Gln Asn Gly Leu Ala Leu Gln Arg Cys Leu
35 40 45

His Ala Thr Ala Thr Arg Ala Leu
50 55

<210> 468

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

<220>
<223> Q16775 mitochondrial targeting peptide

<400> 468

Met Val Val Gly Arg Gly Leu Leu Gly Arg Arg Ser Leu
1 5 10

<210> 469
<211> 35
<212> PRT
<213> Artificial Sequence

<220>
<223> Q16795 mitochondrial targeting peptide

<400> 469

Met Ala Ala Ala Ala Gln Ser Arg Val Val Arg Val Leu Ser Met Ser
1 5 10 15

Arg Ser Ala Ile Thr Ala Ile Ala Thr Ser Val Cys His Gly Pro Pro
20 25 30

Cys Arg Gln
35

<210> 470
<211> 32
<212> PRT
<213> Artificial Sequence

<220>
<223> Q16822 mitochondrial targeting peptide

<400> 470

Met Ala Ala Leu Tyr Arg Pro Gly Leu Arg Leu Asn Trp His Gly Leu
1 5 10 15

Ser Pro Leu Gly Trp Pro Ser Cys Arg Ser Ile Gln Thr Leu Arg Val
20 25 30

<210> 471
<211> 12
<212> PRT
<213> Artificial Sequence

<220>
<223> Q16836 mitochondrial targeting peptide

<400> 471

Met Ala Phe Val Thr Arg Gln Phe Met Arg Ser Val
1 5 10

<210> 472

<211> 39
<212> PRT
<213> Artificial Sequence

<220>
<223> Q16854 mitochondrial targeting peptide

<400> 472

Met Ala Ala Gly Arg Leu Phe Leu Ser Arg Leu Arg Ala Pro Phe Ser
1 5 10 15

Ser Met Ala Lys Ser Pro Leu Glu Gly Val Ser Ser Ser Arg Gly Leu
20 25 30

His Ala Gly Arg Gly Pro Arg
35

<210> 473
<211> 33
<212> PRT
<213> Artificial Sequence

<220>
<223> Q16891 mitochondrial targeting peptide

<400> 473

Met Leu Arg Ala Cys Gln Leu Ser Gly Val Thr Ala Ala Ala Gln Ser
1 5 10 15

Cys Leu Cys Gly Lys Phe Val Leu Arg Pro Leu Arg Pro Cys Arg Arg
20 25 30

Tyr

<210> 474
<211> 25
<212> PRT
<213> Artificial Sequence

<220>
<223> Q2VYF4 mitochondrial targeting peptide

<400> 474

Met Ala Phe Tyr Ser Tyr Asn Ser Val Leu Ala Ile Ala Arg Thr Arg
1 5 10 15

Phe Pro Ser His Phe Val His Pro Thr
20 25

<210> 475
<211> 28
<212> PRT
<213> Artificial Sequence

<220>
<223> Q32NB8 mitochondrial targeting peptide

<400> 475

Met Ala Val Ala Ala Ala Ala Ala Gly Pro Val Phe Trp Arg Arg
1 5 10 15

Leu Leu Gly Leu Leu Pro Gly Arg Pro Gly Leu Ala
20 25

<210> 476
<211> 44
<212> PRT
<213> Artificial Sequence

<220>
<223> Q330K2 mitochondrial targeting peptide

<400> 476

Met Ala Ala Ser Ala His Gly Ser Val Trp Gly Pro Leu Arg Leu Gly
1 5 10 15

Ile Pro Gly Leu Cys Cys Arg Arg Pro Pro Leu Gly Leu Tyr Ala Arg
20 25 30

Met Arg Arg Leu Pro Gly Pro Glu Val Ser Gly Arg
35 40

<210> 477
<211> 19
<212> PRT
<213> Artificial Sequence

<220>
<223> Q3SY69 mitochondrial targeting peptide

<400> 477

Met Leu Arg Arg Gly Ser Gln Ala Leu Arg Arg Phe Ser Thr Gly Arg
1 5 10 15

Val Tyr Phe

<210> 478
<211> 44
<212> PRT
<213> Artificial Sequence

<220>
<223> Q3ZCQ8 mitochondrial targeting peptide

<400> 478

Met Ala Ala Ser Ala Ala Val Phe Ser Arg Leu Arg Ser Gly Leu Arg
1 5 10 15

Leu Gly Ser Arg Gly Leu Cys Thr Arg Leu Ala Thr Pro Pro Arg Arg
20 25 30

Ala Pro Asp Gln Ala Ala Glu Ile Gly Ser Arg Gly
35 40

<210> 479
<211> 35
<212> PRT
<213> Artificial Sequence

<220>
<223> Q49AM1 mitochondrial targeting peptide

<400> 479

Met Leu Trp Lys Leu Leu Leu Arg Ser Gln Ser Cys Arg Leu Cys Ser
1 5 10 15

Phe Arg Lys Met Arg Ser Pro Pro Lys Tyr Arg Pro Phe Leu Ala Cys
20 25 30

Phe Thr Tyr
35

<210> 480
<211> 62
<212> PRT
<213> Artificial Sequence

<220>
<223> Q4G0N4 mitochondrial targeting peptide

<400> 480

Met Thr Cys Tyr Arg Gly Phe Leu Leu Gly Ser Cys Cys Arg Val Ala
1 5 10 15

Gly Gly Arg Ala Ala Ala Leu Arg Gly Pro Gly Ala Gly Gly Pro Ala
20 25 30

Ala Arg Pro Arg Leu Gly Gly Asp Gly Gly Gly Arg Arg His Leu Gly
35 40 45

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

<210> 481
<211> 83
<212> PRT
<213> Artificial Sequence

<220>
<223> Q4G176 mitochondrial targeting peptide

<400> 481

Met Leu Pro His Val Val Leu Thr Phe Arg Arg Leu Gly Cys Ala Leu
1 5 10 15

Ala Ser Cys Arg Leu Ala Pro Ala Arg His Arg Gly Ser Gly Leu Leu

20 25 30

His Thr Ala Pro Val Ala Arg Ser Asp Arg Ser Ala Pro Val Phe Thr
35 40 45

Arg Ala Leu Ala Phe Gly Asp Arg Ile Ala Leu Val Asp Gln His Gly
50 55 60

Arg His Thr Tyr Arg Glu Leu Tyr Ser Arg Ser Leu Arg Leu Ser Gln
65 70 75 80

Glu Ile Cys

<210> 482
<211> 31
<212> PRT
<213> Artificial Sequence

<220>
<223> Q4U2R6 mitochondrial targeting peptide

<400> 482

Met Ala Gly Asn Leu Leu Ser Gly Ala Gly Arg Arg Leu Trp Asp Trp
1 5 10 15

Val Pro Leu Ala Cys Arg Ser Phe Ser Leu Gly Val Pro Arg Leu
20 25 30

<210> 483
<211> 27
<212> PRT
<213> Artificial Sequence

<220>
<223> Q53FZ2 mitochondrial targeting peptide

<400> 483

Met Leu Ala Arg Val Thr Arg Lys Met Leu Arg His Ala Lys Cys Phe
1 5 10 15

Gln Arg Leu Ala Ile Phe Gly Ser Val Arg Ala
20 25

<210> 484
<211> 31
<212> PRT
<213> Artificial Sequence

<220>
<223> Q53H12 mitochondrial targeting peptide

<400> 484

Met Thr Val Phe Phe Lys Thr Leu Arg Asn His Trp Lys Lys Thr Thr
1 5 10 15

Ala Gly Leu Cys Leu Leu Thr Trp Gly Gly His Trp Leu Tyr Gly
20 25 30

<210> 485
<211> 98
<212> PRT
<213> Artificial Sequence

<220>
<223> Q5EBM0 mitochondrial targeting peptide

<400> 485

Met Ala Phe Ala Arg Arg Leu Leu Arg Gly Pro Leu Ser Gly Pro Leu
1 5 10 15

Leu Gly Arg Arg Gly Val Cys Ala Gly Ala Met Ala Pro Pro Arg Arg
20 25 30

Phe Val Leu Glu Leu Pro Asp Cys Thr Leu Ala His Phe Ala Leu Gly
35 40 45

Ala Asp Ala Pro Gly Asp Ala Asp Ala Pro Asp Pro Arg Leu Ala Ala
50 55 60

Leu Leu Gly Pro Pro Glu Arg Ser Tyr Ser Leu Cys Val Pro Val Thr
65 70 75 80

Pro Asp Ala Gly Cys Gly Ala Arg Val Arg Ala Ala Arg Leu His Gln
85 90 95

Arg Leu

<210> 486
<211> 42
<212> PRT
<213> Artificial Sequence

<220>
<223> Q5HYK3 mitochondrial targeting peptide

<400> 486

Met Ala Ala Pro Gly Ser Cys Ala Leu Trp Ser Tyr Cys Gly Arg Gly
1 5 10 15

Trp Ser Arg Ala Met Arg Gly Cys Gln Leu Leu Gly Leu Arg Ser Ser
20 25 30

Trp Pro Gly Asp Leu Leu Ser Ala Arg Leu
35 40

<210> 487
<211> 41
<212> PRT

<213> Artificial Sequence

<220>
<223> Q5JPH6 mitochondrial targeting peptide

<400> 487

Met Ala Ala Leu Leu Arg Arg Leu Leu Gln Arg Glu Arg Pro Ser Ala
1 5 10 15

Ala Ser Gly Arg Pro Val Gly Arg Arg Glu Ala Asn Leu Gly Thr Asp
20 25 30

Ala Gly Val Ala Val Arg Val Arg Phe
35 40

<210> 488
<211> 15
<212> PRT
<213> Artificial Sequence

<220>
<223> Q5JRX3 mitochondrial targeting peptide

<400> 488

Met Trp Arg Cys Gly Gly Arg Gln Gly Leu Cys Val Leu Arg Arg
1 5 10 15

<210> 489
<211> 23
<212> PRT
<213> Artificial Sequence

<220>
<223> Q5JTZ9 mitochondrial targeting peptide

<400> 489

Met Ala Ala Ser Val Ala Ala Ala Ala Arg Arg Leu Arg Arg Ala Ile
1 5 10 15

Arg Arg Ser Pro Ala Trp Arg
20

<210> 490
<211> 26
<212> PRT
<213> Artificial Sequence

<220>
<223> Q5ST30 mitochondrial targeting peptide

<400> 490

Met Pro His Leu Pro Leu Ala Ser Phe Arg Pro Pro Phe Trp Gly Leu
1 5 10 15

Arg His Ser Arg Gly Leu Pro Arg Phe His
20 25

<210> 491
<211> 49
<212> PRT
<213> Artificial Sequence

<220>
<223> Q5SXM8 mitochondrial targeting peptide

<400> 491

Met Leu Arg Thr Ala Leu Arg Gly Ala Pro Arg Leu Leu Ser Arg Val
1 5 10 15

Gln Pro Arg Ala Pro Cys Leu Arg Arg Leu Trp Gly Arg Gly Ala Arg
20 25 30

Pro Glu Val Ala Gly Arg Arg Arg Ala Trp Ala Trp Gly Trp Arg Arg
35 40 45

Ser

<210> 492
<211> 16
<212> PRT
<213> Artificial Sequence

<220>
<223> Q5T160 mitochondrial targeting peptide

<400> 492

Met Ala Cys Gly Phe Arg Arg Ala Ile Ala Cys Gln Leu Ser Arg Val
1 5 10 15

<210> 493
<211> 36
<212> PRT
<213> Artificial Sequence

<220>
<223> Q5T1C6 mitochondrial targeting peptide

<400> 493

Met Leu Arg Ser Cys Ala Ala Arg Leu Arg Thr Leu Gly Ala Leu Cys
1 5 10 15

Leu Pro Pro Val Gly Arg Arg Leu Pro Gly Ser Glu Pro Arg Pro Glu
20 25 30

Leu Arg Ser Phe
35

<210> 494
<211> 9
<212> PRT
<213> Artificial Sequence

<220>
<223> Q5T1J5 mitochondrial targeting peptide

<400> 494

Met Pro Arg Gly Ser Arg Ser Arg Thr
1 5

<210> 495
<211> 39
<212> PRT
<213> Artificial Sequence

<220>
<223> Q5T440 mitochondrial targeting peptide

<400> 495

Met Ala Thr Ala Ala Leu Leu Arg Gly Ala Thr Pro Gly Arg Gly Gly
1 5 10 15

Pro Val Trp Arg Trp Arg Leu Arg Ala Ala Pro Arg Cys Arg Leu Ala
20 25 30

His Ser Ser Cys Ser Pro Gly
35

<210> 496
<211> 60
<212> PRT
<213> Artificial Sequence

<220>
<223> Q5T653 mitochondrial targeting peptide

<400> 496

Met Ala Leu Cys Ala Leu Thr Arg Ala Leu Arg Ser Leu Asn Leu Ala
1 5 10 15

Pro Pro Thr Val Ala Ala Pro Ala Pro Ser Leu Phe Pro Ala Ala Gln
20 25 30

Met Met Asn Asn Gly Leu Leu Gln Gln Pro Ser Ala Leu Met Leu Leu
35 40 45

Pro Cys Arg Pro Val Leu Thr Ser Val Ala Leu Asn
50 55 60

<210> 497
<211> 57
<212> PRT
<213> Artificial Sequence

<220>
<223> Q5TC12 mitochondrial targeting peptide

<400> 497

Met Ala Ala Val Val Val Ala Ala Ala Gly Gly Ala Gly Pro Ala Val

1 5 10 15

Leu Gln Val Ala Gly Leu Tyr Arg Gly Leu Cys Ala Val Arg Ser Arg
20 25 30

Ala Leu Gly Leu Gly Leu Val Ser Pro Ala Gln Leu Arg Val Phe Pro
35 40 45

Val Arg Pro Gly Ser Gly Arg Pro Glu
50 55

<210> 498
<211> 36
<212> PRT
<213> Artificial Sequence

<220>
<223> Q5TEU4 mitochondrial targeting peptide

<400> 498

Met Leu Arg Pro Ala Gly Leu Trp Arg Leu Cys Arg Arg Pro Trp Ala
1 5 10 15

Ala Arg Val Pro Ala Glu Asn Leu Gly Arg Arg Glu Val Thr Ser Gly
20 25 30

Val Ser Pro Arg
35

<210> 499
<211> 48
<212> PRT
<213> Artificial Sequence

<220>
<223> Q5U4N7 mitochondrial targeting peptide

<400> 499

Met Ile Gln Ser Ser Gln Pro Met Ser Leu Lys Leu Thr Cys Ser Ala
1 5 10 15

Phe Arg Leu Gln Arg Ala Leu Arg Phe Leu Leu Gly Arg Leu Pro Trp
20 25 30

Arg Val Ala Ser Gly Ala Arg Arg Phe Arg Arg Trp Leu Asn Arg Tyr
35 40 45

<210> 500
<211> 20
<212> PRT
<213> Artificial Sequence

<220>
<223> Q5VUM1 mitochondrial targeting peptide

<400> 500

Met Thr Pro Ser Arg Leu Pro Trp Leu Leu Ser Trp Val Ser Ala Thr
1 5 10 15

Ala Trp Arg Ala
20

<210> 501
<211> 46
<212> PRT
<213> Artificial Sequence

<220>
<223> Q68CK6 mitochondrial targeting peptide

<400> 501

Met His Trp Leu Arg Lys Val Gln Gly Leu Cys Thr Leu Trp Gly Thr
1 5 10 15

Gln Met Ser Ser Arg Thr Leu Tyr Ile Asn Ser Arg Gln Leu Val Ser
20 25 30

Leu Gln Trp Gly His Gln Glu Val Pro Ala Lys Phe Asn Phe
35 40 45

<210> 502
<211> 70
<212> PRT
<213> Artificial Sequence

<220>
<223> Q6DKK2 mitochondrial targeting peptide

<400> 502

Met Phe Arg Leu Leu Ser Trp Ser Leu Gly Arg Gly Phe Leu Arg Ala
1 5 10 15

Ala Gly Arg Arg Cys Arg Gly Cys Ser Ala Arg Leu Leu Pro Gly Leu
20 25 30

Ala Gly Gly Pro Gly Pro Glu Val Gln Val Pro Pro Ser Arg Val Ala
35 40 45

Pro His Gly Arg Gly Pro Gly Leu Leu Pro Leu Leu Ala Ala Leu Ala
50 55 60

Trp Phe Ser Arg Pro Ala
65 70

<210> 503
<211> 20
<212> PRT
<213> Artificial Sequence

<220>
<223> Q6IN84 mitochondrial targeting peptide

<400> 503

Met Ala Leu Leu Ser Thr Val Arg Gly Ala Thr Trp Gly Arg Leu Val
1 5 10 15

Thr Arg His Phe
20

<210> 504
<211> 26
<212> PRT
<213> Artificial Sequence

<220>
<223> Q6J4K2 mitochondrial targeting peptide

<400> 504

Met Ala Gly Arg Arg Leu Asn Leu Arg Trp Ala Leu Ser Val Leu Cys
1 5 10 15

Val Leu Leu Met Ala Glu Thr Val Ser Gly
20 25

<210> 505
<211> 16
<212> PRT
<213> Artificial Sequence

<220>
<223> Q6L8Q7 mitochondrial targeting peptide

<400> 505

Met Trp Arg Leu Pro Gly Ala Arg Ala Ala Leu Arg Val Ile Arg Thr
1 5 10 15

<210> 506
<211> 26
<212> PRT
<213> Artificial Sequence

<220>
<223> Q6NUN0 mitochondrial targeting peptide

<400> 506

Met Arg Pro Trp Leu Arg His Leu Val Leu Gln Ala Leu Arg Asn Ser
1 5 10 15

Arg Ala Phe Cys Gly Ser His Gly Lys Pro
20 25

<210> 507
<211> 32
<212> PRT
<213> Artificial Sequence

<220>
<223> Q6NVY1 mitochondrial targeting peptide

<400> 507

Met Gly Gln Arg Glu Met Trp Arg Leu Met Ser Arg Phe Asn Ala Phe
1 5 10 15

Lys Arg Thr Asn Thr Ile Leu His His Leu Arg Met Ser Lys His Thr
20 25 30

<210> 508
<211> 14
<212> PRT
<213> Artificial Sequence

<220>
<223> Q6P161 mitochondrial targeting peptide

<400> 508

Met Ala Thr Lys Arg Leu Phe Gly Ala Thr Arg Thr Trp Ala
1 5 10

<210> 509
<211> 30
<212> PRT
<213> Artificial Sequence

<220>
<223> Q6P1L8 mitochondrial targeting peptide

<400> 509

Met Ala Phe Phe Thr Gly Leu Trp Gly Pro Phe Thr Cys Val Ser Arg
1 5 10 15

Val Leu Ser His His Cys Phe Ser Thr Thr Gly Ser Leu Ser
20 25 30

<210> 510
<211> 21
<212> PRT
<213> Artificial Sequence

<220>
<223> Q6P461 mitochondrial targeting peptide

<400> 510

Met Leu Gly Arg Phe Gln Pro Phe Ser Leu Val Arg Ser Phe Arg Leu
1 5 10 15

Gly Phe Glu Ala Cys
20

<210> 511
<211> 52
<212> PRT
<213> Artificial Sequence

<220>
<223> Q6P4F2 mitochondrial targeting peptide

<400> 511

Met Ala Ala Ser Met Ala Arg Gly Gly Val Ser Ala Arg Val Leu Leu
1 5 10 15

Gln Ala Ala Arg Gly Thr Trp Trp Asn Arg Pro Gly Gly Thr Ser Gly
20 25 30

Ser Gly Glu Gly Val Ala Leu Gly Thr Thr Arg Lys Phe Gln Ala Thr
35 40 45

Gly Ser Arg Pro
50

<210> 512
<211> 27
<212> PRT
<213> Artificial Sequence

<220>
<223> Q6P587 mitochondrial targeting peptide

<400> 512

Met Gly Ile Met Ala Ala Ser Arg Pro Leu Ser Arg Phe Trp Glu Trp
1 5 10 15

Gly Lys Asn Ile Val Cys Val Gly Arg Asn Tyr
20 25

<210> 513
<211> 47
<212> PRT
<213> Artificial Sequence

<220>
<223> Q6PI48 mitochondrial targeting peptide

<400> 513

Met Tyr Phe Pro Ser Trp Leu Ser Gln Leu Tyr Arg Gly Leu Ser Arg
1 5 10 15

Pro Ile Arg Arg Thr Thr Gln Pro Ile Trp Gly Ser Leu Tyr Arg Ser
20 25 30

Leu Leu Gln Ser Ser Gln Arg Arg Ile Pro Glu Phe Ser Ser Phe
35 40 45

<210> 514
<211> 27
<212> PRT
<213> Artificial Sequence

<220>
<223> Q6SZW1 mitochondrial targeting peptide

<400> 514

Met Val Leu Thr Leu Leu Leu Ser Ala Tyr Lys Leu Cys Arg Phe Phe
1 5 10 15

Ala Met Ser Gly Pro Arg Pro Gly Ala Glu Arg
20 25

<210> 515
<211> 19
<212> PRT
<213> Artificial Sequence

<220>
<223> Q6UB28 mitochondrial targeting peptide

<400> 515

Met Ala Ala Pro Ser Gly Val His Leu Leu Val Arg Arg Gly Ser His
1 5 10 15

Arg Ile Phe

<210> 516
<211> 31
<212> PRT
<213> Artificial Sequence

<220>
<223> Q6UB35 mitochondrial targeting peptide

<400> 516

Met Gly Thr Arg Leu Pro Leu Val Leu Arg Gln Leu Arg Arg Pro Pro
1 5 10 15

Gln Pro Pro Gly Pro Pro Arg Arg Leu Arg Val Pro Cys Arg Ala
20 25 30

<210> 517
<211> 22
<212> PRT
<213> Artificial Sequence

<220>
<223> Q6UWS5 mitochondrial targeting peptide

<400> 517

Met Ser Arg Ser Ser Lys Val Val Leu Gly Leu Ser Val Leu Leu Thr
1 5 10 15

Ala Ala Thr Val Ala Gly
20

<210> 518
<211> 27
<212> PRT
<213> Artificial Sequence

<220>
<223> Q6UXV4 mitochondrial targeting peptide

<400> 518

Met Ala Ala Ile Arg Met Gly Lys Leu Thr Thr Met Pro Ala Gly Leu
1 5 10 15

Ile Tyr Ala Ser Val Ser Val His Ala Ala Lys
20 25

<210> 519
<211> 29
<212> PRT
<213> Artificial Sequence

<220>
<223> Q6ZSR3 mitochondrial targeting peptide

<400> 519

Met Gly Trp Arg Phe Pro Ser Pro Ser Pro Arg Gln Ala Ser Pro Val
1 5 10 15

Ala Pro Leu Leu Ala Ala Pro Thr Ala Val Arg Ser Cys
20 25

<210> 520
<211> 39
<212> PRT
<213> Artificial Sequence

<220>
<223> Q7L0Y3 mitochondrial targeting peptide

<400> 520

Met Ala Ala Phe Leu Lys Met Ser Val Ser Val Asn Phe Phe Arg Pro
1 5 10 15

Phe Thr Arg Phe Leu Val Pro Phe Thr Leu His Arg Lys Arg Asn Asn
20 25 30

Leu Thr Ile Leu Gln Arg Tyr
35

<210> 521
<211> 29
<212> PRT
<213> Artificial Sequence

<220>
<223> Q7L3T8 mitochondrial targeting peptide

<400> 521

Met Glu Gly Leu Leu Thr Arg Cys Arg Ala Leu Pro Ala Leu Ala Thr
1 5 10 15

Cys Ser Arg Gln Leu Ser Gly Tyr Val Pro Cys Arg Phe

20 25

<210> 522
<211> 46
<212> PRT
<213> Artificial Sequence

<220>
<223> Q7L592 mitochondrial targeting peptide

<400> 522

Met Ser Val Leu Leu Arg Ser Gly Leu Gly Pro Leu Cys Ala Val Ala
1 5 10 15

Arg Ala Ala Ile Pro Phe Ile Trp Arg Gly Lys Tyr Phe Ser Ser Gly
20 25 30

Asn Glu Pro Ala Glu Asn Pro Val Thr Pro Met Leu Arg His
35 40 45

<210> 523
<211> 27
<212> PRT
<213> Artificial Sequence

<220>
<223> Q7L8L6 mitochondrial targeting peptide

<400> 523

Met Ala Ala Thr Leu Lys Ser Leu Lys Leu Val Arg Tyr Arg Ala Phe
1 5 10 15

Cys Ser Pro Ser Ala Phe Gly Ala Val Arg Ser
20 25

<210> 524
<211> 39
<212> PRT
<213> Artificial Sequence

<220>
<223> Q7Z2W9 mitochondrial targeting peptide

<400> 524

Met Ala Ala Ser Ser Leu Thr Val Thr Leu Gly Arg Leu Ala Ser Ala
1 5 10 15

Cys Ser His Ser Ile Leu Arg Pro Ser Gly Pro Gly Ala Ala Ser Leu
20 25 30

Trp Ser Ala Ser Arg Arg Phe
35

<210> 525
<211> 28
<212> PRT

<213> Artificial Sequence

<220>
<223> Q7Z3D6 mitochondrial targeting peptide

<400> 525

Met Pro Phe Thr Leu His Leu Arg Ser Arg Leu Pro Ser Ala Ile Arg
1 5 10 15

Ser Leu Ile Leu Gln Lys Lys Pro Asn Ile Arg Asn
20 25

<210> 526
<211> 29
<212> PRT
<213> Artificial Sequence

<220>
<223> Q7Z4L0 mitochondrial targeting peptide

<400> 526

Met Pro Leu Leu Arg Gly Arg Cys Pro Ala Arg Arg His Tyr Arg Arg
1 5 10 15

Leu Ala Leu Leu Gly Leu Gln Pro Ala Pro Arg Phe Ala
20 25

<210> 527
<211> 24
<212> PRT
<213> Artificial Sequence

<220>
<223> Q7Z5L4 mitochondrial targeting peptide

<400> 527

Met Ile Ile Thr Thr Trp Ile Val Tyr Ile Leu Ala Arg Lys Gly Val
1 5 10 15

Gly Leu Pro Phe Leu Pro Ile Thr
20

<210> 528
<211> 42
<212> PRT
<213> Artificial Sequence

<220>
<223> Q7Z6M4 mitochondrial targeting peptide

<400> 528

Met Ala Ala Phe Gly Arg Gln Val Leu Asp Trp His Arg Leu Ile Pro
1 5 10 15

Leu Thr Trp Ala Cys Met Ala Arg Gln Thr Pro His Leu Gly Glu Gln
20 25 30

Arg Arg Thr Thr Ala Ser Leu Leu Arg Lys
35 40

<210> 529
<211> 33
<212> PRT
<213> Artificial Sequence

<220>
<223> Q7Z7F7 mitochondrial targeting peptide

<400> 529

Met Ala Ala Val Gly Ser Leu Leu Gly Arg Leu Arg Gln Ser Thr Val
1 5 10 15

Lys Ala Thr Gly Pro Ala Leu Arg Arg Leu His Thr Ser Ser Trp Arg
20 25 30

Ala

<210> 530
<211> 28
<212> PRT
<213> Artificial Sequence

<220>
<223> Q7Z7H8 mitochondrial targeting peptide

<400> 530

Met Ala Ala Ala Val Ala Gly Met Leu Arg Gly Gly Leu Leu Pro Gln
1 5 10 15

Ala Gly Arg Leu Pro Thr Leu Gln Thr Val Arg Tyr
20 25

<210> 531
<211> 31
<212> PRT
<213> Artificial Sequence

<220>
<223> Q86SX6 mitochondrial targeting peptide

<400> 531

Met Ser Gly Ser Leu Gly Arg Ala Ala Ala Ala Leu Leu Arg Trp Gly
1 5 10 15

Arg Gly Ala Gly Gly Gly Gly Leu Trp Gly Pro Gly Val Arg Ala
20 25 30

<210> 532
<211> 23
<212> PRT
<213> Artificial Sequence

<220>
<223> Q86TS9 mitochondrial targeting peptide

<400> 532

Met Ala Ala Leu Gly Thr Val Leu Phe Thr Gly Val Arg Arg Leu His
1 5 10 15

Cys Ser Val Ala Ala Trp Ala
20

<210> 533
<211> 8
<212> PRT
<213> Artificial Sequence

<220>
<223> Q86U28 mitochondrial targeting peptide

<400> 533

Met Ala Ala Ala Trp Gly Ser Ser
1 5

<210> 534
<211> 55
<212> PRT
<213> Artificial Sequence

<220>
<223> Q86U90 mitochondrial targeting peptide

<400> 534

Met Ser Pro Ala Arg Arg Cys Arg Gly Met Arg Ala Ala Val Ala Ala
1 5 10 15

Ser Val Gly Leu Ser Glu Gly Pro Ala Gly Ser Arg Ser Gly Arg Leu
20 25 30

Phe Arg Pro Pro Ser Pro Ala Pro Ala Ala Pro Gly Ala Arg Leu Leu
35 40 45

Arg Leu Pro Gly Ser Gly Ala
50 55

<210> 535
<211> 86
<212> PRT
<213> Artificial Sequence

<220>
<223> Q86UT6 mitochondrial targeting peptide

<400> 535

Met Arg Trp Gly His His Leu Pro Arg Ala Ser Trp Gly Ser Gly Phe
1 5 10 15

Arg Arg Ala Leu Gln Arg Pro Asp Asp Arg Ile Pro Phe Leu Ile His

20 25 30

Trp Ser Trp Pro Leu Gln Gly Glu Arg Pro Phe Gly Pro Pro Arg Ala
35 40 45

Phe Ile Arg His His Gly Ser Ser Val Asp Ser Ala Pro Pro Pro Gly
50 55 60

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

Arg His Arg Arg Asn Leu
85

<210> 536
<211> 25
<212> PRT
<213> Artificial Sequence

<220>
<223> Q86XE5 mitochondrial targeting peptide

<400> 536

Met Leu Gly Pro Gln Val Trp Ser Ser Val Arg Gln Gly Leu Ser Arg
1 5 10 15

Ser Leu Ser Arg Asn Val Gly Val Trp
20 25

<210> 537
<211> 35
<212> PRT
<213> Artificial Sequence

<220>
<223> Q86YB7 mitochondrial targeting peptide

<400> 537

Met Leu Arg Val Leu Cys Leu Leu Arg Pro Trp Arg Pro Leu Arg Ala
1 5 10 15

Arg Gly Cys Ala Ser Asp Gly Ala Ala Gly Gly Ser Glu Ile Gln Val
20 25 30

Arg Ala Leu
35

<210> 538
<211> 65
<212> PRT
<213> Artificial Sequence

<220>
<223> Q8IVH4 mitochondrial targeting peptide

<400> 538

Met Pro Met Leu Leu Pro His Pro His Gln His Phe Leu Lys Gly Leu
1 5 10 15

Leu Arg Ala Pro Phe Arg Cys Tyr His Phe Ile Phe His Ser Ser Thr
20 25 30

His Leu Gly Ser Gly Ile Pro Cys Ala Gln Pro Phe Asn Ser Leu Gly
35 40 45

Leu His Cys Thr Lys Trp Met Leu Leu Ser Asp Gly Leu Lys Arg Lys
50 55 60

Leu
65

<210> 539
<211> 21
<212> PRT
<213> Artificial Sequence

<220>
<223> Q8IVS2 mitochondrial targeting peptide

<400> 539

Met Ser Val Arg Val Ala Arg Val Ala Trp Val Arg Gly Leu Gly Ala
1 5 10 15

Ser Tyr Arg Arg Gly
20

<210> 540
<211> 29
<212> PRT
<213> Artificial Sequence

<220>
<223> Q8IWL3 mitochondrial targeting peptide

<400> 540

Met Trp Arg Gly Arg Ala Gly Ala Leu Leu Arg Val Trp Gly Phe Trp
1 5 10 15

Pro Thr Gly Val Pro Arg Arg Arg Pro Leu Ser Cys Asp
20 25

<210> 541
<211> 13
<212> PRT
<213> Artificial Sequence

<220>
<223> Q8IXM3 mitochondrial targeting peptide

<400> 541

Met Gly Val Leu Ala Ala Ala Ala Arg Cys Leu Val Arg

1 5 10

<210> 542
<211> 38
<212> PRT
<213> Artificial Sequence

<220>
<223> Q8IXQ9 mitochondrial targeting peptide

<400> 542

Met Ala Leu Ser Leu Gly Trp Lys Ala His Arg Asn His Cys Gly Leu
1 5 10 15

Leu Leu Gln Ala Leu Arg Ser Ser Gly Leu Leu Leu Phe Pro Cys Gly
20 25 30

Gln Cys Pro Trp Arg Gly
35

<210> 543
<211> 22
<212> PRT
<213> Artificial Sequence

<220>
<223> Q8IYB8 mitochondrial targeting peptide

<400> 543

Met Ser Phe Ser Arg Ala Leu Leu Trp Ala Arg Leu Pro Ala Gly Arg
1 5 10 15

Gln Ala Gly His Arg Ala
20

<210> 544
<211> 22
<212> PRT
<213> Artificial Sequence

<220>
<223> Q8IYU8 mitochondrial targeting peptide

<400> 544

Met Ala Ala Ala Ala Gly Ser Cys Ala Arg Val Ala Ala Trp Gly Gly
1 5 10 15

Lys Leu Arg Arg Gly Leu
20

<210> 545
<211> 41
<212> PRT
<213> Artificial Sequence

<220>
<223> Q8N0V3 mitochondrial targeting peptide

<400> 545

Met Trp Ala Ala Ala Gly Gly Leu Trp Arg Ser Arg Ala Gly Leu Arg
1 5 10 15

Ala Leu Phe Arg Ser Arg Asp Ala Ala Leu Phe Pro Gly Cys Glu Arg
20 25 30

Gly Leu His Cys Ser Ala Val Ser Cys
35 40

<210> 546
<211> 22
<212> PRT
<213> Artificial Sequence

<220>
<223> Q8N0X4 mitochondrial targeting peptide

<400> 546

Met Ala Leu Arg Leu Leu Arg Arg Ala Ala Arg Gly Ala Ala Ala Ala
1 5 10 15

Ala Leu Leu Arg Leu Lys
20

<210> 547
<211> 18
<212> PRT
<213> Artificial Sequence

<220>
<223> Q8N159 mitochondrial targeting peptide

<400> 547

Met Ala Thr Ala Leu Met Ala Val Val Leu Arg Ala Ala Ala Val Ala
1 5 10 15

Pro Arg

<210> 548
<211> 36
<212> PRT
<213> Artificial Sequence

<220>
<223> Q8N1F1 mitochondrial targeting peptide

<400> 548

Met Phe Pro Gly Ser Leu Ser Arg Gly Arg Arg Ala Ala Val Glu Met
1 5 10 15

Ala Trp Leu Pro Gly Ser Cys Ala Arg Val Ala Phe Ala Ala Gly Ala
20 25 30

Ala Ala Arg Tyr
        35

<210> 549
<211> 29
<212> PRT
<213> Artificial Sequence

<220>
<223> Q8N3J5 mitochondrial targeting peptide

<400> 549

Met Ser Thr Ala Ala Leu Ile Thr Leu Val Arg Ser Gly Gly Asn Gln
1   5   10   15

Val Arg Arg Arg Val Leu Leu Ser Ser Arg Leu Leu Gln
            20   25

<210> 550
<211> 49
<212> PRT
<213> Artificial Sequence

<220>
<223> Q8N442 mitochondrial targeting peptide

<400> 550

Met Trp Thr Leu Val Gly Arg Gly Trp Gly Cys Ala Arg Ala Leu Ala
1   5   10   15

Pro Arg Ala Thr Gly Ala Ala Leu Leu Val Ala Pro Gly Pro Arg Ser
            20   25   30

Ala Pro Thr Leu Gly Ala Ala Pro Glu Ser Trp Ala Thr Asp Arg Leu
        35   40   45

Tyr

<210> 551
<211> 13
<212> PRT
<213> Artificial Sequence

<220>
<223> Q8N465 mitochondrial targeting peptide

<400> 551

Met Leu Pro Arg Arg Pro Leu Ala Trp Pro Ala Trp Leu
1   5   10

<210> 552
<211> 49
<212> PRT
<213> Artificial Sequence

<220>
<223> Q8N4E7 mitochondrial targeting peptide

<400> 552

Met Leu Ser Cys Phe Arg Leu Leu Ser Arg His Ile Ser Pro Ser Leu
1 5 10 15

Ala Ser Leu Arg Pro Val Arg Cys Cys Phe Ala Leu Pro Leu Arg Trp
20 25 30

Ala Pro Gly Arg Pro Leu Asp Pro Arg Gln Ile Ala Pro Arg Arg Pro
35 40 45

Leu

<210> 553
<211> 40
<212> PRT
<213> Artificial Sequence

<220>
<223> Q8N5M1 mitochondrial targeting peptide

<400> 553

Met Trp Arg Ser Cys Leu Arg Leu Arg Asp Gly Gly Arg Arg Leu Leu
1 5 10 15

Asn Arg Pro Ala Gly Gly Pro Ser Ala Ser Met Ser Pro Gly Pro Thr
20 25 30

Ile Pro Ser Pro Ala Arg Ala Tyr
35 40

<210> 554
<211> 29
<212> PRT
<213> Artificial Sequence

<220>
<223> Q8N5Z0 mitochondrial targeting peptide

<400> 554

Met Asn Tyr Ala Arg Phe Ile Thr Ala Ala Ser Ala Ala Arg Asn Pro
1 5 10 15

Ser Pro Ile Arg Thr Met Thr Asp Ile Leu Ser Arg Gly
20 25

<210> 555
<211> 27
<212> PRT
<213> Artificial Sequence

<220>
<223> Q8NCN5 mitochondrial targeting peptide

<400> 555

Met Met Phe Tyr Arg Leu Leu Ser Ile Val Gly Arg Gln Arg Ala Ser
1 5 10 15

Pro Gly Trp Gln Asn Trp Ser Ser Ala Arg Asn
20 25

<210> 556
<211> 47
<212> PRT
<213> Artificial Sequence

<220>
<223> Q8NCW5 mitochondrial targeting peptide

<400> 556

Met Ser Arg Leu Arg Ala Leu Leu Gly Leu Gly Leu Leu Val Ala Gly
1 5 10 15

Ser Arg Val Pro Arg Ile Lys Ser Gln Thr Ile Ala Cys Arg Ser Gly
20 25 30

Pro Thr Trp Trp Gly Pro Gln Arg Leu Asn Ser Gly Gly Arg Trp
35 40 45

<210> 557
<211> 29
<212> PRT
<213> Artificial Sequence

<220>
<223> Q8NE62 mitochondrial targeting peptide

<400> 557

Met Trp Cys Leu Leu Arg Gly Leu Gly Arg Pro Gly Ala Leu Ala Arg
1 5 10 15

Gly Ala Leu Gly Gln Gln Gln Ser Leu Gly Ala Arg Ala
20 25

<210> 558
<211> 50
<212> PRT
<213> Artificial Sequence

<220>
<223> Q8NE86 mitochondrial targeting peptide

<400> 558

Met Ala Ala Ala Ala Gly Arg Ser Leu Leu Leu Leu Leu Ser Ser Arg
1 5 10 15

Gly Gly Gly Gly Gly Gly Ala Gly Gly Cys Gly Ala Leu Thr Ala Gly
20 25 30

Cys Phe Pro Gly Leu Gly Val Ser Arg His Arg Gln Gln Gln His His
35 40 45

Arg Thr
50

<210> 559
<211> 17
<212> PRT
<213> Artificial Sequence

<220>
<223> Q8NFF5 mitochondrial targeting peptide

<400> 559

Met Gly Trp Asp Leu Gly Thr Arg Leu Phe Gln Arg Gln Glu Gln Arg
1 5 10 15

Ser

<210> 560
<211> 162
<212> PRT
<213> Artificial Sequence

<220>
<223> Q8NI60 mitochondrial targeting peptide

<400> 560

Met Ala Ala Ile Leu Gly Asp Thr Ile Met Val Ala Lys Gly Leu Val
1 5 10 15

Lys Leu Thr Gln Ala Ala Val Glu Thr His Leu Gln His Leu Gly Ile
20 25 30

Gly Gly Glu Leu Ile Met Ala Ala Arg Ala Leu Gln Ser Thr Ala Val
35 40 45

Glu Gln Ile Gly Met Phe Leu Gly Lys Val Gln Gly Gln Asp Lys His
50 55 60

Glu Glu Tyr Phe Ala Glu Asn Phe Gly Gly Pro Glu Gly Glu Phe His
65 70 75 80

Phe Ser Val Pro His Ala Ala Gly Ala Ser Thr Asp Phe Ser Ser Ala
85 90 95

Ser Ala Pro Asp Gln Ser Ala Pro Pro Ser Leu Gly His Ala His Ser
100 105 110

Glu Gly Pro Ala Pro Ala Tyr Val Ala Ser Gly Pro Phe Arg Glu Ala
115 120 125

Gly Phe Pro Gly Gln Ala Ser Ser Pro Leu Gly Arg Ala Asn Gly Arg
130 135 140

Leu Phe Ala Asn Pro Arg Asp Ser Phe Ser Ala Met Gly Phe Gln Arg
145 150 155 160

Arg Phe

<210> 561
<211> 32
<212> PRT
<213> Artificial Sequence

<220>
<223> Q8TAA5 mitochondrial targeting peptide

<400> 561

Met Ala Val Arg Ser Leu Trp Ala Gly Arg Leu Arg Val Gln Arg Leu
1 5 10 15

Leu Ala Trp Ser Ala Ala Trp Glu Ser Lys Gly Trp Pro Leu Pro Phe
20 25 30

<210> 562
<211> 38
<212> PRT
<213> Artificial Sequence

<220>
<223> Q8TB37 mitochondrial targeting peptide

<400> 562

Met Gly Ile Trp Gln Arg Leu Leu Leu Phe Gly Gly Val Ser Leu Arg
1 5 10 15

Ala Gly Gly Gly Ala Thr Ala Pro Leu Gly Gly Ser Arg Ala Met Val
20 25 30

Cys Gly Arg Gln Leu Ser
35

<210> 563
<211> 34
<212> PRT
<213> Artificial Sequence

<220>
<223> Q8TCC3 mitochondrial targeting peptide

<400> 563

Met Ala Gly Ile Leu Arg Leu Val Val Gln Trp Pro Pro Gly Arg Leu
1 5 10 15

Gln Thr Val Thr Lys Gly Val Glu Ser Leu Ile Cys Thr Asp Trp Ile

20 25 30

Arg His

<210> 564
<211> 45
<212> PRT
<213> Artificial Sequence

<220>
<223> Q8TCS8 mitochondrial targeting peptide

<400> 564

Met Ala Ala Cys Arg Tyr Cys Cys Ser Cys Leu Arg Leu Arg Pro Leu
1 5 10 15

Ser Asp Gly Pro Phe Leu Leu Pro Arg Arg Asp Arg Ala Leu Thr Gln
20 25 30

Leu Gln Val Arg Ala Leu Trp Ser Ser Ala Gly Ser Arg
35 40 45

<210> 565
<211> 25
<212> PRT
<213> Artificial Sequence

<220>
<223> Q8TF08 mitochondrial targeting peptide

<400> 565

Met Met Phe Pro Leu Ala Arg Asn Ala Leu Ser Ser Leu Lys Ile Gln
1 5 10 15

Ser Ile Leu Gln Ser Met Ala Arg His
20 25

<210> 566
<211> 27
<212> PRT
<213> Artificial Sequence

<220>
<223> Q8WUK0 mitochondrial targeting peptide

<400> 566

Met Ala Ala Thr Ala Leu Leu Glu Ala Gly Leu Ala Arg Val Leu Phe
1 5 10 15

Tyr Pro Thr Leu Leu Tyr Thr Leu Phe Arg Gly
20 25

<210> 567
<211> 27
<212> PRT

<213> Artificial Sequence

<220>
<223> Q8WVM0 mitochondrial targeting peptide

<400> 567

Met Ala Ala Ser Gly Lys Leu Ser Thr Cys Arg Leu Pro Pro Leu Pro
1 5 10 15

Thr Ile Arg Glu Ile Ile Lys Leu Leu Arg Leu
20 25

<210> 568
<211> 96
<212> PRT
<213> Artificial Sequence

<220>
<223> Q8WWC4 mitochondrial targeting peptide

<400> 568

Met Ala Leu Ala Ala Arg Leu Leu Pro Gln Phe Leu His Ser Arg Ser
1 5 10 15

Leu Pro Cys Gly Ala Val Arg Leu Arg Thr Pro Ala Val Ala Glu Val
20 25 30

Arg Leu Pro Ser Ala Thr Leu Cys Tyr Phe Cys Arg Cys Arg Leu Gly
35 40 45

Leu Gly Ala Ala Leu Phe Pro Arg Ser Ala Arg Ala Leu Ala Ala Ser
50 55 60

Ala Leu Pro Ala Gln Gly Ser Arg Trp Pro Val Leu Ser Ser Pro Gly
65 70 75 80

Leu Pro Ala Ala Phe Ala Ser Phe Pro Ala Cys Pro Gln Arg Ser Tyr
85 90 95

<210> 569
<211> 40
<212> PRT
<213> Artificial Sequence

<220>
<223> Q8WWV3 mitochondrial targeting peptide

<400> 569

Met Glu Phe Leu Lys Thr Cys Val Leu Arg Arg Asn Ala Cys Thr Ala
1 5 10 15

Val Cys Phe Trp Arg Ser Lys Val Val Gln Lys Pro Ser Val Arg Arg
20 25 30

Ile Ser Thr Thr Ser Pro Arg Ser

35 40

<210> 570
<211> 16
<212> PRT
<213> Artificial Sequence

<220>
<223> Q8WYQ3 mitochondrial targeting peptide

<400> 570

Met Pro Arg Gly Ser Arg Ser Ala Ala Ser Arg Pro Ala Ser Arg Pro
1 5 10 15

<210> 571
<211> 65
<212> PRT
<213> Artificial Sequence

<220>
<223> Q92665 mitochondrial targeting peptide

<400> 571

Met Phe Pro Arg Val Ser Thr Phe Leu Pro Leu Arg Pro Leu Ser Arg
1 5 10 15

His Pro Leu Ser Ser Gly Ser Pro Glu Thr Ser Ala Ala Ala Ile Met
20 25 30

Leu Leu Thr Val Arg His Gly Thr Val Arg Tyr Arg Ser Ser Ala Leu
35 40 45

Leu Ala Arg Thr Lys Asn Asn Ile Gln Arg Tyr Phe Gly Thr Asn Ser
50 55 60

Val
65

<210> 572
<211> 29
<212> PRT
<213> Artificial Sequence

<220>
<223> Q92667 mitochondrial targeting peptide

<400> 572

Met Ala Ile Gln Phe Arg Ser Leu Phe Pro Leu Ala Leu Pro Gly Met
1 5 10 15

Leu Ala Leu Leu Gly Trp Trp Trp Phe Phe Ser Arg Lys
20 25

<210> 573
<211> 44
<212> PRT

<213> Artificial Sequence

<220>
<223> Q92947 mitochondrial targeting peptide

<400> 573

Met Ala Leu Arg Gly Val Ser Val Arg Leu Leu Ser Arg Gly Pro Gly
1 5 10 15

Leu His Val Leu Arg Thr Trp Val Ser Ser Ala Ala Gln Thr Glu Lys
20 25 30

Gly Gly Arg Thr Gln Ser Gln Leu Ala Lys Ser Ser
35 40

<210> 574
<211> 50
<212> PRT
<213> Artificial Sequence

<220>
<223> Q969P6 mitochondrial targeting peptide

<400> 574

Met Arg Val Val Arg Leu Leu Arg Leu Arg Ala Ala Leu Thr Leu Leu
1 5 10 15

Gly Glu Val Pro Arg Arg Pro Ala Ser Arg Gly Val Pro Gly Ser Arg
20 25 30

Arg Thr Gln Lys Gly Ser Gly Ala Arg Trp Glu Lys Glu Lys His Glu
35 40 45

Asp Gly
50

<210> 575
<211> 81
<212> PRT
<213> Artificial Sequence

<220>
<223> Q969Y2 mitochondrial targeting peptide

<400> 575

Met Trp Arg Gly Leu Trp Thr Leu Ala Ala Gln Ala Ala Arg Gly Pro
1 5 10 15

Arg Arg Leu Cys Thr Arg Arg Ser Ser Gly Ala Pro Ala Pro Gly Ser
20 25 30

Gly Ala Thr Ile Phe Ala Leu Ser Ser Gly Gln Gly Arg Cys Gly Ile
35 40 45

Ala Val Ile Arg Thr Ser Gly Pro Ala Ser Gly His Ala Leu Arg Ile

50 55 60

Leu Thr Ala Pro Arg Asp Leu Pro Leu Ala Arg His Ala Ser Leu Arg
65 70 75 80

Leu

<210> 576
<211> 107
<212> PRT
<213> Artificial Sequence

<220>
<223> Q969Z0 mitochondrial targeting peptide

<400> 576

Met Ala Ala His Leu Val Lys Arg Cys Thr Cys Leu Leu Arg Glu Ala
1 5 10 15

Ala Arg Gln Ala Pro Ala Met Ala Pro Val Gly Arg Leu Arg Leu Ala
20 25 30

Trp Val Ala His Lys Thr Leu Thr Ser Ser Ala Thr Ser Pro Ile Ser
35 40 45

His Leu Pro Gly Ser Leu Met Glu Pro Val Glu Lys Glu Arg Ala Ser
50 55 60

Thr Pro Tyr Ile Glu Lys Gln Val Asp His Leu Ile Lys Lys Ala Thr
65 70 75 80

Arg Pro Glu Glu Leu Leu Glu Leu Leu Gly Gly Ser His Asp Leu Asp
85 90 95

Ser Asn Gln Ala Ala Met Val Leu Ile Arg Leu
100 105

<210> 577
<211> 35
<212> PRT
<213> Artificial Sequence

<220>
<223> Q969Z3 mitochondrial targeting peptide

<400> 577

Met Gly Ala Ser Ser Ser Ser Ala Leu Ala Arg Leu Gly Leu Pro Ala
1 5 10 15

Arg Pro Trp Pro Arg Trp Leu Gly Val Ala Ala Leu Gly Leu Ala Ala
20 25 30

Val Ala Leu

35

<210> 578
<211> 9
<212> PRT
<213> Artificial Sequence

<220>
<223> Q96A35 mitochondrial targeting peptide

<400> 578

Met Arg Leu Ser Ala Leu Leu Ala Leu
1 5

<210> 579
<211> 24
<212> PRT
<213> Artificial Sequence

<220>
<223> Q96BW9 mitochondrial targeting peptide

<400> 579

Met Ala Leu Gln Thr Leu Gln Ser Ser Trp Val Thr Phe Arg Lys Ile
1 5 10 15

Leu Ser His Phe Pro Glu Glu Leu
20

<210> 580
<211> 25
<212> PRT
<213> Artificial Sequence

<220>
<223> Q96CB9 mitochondrial targeting peptide

<400> 580

Met Ala Ala Leu Thr Leu Arg Gly Val Arg Glu Leu Leu Lys Arg Val
1 5 10 15

Asp Leu Ala Thr Val Pro Arg Arg His
20 25

<210> 581
<211> 41
<212> PRT
<213> Artificial Sequence

<220>
<223> Q96CM8 mitochondrial targeting peptide

<400> 581

Met Ala Val Tyr Val Gly Met Leu Arg Leu Gly Arg Leu Cys Ala Gly
1 5 10 15

Ser Ser Gly Val Leu Gly Ala Arg Ala Ala Leu Ser Arg Ser Trp Gln

20 25 30

Glu Ala Arg Leu Gln Gly Val Arg Phe
35 40

<210> 582
<211> 17
<212> PRT
<213> Artificial Sequence

<220>
<223> Q96DC8 mitochondrial targeting peptide

<400> 582

Met Ala Ala Val Ala Val Leu Arg Ala Phe Gly Ala Ser Gly Pro Met
1 5 10 15

Cys

<210> 583
<211> 26
<212> PRT
<213> Artificial Sequence

<220>
<223> Q96DV4 mitochondrial targeting peptide

<400> 583

Met Ala Ala Pro Trp Trp Arg Ala Ala Leu Cys Glu Cys Arg Arg Trp
1 5 10 15

Arg Gly Phe Ser Thr Ser Ala Val Leu Gly
20 25

<210> 584
<211> 55
<212> PRT
<213> Artificial Sequence

<220>
<223> Q96E11 mitochondrial targeting peptide

<400> 584

Met Ala Leu Gly Leu Lys Cys Phe Arg Met Val His Pro Thr Phe Arg
1 5 10 15

Asn Tyr Leu Ala Ala Ser Ile Arg Pro Val Ser Glu Val Thr Leu Lys
20 25 30

Thr Val His Glu Arg Gln His Gly His Arg Gln Tyr Met Ala Tyr Ser
35 40 45

Ala Val Pro Val Arg His Phe
50 55

<210> 585
<211> 68
<212> PRT
<213> Artificial Sequence

<220>
<223> Q96E29 mitochondrial targeting peptide

<400> 585

Met Ala Leu Ser Ala Gln Gln Ile Pro Arg Trp Phe Asn Ser Val Lys
1 5 10 15

Leu Arg Ser Leu Ile Asn Ala Ala Gln Leu Thr Lys Arg Phe Thr Arg
20 25 30

Pro Ala Arg Thr Leu Leu His Gly Phe Ser Ala Gln Pro Gln Ile Ser
35 40 45

Ser Asp Asn Cys Phe Leu Gln Trp Gly Phe Lys Thr Tyr Arg Thr Ser
50 55 60

Ser Leu Trp Asn
65

<210> 586
<211> 13
<212> PRT
<213> Artificial Sequence

<220>
<223> Q96E52 mitochondrial targeting peptide

<400> 586

Met Ser Phe Ile Cys Gly Leu Gln Ser Ala Ala Arg Asn
1 5 10

<210> 587
<211> 35
<212> PRT
<213> Artificial Sequence

<220>
<223> Q96EL2 mitochondrial targeting peptide

<400> 587

Met Ala Ala Ser Val Cys Ser Gly Leu Leu Gly Pro Arg Val Leu Ser
1 5 10 15

Trp Ser Arg Glu Leu Pro Cys Ala Trp Arg Ala Leu His Thr Ser Pro
20 25 30

Val Cys Ala
35

<210> 588

<211> 37
<212> PRT
<213> Artificial Sequence

<220>
<223> Q96EY7 mitochondrial targeting peptide

<400> 588

Met Ala Val Val Ser Ala Val Arg Trp Leu Gly Leu Arg Ser Arg Leu
1 5 10 15

Gly Gln Pro Leu Thr Gly Arg Arg Ala Gly Leu Cys Glu Gln Ala Arg
20 25 30

Ser Cys Arg Phe Tyr
35

<210> 589
<211> 32
<212> PRT
<213> Artificial Sequence

<220>
<223> Q96EY8 mitochondrial targeting peptide

<400> 589

Met Ala Val Cys Gly Leu Gly Ser Arg Leu Gly Leu Gly Ser Arg Leu
1 5 10 15

Gly Leu Arg Gly Cys Phe Gly Ala Ala Arg Leu Leu Tyr Pro Arg Phe
20 25 30

<210> 590
<211> 28
<212> PRT
<213> Artificial Sequence

<220>
<223> Q96GC5 mitochondrial targeting peptide

<400> 590

Met Ser Gly Thr Leu Glu Lys Val Leu Cys Leu Arg Asn Asn Thr Ile
1 5 10 15

Phe Lys Gln Ala Phe Ser Leu Leu Arg Phe Arg Thr
20 25

<210> 591
<211> 29
<212> PRT
<213> Artificial Sequence

<220>
<223> Q96GW9 mitochondrial targeting peptide

<400> 591

Met Leu Arg Thr Ser Val Leu Arg Leu Leu Gly Arg Thr Gly Ala Ser

1 5 10 15

Arg Leu Ser Leu Leu Glu Asp Phe Gly Pro Arg Tyr Tyr
20 25

<210> 592
<211> 34
<212> PRT
<213> Artificial Sequence

<220>
<223> Q96H96 mitochondrial targeting peptide

<400> 592

Met Leu Gly Ser Arg Ala Ala Gly Phe Ala Arg Gly Leu Arg Ala Leu
1 5 10 15

Ala Leu Ala Trp Leu Pro Gly Trp Arg Gly Arg Ser Phe Ala Leu Ala
20 25 30

Arg Ala

<210> 593
<211> 35
<212> PRT
<213> Artificial Sequence

<220>
<223> Q96I23 mitochondrial targeting peptide

<400> 593

Met Leu Ser Gly Ala Arg Cys Arg Leu Ala Ser Ala Leu Arg Gly Thr
1 5 10 15

Arg Ala Pro Pro Ser Ala Val Ala Arg Arg Cys Leu His Ala Ser Gly
20 25 30

Ser Arg Pro
35

<210> 594
<211> 14
<212> PRT
<213> Artificial Sequence

<220>
<223> Q96I59 mitochondrial targeting peptide

<400> 594

Met Leu Gly Val Arg Cys Leu Leu Arg Ser Val Arg Phe Cys
1 5 10

<210> 595
<211> 37
<212> PRT

<213> Artificial Sequence

<220>
<223> Q96I99 mitochondrial targeting peptide

<400> 595

Met Ala Ser Pro Val Ala Ala Gln Ala Gly Lys Leu Leu Arg Ala Leu
1 5 10 15

Ala Leu Arg Pro Arg Phe Leu Ala Ala Gly Ser Gln Ala Val Gln Leu
20 25 30

Thr Ser Arg Arg Trp
35

<210> 596
<211> 39
<212> PRT
<213> Artificial Sequence

<220>
<223> Q96IL0 mitochondrial targeting peptide

<400> 596

Met Leu Pro Cys Ala Ala Gly Ala Arg Gly Arg Gly Ala Met Val Val
1 5 10 15

Leu Arg Ala Gly Lys Lys Thr Phe Leu Pro Pro Leu Cys Arg Ala Phe
20 25 30

Ala Cys Arg Gly Cys Gln Leu
35

<210> 597
<211> 15
<212> PRT
<213> Artificial Sequence

<220>
<223> Q96MF6 mitochondrial targeting peptide

<400> 597

Met Ala Trp Ala Gly Ser Arg Arg Val Pro Ala Gly Thr Arg Ala
1 5 10 15

<210> 598
<211> 36
<212> PRT
<213> Artificial Sequence

<220>
<223> Q96PE7 mitochondrial targeting peptide

<400> 598

Met Ala Arg Val Leu Lys Ala Ala Ala Ala Asn Ala Val Gly Leu Phe
1 5 10 15

Ser Arg Leu Gln Ala Pro Ile Pro Thr Val Arg Ala Ser Ser Thr Ser
20 25 30

Gln Pro Leu Asp
35

<210> 599
<211> 41
<212> PRT
<213> Artificial Sequence

<220>
<223> Q96Q11 mitochondrial targeting peptide

<400> 599

Met Leu Arg Cys Leu Tyr His Trp His Arg Pro Val Leu Asn Arg Arg
1 5 10 15

Trp Ser Arg Leu Cys Leu Pro Lys Gln Tyr Leu Phe Thr Met Lys Leu
20 25 30

Gln Ser Pro Glu Phe Gln Ser Leu Phe
35 40

<210> 600
<211> 35
<212> PRT
<213> Artificial Sequence

<220>
<223> Q96QE5 mitochondrial targeting peptide

<400> 600

Met Ser Gly Ser Val Leu Phe Thr Ala Gly Glu Arg Trp Arg Cys Phe
1 5 10 15

Leu Thr Pro Ser Arg Ser Ser Leu Tyr Trp Ala Leu His Asn Phe Cys
20 25 30

Cys Arg Lys
35

<210> 601
<211> 36
<212> PRT
<213> Artificial Sequence

<220>
<223> Q96RP9 mitochondrial targeting peptide

<400> 601

Met Arg Leu Leu Gly Ala Ala Ala Val Ala Ala Leu Gly Arg Gly Arg
1 5 10 15

Ala Pro Ala Ser Leu Gly Trp Gln Arg Lys Gln Val Asn Trp Lys Ala

20 25 30

Cys Arg Trp Ser
35

<210> 602
<211> 41
<212> PRT
<213> Artificial Sequence

<220>
<223> Q96RQ3 mitochondrial targeting peptide

<400> 602

Met Ala Ala Ala Ser Ala Val Ser Val Leu Leu Val Ala Ala Glu Arg
1 5 10 15

Asn Arg Trp His Arg Leu Pro Ser Leu Leu Leu Pro Pro Arg Thr Trp
20 25 30

Val Trp Arg Gln Arg Thr Met Lys Tyr
35 40

<210> 603
<211> 31
<212> PRT
<213> Artificial Sequence

<220>
<223> Q96RR1 mitochondrial targeting peptide

<400> 603

Met Trp Val Leu Leu Arg Ser Gly Tyr Pro Leu Arg Ile Leu Leu Pro
1 5 10 15

Leu Arg Gly Glu Trp Met Gly Arg Arg Gly Leu Pro Arg Asn Leu
20 25 30

<210> 604
<211> 57
<212> PRT
<213> Artificial Sequence

<220>
<223> Q99551 mitochondrial targeting peptide

<400> 604

Met Gln Ser Leu Ser Leu Gly Gln Thr Ser Ile Ser Lys Gly Leu Asn
1 5 10 15

Tyr Leu Thr Ile Met Ala Pro Gly Asn Leu Trp His Met Arg Asn Asn
20 25 30

Phe Leu Phe Gly Ser Arg Cys Trp Met Thr Arg Phe Ser Ala Glu Asn
35 40 45

Ile Phe Lys Ser Val Ser Phe Arg Leu
    50   55

<210> 605
<211> 29
<212> PRT
<213> Artificial Sequence

<220>
<223> Q99643 mitochondrial targeting peptide

<400> 605

Met Ala Ala Leu Leu Leu Arg His Val Gly Arg His Cys Leu Arg Ala
1   5   10   15

His Phe Ser Pro Gln Leu Cys Ile Arg Asn Ala Val Pro
            20   25

<210> 606
<211> 59
<212> PRT
<213> Artificial Sequence

<220>
<223> Q99757 mitochondrial targeting peptide

<400> 606

Met Ala Gln Arg Leu Leu Leu Arg Arg Phe Leu Ala Ser Val Ile Ser
1   5   10   15

Arg Lys Pro Ser Gln Gly Gln Trp Pro Pro Leu Thr Ser Arg Ala Leu
            20   25   30

Gln Thr Pro Gln Cys Ser Pro Gly Gly Leu Thr Val Thr Pro Asn Pro
        35   40   45

Ala Arg Thr Ile Tyr Thr Thr Arg Ile Ser Leu
    50   55

<210> 607
<211> 40
<212> PRT
<213> Artificial Sequence

<220>
<223> Q99766 mitochondrial targeting peptide

<400> 607

Met Cys Cys Ala Val Ser Glu Gln Arg Leu Thr Cys Ala Asp Gln Met
1   5   10   15

Met Pro Phe Gly Lys Ile Ser Gln Gln Leu Cys Gly Val Lys Lys Leu
            20   25   30

Pro Trp Ser Cys Asp Ser Arg Tyr

35 40

<210> 608
<211> 35
<212> PRT
<213> Artificial Sequence

<220>
<223> Q99797 mitochondrial targeting peptide

<400> 608

Met Leu Cys Val Gly Arg Leu Gly Gly Leu Gly Ala Arg Ala Ala Ala
1 5 10 15

Leu Pro Pro Arg Arg Ala Gly Arg Gly Ser Leu Glu Ala Gly Ile Arg
20 25 30

Ala Arg Arg
35

<210> 609
<211> 27
<212> PRT
<213> Artificial Sequence

<220>
<223> Q99798 mitochondrial targeting peptide

<400> 609

Met Ala Pro Tyr Ser Leu Leu Val Thr Arg Leu Gln Lys Ala Leu Gly
1 5 10 15

Val Arg Gln Tyr His Val Ala Ser Val Leu Cys
20 25

<210> 610
<211> 35
<212> PRT
<213> Artificial Sequence

<220>
<223> Q99807 mitochondrial targeting peptide

<400> 610

Met Ser Cys Ala Gly Ala Ala Ala Ala Pro Arg Leu Trp Arg Leu Arg
1 5 10 15

Pro Gly Ala Arg Arg Ser Leu Ser Ala Tyr Gly Arg Arg Thr Ser Val
20 25 30

Arg Phe Arg
35

<210> 611
<211> 16
<212> PRT

<213> Artificial Sequence

<220>
<223> Q9BQ52 mitochondrial targeting peptide

<400> 611

Met Trp Ala Leu Cys Ser Leu Leu Arg Ser Ala Ala Gly Arg Thr Met
1 5 10 15

<210> 612
<211> 48
<212> PRT
<213> Artificial Sequence

<220>
<223> Q9BQ95 mitochondrial targeting peptide

<400> 612

Met Ser Trp Val Gln Ala Thr Leu Leu Ala Arg Gly Leu Cys Arg Ala
1 5 10 15

Trp Gly Gly Thr Cys Gly Ala Ala Leu Thr Gly Thr Ser Ile Ser Gln
20 25 30

Val Pro Arg Arg Leu Pro Arg Gly Leu His Cys Ser Ala Ala Ala His
35 40 45

<210> 613
<211> 13
<212> PRT
<213> Artificial Sequence

<220>
<223> Q9BRT2 mitochondrial targeting peptide

<400> 613

Met Ala Ala Ser Arg Tyr Arg Arg Phe Leu Lys Leu Cys
1 5 10

<210> 614
<211> 35
<212> PRT
<213> Artificial Sequence

<220>
<223> Q9BSE5 mitochondrial targeting peptide

<400> 614

Met Leu Arg Leu Leu Ala Ser Gly Cys Ala Arg Gly Pro Gly Pro Gly
1 5 10 15

Val Gly Ala Arg Pro Ala Ala Gly Leu Phe His Pro Gly Arg Arg Gln
20 25 30

Ser Arg Gln
35

<210> 615
<211> 20
<212> PRT
<213> Artificial Sequence

<220>
<223> Q9BT30 mitochondrial targeting peptide

<400> 615

Met Ala Gly Thr Gly Leu Leu Ala Leu Arg Thr Leu Pro Gly Pro Ser
1 5 10 15

Trp Val Arg Gly
20

<210> 616
<211> 81
<212> PRT
<213> Artificial Sequence

<220>
<223> Q9BUB7 mitochondrial targeting peptide

<400> 616

Met Leu Phe Leu Ala Leu Gly Ser Pro Trp Ala Val Glu Leu Pro Leu
1 5 10 15

Cys Gly Arg Arg Thr Ala Leu Cys Ala Ala Ala Ala Leu Arg Gly Pro
20 25 30

Arg Ala Ser Val Ser Arg Ala Ser Ser Ser Ser Gly Pro Ser Gly Pro
35 40 45

Val Ala Gly Trp Ser Thr Gly Pro Ser Gly Ala Ala Arg Leu Leu Arg
50 55 60

Arg Pro Gly Arg Ala Gln Ile Pro Val Tyr Trp Glu Gly Tyr Val Arg
65 70 75 80

Phe

<210> 617
<211> 12
<212> PRT
<213> Artificial Sequence

<220>
<223> Q9BUE6 mitochondrial targeting peptide

<400> 617

Met Ser Ala Ser Leu Val Arg Ala Thr Val Arg Ala
1 5 10

<210> 618

<211> 53
<212> PRT
<213> Artificial Sequence

<220>
<223> Q9BV79 mitochondrial targeting peptide

<400> 618

Met Trp Val Cys Ser Thr Leu Trp Arg Val Arg Thr Pro Ala Arg Gln
1 5 10 15

Trp Arg Gly Leu Leu Pro Ala Ser Gly Cys His Gly Pro Ala Ala Ser
20 25 30

Ser Tyr Ser Ala Ser Ala Glu Pro Ala Arg Val Arg Ala Leu Val Tyr
35 40 45

Gly His His Gly Asp
50

<210> 619
<211> 18
<212> PRT
<213> Artificial Sequence

<220>
<223> Q9BVV7 mitochondrial targeting peptide

<400> 619

Met Ile Cys Thr Phe Leu Arg Ala Val Gln Tyr Thr Glu Lys Leu His
1 5 10 15

Arg Ser

<210> 620
<211> 46
<212> PRT
<213> Artificial Sequence

<220>
<223> Q9BW91 mitochondrial targeting peptide

<400> 620

Met Ala Gly Arg Leu Leu Gly Lys Ala Leu Ala Ala Val Ser Leu Ser
1 5 10 15

Leu Ala Leu Ala Ser Val Thr Ile Arg Ser Ser Arg Cys Arg Gly Ile
20 25 30

Gln Ala Phe Arg Asn Ser Phe Ser Ser Ser Trp Phe His Leu
35 40 45

<210> 621
<211> 17
<212> PRT

<213> Artificial Sequence

<220>
<223> Q9BX68 mitochondrial targeting peptide

<400> 621

Met Ala Ala Ala Val Val Leu Ala Ala Gly Leu Arg Ala Ala Arg Arg
1 5 10 15

Ala

<210> 622
<211> 77
<212> PRT
<213> Artificial Sequence

<220>
<223> Q9BXM7 mitochondrial targeting peptide

<400> 622

Met Ala Val Arg Gln Ala Leu Gly Arg Gly Leu Gln Leu Gly Arg Ala
1 5 10 15

Leu Leu Leu Arg Phe Thr Gly Lys Pro Gly Arg Ala Tyr Gly Leu Gly
20 25 30

Arg Pro Gly Pro Ala Ala Gly Cys Val Arg Gly Glu Arg Pro Gly Trp
35 40 45

Ala Ala Gly Pro Gly Ala Glu Pro Arg Arg Val Gly Leu Gly Leu Pro
50 55 60

Asn Arg Leu Arg Phe Phe Arg Gln Ser Val Ala Gly Leu
65 70 75

<210> 623
<211> 39
<212> PRT
<213> Artificial Sequence

<220>
<223> Q9BYC2 mitochondrial targeting peptide

<400> 623

Met Ala Ala Leu Arg Leu Leu Ala Ser Val Leu Gly Arg Gly Val Pro
1 5 10 15

Ala Gly Gly Ser Gly Leu Ala Leu Ser Gln Gly Cys Ala Arg Cys Phe
20 25 30

Ala Thr Ser Pro Arg Leu Arg
35

<210> 624

<211> 45
<212> PRT
<213> Artificial Sequence

<220>
<223> Q9BYC9 mitochondrial targeting peptide

<400> 624

Met Val Phe Leu Thr Ala Gln Leu Trp Leu Arg Asn Arg Val Thr Asp
1 5 10 15

Arg Tyr Phe Arg Ile Gln Glu Val Leu Lys His Ala Arg His Phe Arg
20 25 30

Gly Arg Lys Asn Arg Cys Tyr Arg Leu Ala Val Arg Thr
35 40 45

<210> 625
<211> 50
<212> PRT
<213> Artificial Sequence

<220>
<223> Q9BYD6 mitochondrial targeting peptide

<400> 625

Met Ala Ala Ala Val Arg Cys Met Gly Arg Ala Leu Ile His His Gln
1 5 10 15

Arg His Ser Leu Ser Lys Met Val Tyr Gln Thr Ser Leu Cys Ser Cys
20 25 30

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

Ser Ala
50

<210> 626
<211> 27
<212> PRT
<213> Artificial Sequence

<220>
<223> Q9BYN8 mitochondrial targeting peptide

<400> 626

Met Leu Arg Ala Leu Ser Arg Leu Gly Ala Gly Thr Pro Cys Arg Pro
1 5 10 15

Arg Ala Pro Leu Val Leu Pro Ala Arg Gly Arg
20 25

<210> 627
<211> 37
<212> PRT

<213> Artificial Sequence

<220>
<223> Q9BYT8 mitochondrial targeting peptide

<400> 627

Met Ile Ala Arg Cys Leu Leu Ala Val Arg Ser Leu Arg Arg Val Gly
1 5 10 15

Gly Ser Arg Ile Leu Leu Arg Met Thr Leu Gly Arg Glu Val Met Ser
20 25 30

Pro Leu Gln Ala Met
35

<210> 628
<211> 41
<212> PRT
<213> Artificial Sequence

<220>
<223> Q9BYV1 mitochondrial targeting peptide

<400> 628

Met Thr Leu Ile Trp Arg His Leu Leu Arg Pro Leu Cys Leu Val Thr
1 5 10 15

Ser Ala Pro Arg Ile Leu Glu Met His Pro Phe Leu Ser Leu Gly Thr
20 25 30

Ser Arg Thr Ser Val Thr Lys Leu Ser
35 40

<210> 629
<211> 46
<212> PRT
<213> Artificial Sequence

<220>
<223> Q9BZ23 mitochondrial targeting peptide

<400> 629

Met Arg Arg Leu Gly Pro Phe His Pro Arg Val His Trp Ala Ala Pro
1 5 10 15

Pro Ser Leu Ser Ser Gly Leu His Arg Leu Leu Phe Leu Arg Gly Thr
20 25 30

Arg Ile Pro Ser Ser Thr Thr Leu Ser Pro Pro Arg His Asp
35 40 45

<210> 630
<211> 29
<212> PRT
<213> Artificial Sequence

<220>
<223> Q9BZE1 mitochondrial targeting peptide

<400> 630

Met Ala Leu Ala Ser Gly Pro Ala Arg Arg Ala Leu Ala Gly Ser Gly
1 5 10 15

Gln Leu Gly Leu Gly Gly Phe Gly Ala Pro Arg Arg Gly
20 25

<210> 631
<211> 42
<212> PRT
<213> Artificial Sequence

<220>
<223> Q9GZT6 mitochondrial targeting peptide

<400> 631

Met Asn Ser Arg Gln Ala Trp Arg Leu Phe Leu Ser Gln Gly Arg Gly
1 5 10 15

Asp Arg Trp Val Ser Arg Pro Arg Gly His Phe Ser Pro Ala Leu Arg
20 25 30

Arg Glu Phe Phe Thr Thr Thr Thr Lys Glu
35 40

<210> 632
<211> 36
<212> PRT
<213> Artificial Sequence

<220>
<223> Q9H078 mitochondrial targeting peptide

<400> 632

Met Leu Gly Ser Leu Val Leu Arg Arg Lys Ala Leu Ala Pro Arg Leu
1 5 10 15

Leu Leu Arg Leu Leu Arg Ser Pro Thr Leu Arg Gly His Gly Gly Ala
20 25 30

Ser Gly Arg Asn
35

<210> 633
<211> 34
<212> PRT
<213> Artificial Sequence

<220>
<223> Q9H1K1 mitochondrial targeting peptide

<400> 633

Met Ala Ala Ala Gly Ala Phe Arg Leu Arg Arg Ala Ala Ser Ala Leu

1 5 10 15

Leu Leu Arg Ser Pro Arg Leu Pro Ala Arg Glu Leu Ser Ala Pro Ala
20 25 30

Arg Leu

<210> 634
<211> 31
<212> PRT
<213> Artificial Sequence

<220>
<223> Q9H2K0 mitochondrial targeting peptide

<400> 634

Met Ala Ala Leu Phe Leu Lys Arg Leu Thr Leu Gln Thr Val Lys Ser
1 5 10 15

Glu Asn Ser Cys Ile Arg Cys Phe Gly Lys His Ile Leu Gln Lys
20 25 30

<210> 635
<211> 32
<212> PRT
<213> Artificial Sequence

<220>
<223> Q9H2U2 mitochondrial targeting peptide

<400> 635

Met Ser Ala Leu Leu Arg Leu Leu Arg Thr Gly Ala Pro Ala Ala Ala
1 5 10 15

Cys Leu Arg Leu Gly Thr Ser Ala Gly Thr Gly Ser Arg Arg Ala Met
20 25 30

<210> 636
<211> 52
<212> PRT
<213> Artificial Sequence

<220>
<223> Q9H300 mitochondrial targeting peptide

<400> 636

Met Ala Trp Arg Gly Trp Ala Gln Arg Gly Trp Gly Cys Gly Gln Ala
1 5 10 15

Trp Gly Ala Ser Val Gly Gly Arg Ser Cys Glu Glu Leu Thr Ala Val
20 25 30

Leu Thr Pro Pro Gln Leu Leu Gly Arg Arg Phe Asn Phe Phe Ile Gln
35 40 45

Gln Lys Cys Gly
    50

<210> 637
<211> 47
<212> PRT
<213> Artificial Sequence

<220>
<223> Q9H3H1 mitochondrial targeting peptide

<400> 637

Met Ala Ser Val Ala Ala Ala Arg Ala Val Pro Val Gly Ser Gly Leu
1   5   10   15

Arg Gly Leu Gln Arg Thr Leu Pro Leu Val Val Ile Leu Gly Ala Thr
            20   25   30

Gly Thr Gly Lys Ser Thr Leu Ala Leu Gln Leu Gly Gln Arg Leu
        35   40   45

<210> 638
<211> 35
<212> PRT
<213> Artificial Sequence

<220>
<223> Q9H3J6 mitochondrial targeting peptide

<400> 638

Met Ser Thr Val Gly Leu Phe His Phe Pro Thr Pro Leu Thr Arg Ile
1   5   10   15

Cys Pro Ala Pro Trp Gly Leu Arg Leu Trp Glu Lys Leu Thr Leu Leu
            20   25   30

Ser Pro Gly
        35

<210> 639
<211> 44
<212> PRT
<213> Artificial Sequence

<220>
<223> Q9H3K2 mitochondrial targeting peptide

<400> 639

Met Leu Ala Ala Arg Leu Val Cys Leu Arg Thr Leu Pro Ser Arg Val
1   5   10   15

Phe His Pro Ala Phe Thr Lys Ala Ser Pro Val Val Lys Asn Ser Ile
            20   25   30

Thr Lys Asn Gln Trp Leu Leu Thr Pro Ser Arg Glu

35 40

<210> 640
<211> 38
<212> PRT
<213> Artificial Sequence

<220>
<223> Q9H3L0 mitochondrial targeting peptide

<400> 640

Met Ala Asn Val Leu Cys Asn Arg Ala Arg Leu Val Ser Tyr Leu Pro
1 5 10 15

Gly Phe Cys Ser Leu Val Lys Arg Val Val Asn Pro Lys Ala Phe Ser
20 25 30

Thr Ala Gly Ser Ser Gly
35

<210> 641
<211> 29
<212> PRT
<213> Artificial Sequence

<220>
<223> Q9H4B0 mitochondrial targeting peptide

<400> 641

Met Leu Ile Leu Thr Lys Thr Ala Gly Val Phe Phe Lys Pro Ser Lys
1 5 10 15

Arg Lys Val Tyr Glu Phe Leu Arg Ser Phe Asn Phe His
20 25

<210> 642
<211> 47
<212> PRT
<213> Artificial Sequence

<220>
<223> Q9H4I9 mitochondrial targeting peptide

<400> 642

Met Ala Ser Gly Ala Ala Arg Trp Leu Val Leu Ala Pro Val Arg Ser
1 5 10 15

Gly Ala Leu Arg Ser Gly Pro Ser Leu Arg Lys Asp Gly Asp Val Ser
20 25 30

Ala Ala Trp Ser Gly Ser Gly Arg Ser Leu Val Pro Ser Arg Ser
35 40 45

<210> 643
<211> 19
<212> PRT

<213> Artificial Sequence

<220>
<223> Q9H5Q4 mitochondrial targeting peptide

<400> 643

Met Trp Ile Pro Val Val Gly Leu Pro Arg Arg Leu Arg Leu Ser Ala
1 5 10 15

Leu Ala Gly

<210> 644
<211> 29
<212> PRT
<213> Artificial Sequence

<220>
<223> Q9H6R3 mitochondrial targeting peptide

<400> 644

Met Lys Pro Ser Trp Leu Gln Cys Arg Lys Val Thr Ser Ala Gly Gly
1 5 10 15

Leu Gly Gly Pro Leu Pro Gly Ser Ser Pro Ala Arg Gly
20 25

<210> 645
<211> 19
<212> PRT
<213> Artificial Sequence

<220>
<223> Q9H7H0 mitochondrial targeting peptide

<400> 645

Met Ala Ala Ala Leu Lys Cys Leu Leu Thr Leu Gly Arg Trp Cys Pro
1 5 10 15

Gly Leu Gly

<210> 646
<211> 37
<212> PRT
<213> Artificial Sequence

<220>
<223> Q9H8M1 mitochondrial targeting peptide

<400> 646

Met Ala Ala Arg Thr Gly His Thr Ala Leu Arg Arg Val Val Ser Gly
1 5 10 15

Cys Arg Pro Lys Ser Ala Thr Ala Ala Gly Ala Gln Ala Pro Val Arg
20 25 30

Asn Gly Arg Tyr Leu
        35

<210> 647
<211> 30
<212> PRT
<213> Artificial Sequence

<220>
<223> Q9H9J2 mitochondrial targeting peptide

<400> 647

Met Ala Ser Gly Leu Val Arg Leu Leu Gln Gln Gly His Arg Cys Leu
1   5   10   15

Leu Ala Pro Val Ala Pro Lys Leu Val Pro Pro Val Arg Gly
            20   25   30

<210> 648
<211> 51
<212> PRT
<213> Artificial Sequence

<220>
<223> Q9H9P8 mitochondrial targeting peptide

<400> 648

Met Val Pro Ala Leu Arg Tyr Leu Val Gly Ala Cys Gly Arg Ala Arg
1   5   10   15

Gly Leu Phe Ala Gly Gly Ser Pro Gly Ala Cys Gly Phe Ala Ser Gly
            20   25   30

Arg Pro Arg Pro Leu Cys Gly Gly Ser Arg Ser Ala Ser Thr Ser Ser
        35   40   45

Phe Asp Ile
    50

<210> 649
<211> 17
<212> PRT
<213> Artificial Sequence

<220>
<223> Q9HA92 mitochondrial targeting peptide

<400> 649

Met Ala Leu Pro Gly Ala Arg Ala Arg Gly Trp Ala Ala Ala Ala Arg
1   5   10   15

Ala

<210> 650

<211> 38
<212> PRT
<213> Artificial Sequence

<220>
<223> Q9HAC7 mitochondrial targeting peptide

<400> 650

Met Pro Ser Glu Thr His Ala Met Leu Ala Thr Leu Ala Arg Val Ala
1 5 10 15

Ala Leu Arg Arg Thr Cys Leu Phe Ser Gly Arg Gly Gly Gly Arg Gly
20 25 30

Leu Trp Thr Gly Arg Pro
35

<210> 651
<211> 27
<212> PRT
<213> Artificial Sequence

<220>
<223> Q9HAV7 mitochondrial targeting peptide

<400> 651

Met Ala Ala Gln Cys Val Arg Leu Ala Arg Arg Ser Leu Pro Ala Leu
1 5 10 15

Ala Leu Ser Leu Arg Pro Ser Pro Arg Leu Leu
20 25

<210> 652
<211> 47
<212> PRT
<213> Artificial Sequence

<220>
<223> Q9HB07 mitochondrial targeting peptide

<400> 652

Met Gly His Gln Phe Leu Arg Gly Leu Leu Thr Leu Leu Leu Pro Pro
1 5 10 15

Pro Pro Leu Tyr Thr Arg His Arg Met Leu Gly Pro Glu Ser Val Pro
20 25 30

Pro Pro Lys Arg Ser Arg Ser Lys Leu Met Ala Pro Pro Arg Ile
35 40 45

<210> 653
<211> 39
<212> PRT
<213> Artificial Sequence

<220>
<223> Q9HBH1 mitochondrial targeting peptide

<400> 653

Met Ala Arg Leu Trp Gly Ala Leu Ser Leu Trp Pro Leu Trp Ala Ala
1 5 10 15

Val Pro Trp Gly Gly Ala Ala Ala Val Gly Val Arg Ala Cys Ser Ser
20 25 30

Thr Ala Ala Pro Asp Gly Val
35

<210> 654
<211> 40
<212> PRT
<213> Artificial Sequence

<220>
<223> Q9HC36 mitochondrial targeting peptide

<400> 654

Met Ala Ala Leu Val Arg Pro Ala Arg Phe Val Val Arg Pro Leu Leu
1 5 10 15

Gln Val Val Gln Ala Trp Asp Leu Asp Ala Arg Arg Trp Val Arg Ala
20 25 30

Leu Arg Arg Ser Pro Val Lys Val
35 40

<210> 655
<211> 22
<212> PRT
<213> Artificial Sequence

<220>
<223> Q9HCC0 mitochondrial targeting peptide

<400> 655

Met Trp Ala Val Leu Arg Leu Ala Leu Arg Pro Cys Ala Arg Ala Ser
1 5 10 15

Pro Ala Gly Pro Arg Ala
20

<210> 656
<211> 49
<212> PRT
<213> Artificial Sequence

<220>
<223> Q9HD23 mitochondrial targeting peptide

<400> 656

Met Glu Cys Leu Arg Ser Leu Pro Cys Leu Leu Pro Arg Ala Met Arg
1 5 10 15

Leu Pro Arg Arg Thr Leu Cys Ala Leu Ala Leu Asp Val Thr Ser Val
20 25 30

Gly Pro Pro Val Ala Ala Cys Gly Arg Arg Ala Asn Leu Ile Gly Arg
35 40 45

Ser

<210> 657
<211> 36
<212> PRT
<213> Artificial Sequence

<220>
<223> Q9NNW7 mitochondrial targeting peptide

<400> 657

Met Ala Ala Met Ala Val Ala Leu Arg Gly Leu Gly Gly Arg Phe Arg
1 5 10 15

Trp Arg Thr Gln Ala Val Ala Gly Gly Val Arg Gly Ala Ala Arg Gly
20 25 30

Ala Ala Ala Gly
35

<210> 658
<211> 34
<212> PRT
<213> Artificial Sequence

<220>
<223> Q9NP81 mitochondrial targeting peptide

<400> 658

Met Ala Ala Ser Met Ala Arg Arg Leu Trp Pro Leu Leu Thr Arg Arg
1 5 10 15

Gly Phe Arg Pro Arg Gly Gly Cys Ile Ser Asn Asp Ser Pro Arg Arg
20 25 30

Ser Phe

<210> 659
<211> 31
<212> PRT
<213> Artificial Sequence

<220>
<223> Q9NPB1 mitochondrial targeting peptide

<400> 659

Met Ile Arg Leu Gly Gly Trp Cys Ala Arg Arg Leu Cys Ser Ala Ala

1 5 10 15

Val Pro Ala Gly Arg Arg Gly Ala Ala Gly Gly Leu Gly Leu Ala
20 25 30

<210> 660
<211> 32
<212> PRT
<213> Artificial Sequence

<220>
<223> Q9NPH0 mitochondrial targeting peptide

<400> 660

Met Ile Thr Gly Val Phe Ser Met Arg Leu Trp Thr Pro Val Gly Val
1 5 10 15

Leu Thr Ser Leu Ala Tyr Cys Leu His Gln Arg Arg Val Ala Leu Ala
20 25 30

<210> 661
<211> 46
<212> PRT
<213> Artificial Sequence

<220>
<223> Q9NQ50 mitochondrial targeting peptide

<400> 661

Met Thr Ala Ser Val Leu Arg Ser Ile Ser Leu Ala Leu Arg Pro Thr
1 5 10 15

Ser Gly Leu Leu Gly Thr Trp Gln Thr Gln Leu Arg Glu Thr His Gln
20 25 30

Arg Ala Ser Leu Leu Ser Phe Trp Glu Leu Ile Pro Met Arg
35 40 45

<210> 662
<211> 58
<212> PRT
<213> Artificial Sequence

<220>
<223> Q9NQZ5 mitochondrial targeting peptide

<400> 662

Met Leu Pro Arg Arg Leu Leu Ala Ala Trp Leu Ala Gly Thr Arg Gly
1 5 10 15

Gly Gly Leu Leu Ala Leu Leu Ala Asn Gln Cys Arg Phe Val Thr Gly
20 25 30

Leu Arg Val Arg Arg Ala Gln Gln Ile Ala Gln Leu Tyr Gly Arg Leu
35 40 45

Tyr Ser Glu Ser Ser Arg Arg Val Leu Leu
    50   55

<210> 663
<211> 55
<212> PRT
<213> Artificial Sequence

<220>
<223> Q9NR28 mitochondrial targeting peptide

<400> 663

Met Ala Ala Leu Lys Ser Trp Leu Ser Arg Ser Val Thr Ser Phe Phe
1   5   10   15

Arg Tyr Arg Gln Cys Leu Cys Val Pro Val Val Ala Asn Phe Lys Lys
            20   25   30

Arg Cys Phe Ser Glu Leu Ile Arg Pro Trp His Lys Thr Val Thr Ile
        35   40   45

Gly Phe Gly Val Thr Leu Cys
    50   55

<210> 664
<211> 105
<212> PRT
<213> Artificial Sequence

<220>
<223> Q9NRK6 mitochondrial targeting peptide

<400> 664

Met Arg Gly Pro Pro Ala Trp Pro Leu Arg Leu Leu Glu Pro Pro Ser
1   5   10   15

Pro Ala Glu Pro Gly Arg Leu Leu Pro Val Ala Cys Val Trp Ala Ala
            20   25   30

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

Ala Arg Leu Trp Gly Ala Gly Pro Ala Leu Leu Trp Gly Val Gly Ala
    50   55   60

Ala Arg Arg Trp Arg Ser Gly Cys Arg Gly Gly Gly Pro Gly Ala Ser
65   70   75   80

Arg Gly Val Leu Gly Leu Ala Arg Leu Leu Gly Leu Trp Ala Arg Gly
                85   90   95

Pro Gly Ser Cys Arg Cys Gly Ala Phe
            100   105

<210> 665
<211> 30
<212> PRT
<213> Artificial Sequence

<220>
<223> Q9NRP4 mitochondrial targeting peptide

<400> 665

Met Pro Gly Arg His Val Ser Arg Val Arg Ala Leu Tyr Lys Arg Val
1 5 10 15

Leu Gln Leu His Arg Val Leu Pro Pro Asp Leu Lys Ser Leu
20 25 30

<210> 666
<211> 8
<212> PRT
<213> Artificial Sequence

<220>
<223> Q9NRX2 mitochondrial targeting peptide

<400> 666

Met Arg Leu Ser Val Ala Ala Ala
1 5

<210> 667
<211> 19
<212> PRT
<213> Artificial Sequence

<220>
<223> Q9NS18 mitochondrial targeting peptide

<400> 667

Met Ile Trp Arg Arg Ala Ala Leu Ala Gly Thr Arg Leu Val Trp Ser
1 5 10 15

Arg Ser Gly

<210> 668
<211> 48
<212> PRT
<213> Artificial Sequence

<220>
<223> Q9NSE4 mitochondrial targeting peptide

<400> 668

Met Arg Trp Gly Leu Arg Pro Arg Gly Pro Gly Ala Ala Ala Leu Ala
1 5 10 15

Thr Ala Arg Ser Leu Trp Gly Thr Pro Arg Leu Pro Cys Ser Pro Gly
20 25 30

Trp Gln Gly Ala Thr Lys Arg Leu Leu Val Arg Ser Val Ser Gly Ala
35 40 45

<210> 669
<211> 37
<212> PRT
<213> Artificial Sequence

<220>
<223> Q9NUB1 mitochondrial targeting peptide

<400> 669

Met Ala Ala Arg Thr Leu Gly Arg Gly Val Gly Arg Leu Leu Gly Ser
1 5 10 15

Leu Arg Gly Leu Ser Gly Gln Pro Ala Arg Pro Pro Cys Gly Val Ser
20 25 30

Ala Pro Arg Arg Ala
35

<210> 670
<211> 52
<212> PRT
<213> Artificial Sequence

<220>
<223> Q9NUJ1 mitochondrial targeting peptide

<400> 670

Met Ala Val Ala Arg Leu Ala Ala Val Ala Ala Trp Val Pro Cys Arg
1 5 10 15

Ser Trp Gly Trp Ala Ala Val Pro Phe Gly Pro His Arg Gly Leu Ser
20 25 30

Val Leu Leu Ala Arg Ile Pro Gln Arg Ala Pro Arg Trp Leu Pro Ala
35 40 45

Cys Arg Gln Lys
50

<210> 671
<211> 55
<212> PRT
<213> Artificial Sequence

<220>
<223> Q9NUT2 mitochondrial targeting peptide

<400> 671

Met Leu Val His Leu Phe Arg Val Gly Ile Arg Gly Gly Pro Phe Pro
1 5 10 15

Gly Arg Leu Leu Pro Pro Leu Arg Phe Gln Thr Phe Ser Ala Val Arg

20 25 30

Asn Thr Trp Arg Asn Gly Lys Thr Gly Gln Leu His Lys Ala Glu Gly
35 40 45

Glu Tyr Ser Asp Gly Tyr Arg
50 55

<210> 672
<211> 15
<212> PRT
<213> Artificial Sequence

<220>
<223> Q9NVH6 mitochondrial targeting peptide

<400> 672

Met Trp Tyr His Arg Leu Ser His Leu His Ser Arg Leu Gln Asp
1 5 10 15

<210> 673
<211> 34
<212> PRT
<213> Artificial Sequence

<220>
<223> Q9NVS2 mitochondrial targeting peptide

<400> 673

Met Ala Ala Leu Lys Ala Leu Val Ser Gly Cys Gly Arg Leu Leu Arg
1 5 10 15

Gly Leu Leu Ala Gly Pro Ala Ala Thr Ser Trp Ser Arg Leu Pro Ala
20 25 30

Arg Gly

<210> 674
<211> 37
<212> PRT
<213> Artificial Sequence

<220>
<223> Q9NVV4 mitochondrial targeting peptide

<400> 674

Met Ala Val Pro Gly Val Gly Leu Leu Thr Arg Leu Asn Leu Cys Ala
1 5 10 15

Arg Arg Arg Thr Arg Val Gln Arg Pro Ile Val Arg Leu Leu Ser Cys
20 25 30

Pro Gly Thr Val Ala
35

<210> 675
<211> 35
<212> PRT
<213> Artificial Sequence

<220>
<223> Q9NWR8 mitochondrial targeting peptide

<400> 675

Met Leu Gln Arg Gly Leu Trp Pro Trp Arg Thr Arg Leu Leu Pro Thr
1 5 10 15

Pro Gly Thr Trp Arg Pro Ala Arg Pro Trp Pro Leu Pro Pro Pro Pro
20 25 30

Gln Val Leu
35

<210> 676
<211> 12
<212> PRT
<213> Artificial Sequence

<220>
<223> Q9NWS8 mitochondrial targeting peptide

<400> 676

Met Pro Ala Thr Leu Leu Arg Ala Val Ala Arg Ser
1 5 10

<210> 677
<211> 27
<212> PRT
<213> Artificial Sequence

<220>
<223> Q9NWU1 mitochondrial targeting peptide

<400> 677

Met Ser Asn Cys Leu Gln Asn Phe Leu Lys Ile Thr Ser Thr Arg Leu
1 5 10 15

Leu Cys Ser Arg Leu Cys Gln Gln Leu Arg Ser
20 25

<210> 678
<211> 40
<212> PRT
<213> Artificial Sequence

<220>
<223> Q9NWU5 mitochondrial targeting peptide

<400> 678

Met Ala Ala Ala Val Leu Gly Gln Leu Gly Ala Leu Trp Ile His Asn
1 5 10 15

Leu Arg Ser Arg Gly Lys Leu Ala Leu Gly Val Leu Pro Gln Ser Tyr
20 25 30

Ile His Thr Ser Ala Ser Leu Asp
35 40

<210> 679
<211> 29
<212> PRT
<213> Artificial Sequence

<220>
<223> Q9NX14 mitochondrial targeting peptide

<400> 679

Met Ala Ala Gly Leu Phe Gly Leu Ser Ala Arg Arg Leu Leu Ala Ala
1 5 10 15

Ala Ala Thr Arg Gly Leu Pro Ala Ala Arg Val Arg Trp
20 25

<210> 680
<211> 29
<212> PRT
<213> Artificial Sequence

<220>
<223> Q9NX18 mitochondrial targeting peptide

<400> 680

Met Ala Val Ser Thr Val Phe Ser Thr Ser Ser Leu Met Leu Ala Leu
1 5 10 15

Ser Arg His Ser Leu Leu Ser Pro Leu Leu Ser Val Thr
20 25

<210> 681
<211> 36
<212> PRT
<213> Artificial Sequence

<220>
<223> Q9NX20 mitochondrial targeting peptide

<400> 681

Met Trp Arg Leu Leu Ala Arg Ala Ser Ala Pro Leu Leu Arg Val Pro
1 5 10 15

Leu Ser Asp Ser Trp Ala Leu Leu Pro Ala Ser Ala Gly Val Lys Thr
20 25 30

Leu Leu Pro Val
35

<210> 682

<211> 27
<212> PRT
<213> Artificial Sequence

<220>
<223> Q9NX46 mitochondrial targeting peptide

<400> 682

Met Ala Ala Ala Ala Met Ala Ala Ala Ala Gly Gly Gly Ala Gly Ala
1 5 10 15

Ala Arg Ser Leu Ser Arg Phe Arg Gly Cys Leu
20 25

<210> 683
<211> 36
<212> PRT
<213> Artificial Sequence

<220>
<223> Q9NXA8 mitochondrial targeting peptide

<400> 683

Met Arg Pro Leu Gln Ile Val Pro Ser Arg Leu Ile Ser Gln Leu Tyr
1 5 10 15

Cys Gly Leu Lys Pro Pro Ala Ser Thr Arg Asn Gln Ile Cys Leu Lys
20 25 30

Met Ala Arg Pro
35

<210> 684
<211> 85
<212> PRT
<213> Artificial Sequence

<220>
<223> Q9NZJ6 mitochondrial targeting peptide

<400> 684

Met Trp Ser Gly Arg Lys Leu Gly Ser Ser Gly Gly Trp Phe Leu Arg
1 5 10 15

Val Leu Gly Pro Gly Gly Cys Asn Thr Lys Ala Ala Arg Pro Leu Ile
20 25 30

Ser Ser Ala Val Tyr Val Lys Asn Gln Leu Ser Gly Thr Leu Gln Ile
35 40 45

Lys Pro Gly Val Phe Asn Glu Tyr Arg Thr Ile Trp Phe Lys Ser Tyr
50 55 60

Arg Thr Ile Phe Ser Cys Leu Asn Arg Ile Lys Ser Phe Arg Tyr Pro
65 70 75 80

Trp Ala Arg Leu Tyr
85

<210> 685
<211> 21
<212> PRT
<213> Artificial Sequence

<220>
<223> Q9P015 mitochondrial targeting peptide

<400> 685

Met Ala Gly Pro Leu Gln Gly Gly Gly Ala Arg Ala Leu Asp Leu Leu
1 5 10 15

Arg Gly Leu Pro Arg
20

<210> 686
<211> 71
<212> PRT
<213> Artificial Sequence

<220>
<223> Q9P0J1 mitochondrial targeting peptide

<400> 686

Met Pro Ala Pro Thr Gln Leu Phe Phe Pro Leu Ile Arg Asn Cys Glu
1 5 10 15

Leu Ser Arg Ile Tyr Gly Thr Ala Cys Tyr Cys His His Lys His Leu
20 25 30

Cys Cys Ser Ser Ser Tyr Ile Pro Gln Ser Arg Leu Arg Tyr Thr Pro
35 40 45

His Pro Ala Tyr Ala Thr Phe Cys Arg Pro Lys Glu Asn Trp Trp Gln
50 55 60

Tyr Thr Gln Gly Arg Arg Tyr
65 70

<210> 687
<211> 66
<212> PRT
<213> Artificial Sequence

<220>
<223> Q9P2J9 mitochondrial targeting peptide

<400> 687

Met Ser Ser Thr Val Ser Tyr Trp Ile Leu Asn Ser Thr Arg Asn Ser
1 5 10 15

Ile Ala Thr Leu Gln Gly Gly Arg Arg Leu Tyr Ser Arg Tyr Val Ser

20 25 30

Asn Arg Asn Lys Leu Lys Trp Arg Leu Phe Ser Arg Val Pro Pro Thr
35 40 45

Leu Asn Ser Ser Pro Cys Gly Gly Phe Thr Leu Cys Lys Ala Tyr Arg
50 55 60

His Thr
65

<210> 688
<211> 52
<212> PRT
<213> Artificial Sequence

<220>
<223> Q9P2R7 mitochondrial targeting peptide

<400> 688

Met Ala Ala Ser Met Phe Tyr Gly Arg Leu Val Ala Val Ala Thr Leu
1 5 10 15

Arg Asn His Arg Pro Arg Thr Ala Gln Arg Ala Ala Ala Gln Val Leu
20 25 30

Gly Ser Ser Gly Leu Phe Asn Asn His Gly Leu Gln Val Gln Gln Gln
35 40 45

Gln Gln Arg Asn
50

<210> 689
<211> 32
<212> PRT
<213> Artificial Sequence

<220>
<223> Q9UDR5 mitochondrial targeting peptide

<400> 689

Met Leu Gln Val His Arg Thr Gly Leu Gly Arg Leu Gly Val Ser Leu
1 5 10 15

Ser Lys Gly Leu His His Lys Ala Val Leu Ala Val Arg Arg Glu Asp
20 25 30

<210> 690
<211> 26
<212> PRT
<213> Artificial Sequence

<220>
<223> Q9UGC7 mitochondrial targeting peptide

<400> 690

Met Arg Ser Arg Val Leu Trp Gly Ala Ala Arg Trp Leu Trp Pro Arg
1 5 10 15

Arg Ala Val Gly Pro Ala Arg Arg Pro Leu
20 25

<210> 691
<211> 18
<212> PRT
<213> Artificial Sequence

<220>
<223> Q9UGM6 mitochondrial targeting peptide

<400> 691

Met Ala Leu His Ser Met Arg Lys Ala Arg Glu Arg Trp Ser Phe Ile
1 5 10 15

Arg Ala

<210> 692
<211> 50
<212> PRT
<213> Artificial Sequence

<220>
<223> Q9UI17 mitochondrial targeting peptide

<400> 692

Met Leu Arg Pro Gly Ala Gln Leu Leu Arg Gly Leu Leu Leu Arg Ser
1 5 10 15

Cys Pro Leu Gln Gly Ser Pro Gly Arg Pro Arg Ser Val Cys Gly Arg
20 25 30

Glu Gly Glu Glu Lys Pro Pro Leu Ser Ala Glu Thr Gln Trp Lys Asp
35 40 45

Arg Ala
50

<210> 693
<211> 14
<212> PRT
<213> Artificial Sequence

<220>
<223> Q9UI32 mitochondrial targeting peptide

<400> 693

Met Arg Ser Met Lys Ala Leu Gln Lys Ala Leu Ser Arg Ala
1 5 10

<210> 694

<211> 18
<212> PRT
<213> Artificial Sequence

<220>
<223> Q9UI43 mitochondrial targeting peptide

<400> 694

Met Ala Gly Tyr Leu Lys Leu Val Cys Val Ser Phe Gln Arg Gln Gly
1 5 10 15

Phe His

<210> 695
<211> 25
<212> PRT
<213> Artificial Sequence

<220>
<223> Q9UII2 mitochondrial targeting peptide

<400> 695

Met Ala Val Thr Ala Leu Ala Ala Arg Thr Trp Leu Gly Val Trp Gly
1 5 10 15

Val Arg Thr Met Gln Ala Arg Gly Phe
20 25

<210> 696
<211> 23
<212> PRT
<213> Artificial Sequence

<220>
<223> Q9UJ68 mitochondrial targeting peptide

<400> 696

Met Leu Ser Ala Thr Arg Arg Ala Cys Gln Leu Leu Leu Leu His Ser
1 5 10 15

Leu Phe Pro Val Pro Arg Met
20

<210> 697
<211> 28
<212> PRT
<213> Artificial Sequence

<220>
<223> Q9UJZ1 mitochondrial targeting peptide

<400> 697

Met Leu Ala Arg Ala Ala Arg Gly Thr Gly Ala Leu Leu Leu Arg Gly
1 5 10 15

Ser Leu Leu Ala Ser Gly Arg Ala Pro Arg Arg Ala

20 25

<210> 698
<211> 22
<212> PRT
<213> Artificial Sequence

<220>
<223> Q9UKU7 mitochondrial targeting peptide

<400> 698

Met Leu Trp Ser Gly Cys Arg Arg Phe Gly Ala Arg Leu Gly Cys Leu
1 5 10 15

Pro Gly Gly Leu Arg Val
20

<210> 699
<211> 22
<212> PRT
<213> Artificial Sequence

<220>
<223> Q9UL12 mitochondrial targeting peptide

<400> 699

Met Ala Ser Leu Ser Arg Ala Leu Arg Val Ala Ala Ala His Pro Arg
1 5 10 15

Gln Ser Pro Thr Arg Gly
20

<210> 700
<211> 73
<212> PRT
<213> Artificial Sequence

<220>
<223> Q9ULD0 mitochondrial targeting peptide

<400> 700

Met Ser Gln Leu Arg Leu Leu Pro Ser Arg Leu Gly Val Gln Ala Ala
1 5 10 15

Arg Leu Leu Ala Ala His Asp Val Pro Val Phe Gly Trp Arg Ser Arg
20 25 30

Ser Ser Gly Pro Pro Ala Thr Phe Pro Ser Ser Lys Gly Gly Gly Gly
35 40 45

Ser Ser Tyr Met Glu Glu Met Tyr Phe Ala Trp Leu Glu Asn Pro Gln
50 55 60

Ser Val His Lys Ser Trp Asp Ser Phe
65 70

<210> 701
<211> 9
<212> PRT
<213> Artificial Sequence

<220>
<223> Q9UMS0 mitochondrial targeting peptide

<400> 701

Met Ala Ala Thr Ala Arg Arg Gly Trp
1 5

<210> 702
<211> 25
<212> PRT
<213> Artificial Sequence

<220>
<223> Q9Y234 mitochondrial targeting peptide

<400> 702

Met Leu Ile Pro Phe Ser Met Lys Asn Cys Phe Gln Leu Leu Cys Asn
1 5 10 15

Cys Gln Val Pro Ala Ala Gly Phe Lys
20 25

<210> 703
<211> 41
<212> PRT
<213> Artificial Sequence

<220>
<223> Q9Y2C4 mitochondrial targeting peptide

<400> 703

Met Ala Ile Lys Ser Ile Ala Ser Arg Leu Arg Gly Ser Arg Arg Phe
1 5 10 15

Leu Ser Gly Phe Val Ala Gly Ala Val Val Gly Ala Ala Gly Ala Gly
20 25 30

Leu Ala Ala Leu Gln Phe Phe Arg Ser
35 40

<210> 704
<211> 33
<212> PRT
<213> Artificial Sequence

<220>
<223> Q9Y2D0 mitochondrial targeting peptide

<400> 704

Met Val Val Met Asn Ser Leu Arg Val Ile Leu Gln Ala Ser Pro Gly
1 5 10 15

Lys Leu Leu Trp Arg Lys Phe Gln Ile Pro Arg Phe Met Pro Ala Arg
20 25 30

Pro

<210> 705
<211> 71
<212> PRT
<213> Artificial Sequence

<220>
<223> Q9Y2Q9 mitochondrial targeting peptide

<400> 705

Met Ala Ala Leu Cys Arg Thr Arg Ala Val Ala Ala Glu Ser His Phe
1 5 10 15

Leu Arg Val Phe Leu Phe Phe Arg Pro Phe Arg Gly Val Gly Thr Glu
20 25 30

Ser Gly Ser Glu Ser Gly Ser Ser Asn Ala Lys Glu Pro Lys Thr Arg
35 40 45

Ala Gly Gly Phe Ala Ser Ala Leu Glu Arg His Ser Glu Leu Leu Gln
50 55 60

Lys Val Glu Pro Leu Gln Lys
65 70

<210> 706
<211> 20
<212> PRT
<213> Artificial Sequence

<220>
<223> Q9Y2R5 mitochondrial targeting peptide

<400> 706

Met Ser Val Val Arg Ser Ser Val His Ala Arg Trp Ile Val Gly Lys
1 5 10 15

Val Ile Gly Thr
20

<210> 707
<211> 37
<212> PRT
<213> Artificial Sequence

<220>
<223> Q9Y2R9 mitochondrial targeting peptide

<400> 707

Met Ala Ala Pro Ala Val Lys Val Ala Arg Gly Trp Ser Gly Leu Ala

1 5 10 15

Leu Gly Val Arg Arg Ala Val Leu Gln Leu Pro Gly Leu Thr Gln Val
20 25 30

Arg Trp Ser Arg Tyr
35

<210> 708
<211> 25
<212> PRT
<213> Artificial Sequence

<220>
<223> Q9Y2Z2 mitochondrial targeting peptide

<400> 708

Met Phe Tyr Phe Arg Gly Cys Gly Arg Trp Val Ala Val Ser Phe Thr
1 5 10 15

Lys Gln Gln Phe Pro Leu Ala Arg Leu
20 25

<210> 709
<211> 16
<212> PRT
<213> Artificial Sequence

<220>
<223> Q9Y2Z4 mitochondrial targeting peptide

<400> 709

Met Ala Ala Pro Ile Leu Arg Ser Phe Ser Trp Gly Arg Trp Ser Gly
1 5 10 15

<210> 710
<211> 28
<212> PRT
<213> Artificial Sequence

<220>
<223> Q9Y2Z9 mitochondrial targeting peptide

<400> 710

Met Ala Ala Arg Leu Val Ser Arg Cys Gly Ala Val Arg Ala Ala Pro
1 5 10 15

His Ser Gly Pro Leu Val Ser Trp Arg Arg Trp Ser
20 25

<210> 711
<211> 21
<212> PRT
<213> Artificial Sequence

<220>
<223> Q9Y305 mitochondrial targeting peptide

<400> 711

Met Arg Arg Ala Ala Leu Arg Leu Cys Ala Leu Gly Lys Gly Gln Leu
1 5 10 15

Thr Pro Gly Arg Gly
20

<210> 712
<211> 24
<212> PRT
<213> Artificial Sequence

<220>
<223> Q9Y375 mitochondrial targeting peptide

<400> 712

Met Ala Leu Val His Lys Leu Leu Arg Gly Thr Tyr Phe Leu Arg Lys
1 5 10 15

Phe Ser Lys Pro Thr Ser Ala Leu
20

<210> 713
<211> 30
<212> PRT
<213> Artificial Sequence

<220>
<223> Q9Y3A0 mitochondrial targeting peptide

<400> 713

Met Ala Thr Leu Leu Arg Pro Val Leu Arg Arg Leu Cys Gly Leu Pro
1 5 10 15

Gly Leu Gln Arg Pro Ala Ala Glu Met Pro Leu Arg Ala Arg
20 25 30

<210> 714
<211> 25
<212> PRT
<213> Artificial Sequence

<220>
<223> Q9Y3B8 mitochondrial targeting peptide

<400> 714

Met Leu Gly Gly Ser Leu Gly Ser Arg Leu Leu Arg Gly Val Gly Gly
1 5 10 15

Ser His Gly Arg Phe Gly Ala Arg Gly
20 25

<210> 715
<211> 20
<212> PRT

<213> Artificial Sequence

<220>
<223> Q9Y3D2 mitochondrial targeting peptide

<400> 715

Met Ala Arg Leu Leu Trp Leu Leu Arg Gly Leu Thr Leu Gly Thr Ala
1 5 10 15

Pro Arg Arg Ala
20

<210> 716
<211> 34
<212> PRT
<213> Artificial Sequence

<220>
<223> Q9Y3D3 mitochondrial targeting peptide

<400> 716

Met Val His Leu Thr Thr Leu Leu Cys Lys Ala Tyr Arg Gly Gly His
1 5 10 15

Leu Thr Ile Arg Leu Ala Leu Gly Gly Cys Thr Asn Arg Pro Phe Tyr
20 25 30

Arg Ile

<210> 717
<211> 62
<212> PRT
<213> Artificial Sequence

<220>
<223> Q9Y3E5 mitochondrial targeting peptide

<400> 717

Met Pro Ser Lys Ser Leu Val Met Glu Tyr Leu Ala His Pro Ser Thr
1 5 10 15

Leu Gly Leu Ala Val Gly Val Ala Cys Gly Met Cys Leu Gly Trp Ser
20 25 30

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

His Thr Asp Thr Glu Ser Glu Ala Ser Ile Leu Gly Asp Ser
50 55 60

<210> 718
<211> 28
<212> PRT
<213> Artificial Sequence

<220>
<223> Q9Y6E7 mitochondrial targeting peptide

<400> 718

Met Lys Met Ser Phe Ala Leu Thr Phe Arg Ser Ala Lys Gly Arg Trp
1 5 10 15

Ile Ala Asn Pro Ser Gln Pro Cys Ser Lys Ala Ser
20 25

<210> 719
<211> 32
<212> PRT
<213> Artificial Sequence

<220>
<223> Q9Y6G3 mitochondrial targeting peptide

<400> 719

Met Ala Val Ala Ala Val Lys Trp Val Met Ser Lys Arg Thr Ile Leu
1 5 10 15

Lys His Leu Phe Pro Val Gln Asn Gly Ala Leu Tyr Cys Val Cys His
20 25 30

<210> 720
<211> 87
<212> RNA
<213> Artificial Sequence

<220>
<223> miR-142

<400> 720
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uccuacuuua uggaugagug uacugug 87

<210> 721
<211> 23
<212> RNA
<213> Artificial Sequence

<220>
<223> miR-142-3p

<400> 721
uguaguguuu ccuacuuuau gga 23

<210> 722
<211> 23
<212> RNA
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<220>
<223> miR-142-3p binding site

<400> 722
uccauaaagu aggaaacacu aca 23

<210> 723
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<212> RNA
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<220>
<223> miR-142-5p

<400> 723
cauaaaguag aaagcacuac u 21

<210> 724
<211> 21
<212> RNA
<213> Artificial Sequence

<220>
<223> miR-142-5p binding site

<400> 724
aguagugcuu ucuacuuuau g 21

<210> 725
<211> 142
<212> DNA
<213> Artificial Sequence

<220>
<223> Upstream UTR including miR142-3p

<400> 725
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ccccttgggc ctccccccag cccctcctcc ccttcctgca cccgtacccc cgtggtcttt 120

gaataaagtc tgagtgggcg gc 142

<210> 726
<211> 142
<212> DNA
<213> Artificial Sequence

<220>
<223> Upstream UTR including miR142-3p

<400> 726
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ccccttgggc ctccccccag cccctcctcc ccttcctgca cccgtacccc cgtggtcttt 120

gaataaagtc tgagtgggcg gc 142

<210> 727
<211> 142
<212> DNA
<213> Artificial Sequence

<220>
<223> Upstream UTR including miR142-3p

<400> 727
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ctacatgggc ctccccccag cccctcctcc ccttcctgca cccgtacccc cgtggtcttt 120

gaataaagtc tgagtgggcg gc 142

<210> 728
<211> 142
<212> DNA
<213> Artificial Sequence

<220>
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<400> 728
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ataaagtagg aaacactaca cccctcctcc ccttcctgca cccgtacccc cgtggtcttt 120

gaataaagtc tgagtgggcg gc 142

<210> 729
<211> 142
<212> DNA
<213> Artificial Sequence

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<400> 729
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ctcctccccc tctccataaa gtaggaaaca ctacactgca cccgtacccc cgtggtcttt 120

gaataaagtc tgagtgggcg gc 142

<210> 730
<211> 142
<212> DNA
<213> Artificial Sequence

<220>
<223> Upstream UTR including miR142-3p

<400> 730
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ctcctccccc tcctgcaccc gtacccccctc cataaagtag gaaacactac agtggtcttt 120

gaataaagtc tgagtgggcg gc 142

<210> 731
<211> 142
<212> DNA
<213> Artificial Sequence

<220>
<223> Upstream UTR including miR142-3p

<400> 731
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ctcctccccc tcctgcaccc gtacccccgt ggtctttgaa taaagttcca taaagtagga 120

aacactacac tgagtgggcg gc 142

<210> 732
<211> 2250
<212> DNA
<213> Artificial Sequence

<220>
<223> Codon optimized sequence that encodes an MCM polypeptide with the I671V mutation

<400> 732
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gagagcagcg gcagccggct gatccagcag cggctgctgc accagcagca gcccctgcac 120

cccgagtggg ccgccctggc caagaagcag ctgaagggca agaaccccga ggacctgatc 180

tggcacacgc ccgagggcat cagcatcaag cccctgtaca gcaagcggga caccatggac 240

ctgcccgagg agctgcccgg cgtgaagccc ttcacccggg gcccctaccc caccatgtac 300

accttccggc cctggaccat ccggcagtac gccggcttca gcaccgtgga ggagagcaac 360

aagttctaca aggacaacat caaggccggc cagcagggcc tgagcgtggc cttcgacctg 420

gccacccacc ggggctacga cagcgacaac ccacgggtgc ggggcgacgt gggcatggcc 480

ggcgtggcca tcgacaccgt ggaggacacc aagatcctgt tcgacggcat ccctctggag 540

aagatgagcg tgagcatgac catgaacggc gccgtgatcc ccgtgctggc caacttcatc 600

gtgaccggcg aggagcaggg cgtgcccaag gagaagctga ccggcaccat ccagaacgac 660

atcctgaagg agttcatggt gcggaacacc tacatcttcc ctcccgagcc cagcatgaag 720

atcatcgccg acatcttcga gtacaccgcc aagcacatgc ccaagttcaa cagcatcagc 780

atcagcggct accacatgca ggaggccggc gccgacgcca tcctggagct ggcctacacc 840

ctggccgacg gcctggagta cagccggacc ggcctgcagg ccggcctgac catcgacgag 900

ttcgcgcccc ggctgagctt cttctggggc atcggcatga acttctacat ggagatcgcc 960

aagatgcggg ccggccggcg gctgtgggcc cacctgatcg agaagatgtt ccagcccaag 1020

aacagcaaga gcctgctgct gcgggcccac tgccagacca gcggctggag cctgaccgag 1080

caggacccct acaacaacat cgtgcggacc gccatcgagg ccatggccgc cgtgttcggc 1140

ggcacccaga gcctgcacac caacagcttc gacgaggccc tgggcctgcc caccgtgaag 1200

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gccgccctga agctgatcaa cgagatcgag gagatgggcg gcatggccaa ggccgtggcc 1380

gagggcatcc ccaagctgcg gatcgaggag tgcgccgccc ggcggcaggc ccggatcgac 1440

agcggcagcg aggtgatcgt gggcgtgaac aagtaccagc tggagaagga ggacgccgtg 1500

gaggtgctgg ccatcgacaa caccagcgtg cggaaccggc agatcgagaa gctgaagaag 1560

atcaagagca gccgggacca ggccctggcc gagcggtgcc tggccgccct gaccgagtgc 1620

gccgccagcg gcgacggcaa catcctggcc ctggccgtgg acgccagccg ggcccggtgc 1680

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cggatggtga gcggcgccta ccggcaggag ttcggcgaga gcaaggagat caccagcgcc 1800

atcaagcggg tgcacaagtt catggagcgg gagggccggc ggccccggct gctggtggcc 1860

aagatgggcc aggacggcca cgaccggggc gccaaggtga tcgccaccgg cttcgccgac 1920

ctgggcttcg acgtggacat cggcccactg ttccagacgc cccgggaggt ggcccagcag 1980

gccgtggacg ccgacgtgca cgccgtgggc gtgagcaccc tggccgccgg ccacaagacc 2040

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tgcggcggcg tgatcccgcc ccaggactac gagttcctgt tcgaggtggg cgtgagcaac 2160

gtgttcggcc ccggcacccg gatccccaag gccgccgtgc aggtgctgga cgacatcgag 2220

aagtgcctgg agaagaagca gcagagcgtg 2250

<210> 733
<211> 2250
<212> DNA
<213> Artificial Sequence

<220>
<223> Codon optimized sequence that encodes an MCM polypeptide with the I671V mutation

<400> 733
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gagagcagcg gcagccggct gatccagcag cgcctcctcc accagcagca gcccctccac 120

cccgagtggg ccgccctcgc caagaagcag ctcaagggca agaaccccga ggacctcatc 180

tggcacacgc ccgagggcat ctccatcaag cccctctact ccaagcgcga caccatggac 240

ctccccgagg agctccccgg cgtcaagccc ttcacccgcg gcccctaccc caccatgtac 300

accttccgcc cctggaccat ccgccagtac gccggcttct ccaccgtcga ggagtccaac 360

aagttctaca aggacaacat caaggccggc cagcagggcc tctccgtcgc cttcgacctc 420

gccacccacc gcggctacga ctccgacaac ccgcgcgtcc gcggcgacgt cggcatggcc 480

ggcgtcgcca tcgacaccgt cgaggacacc aagatcctct tcgacggcat ccctctcgag 540

aagatgtccg tctccatgac catgaacggc gccgtcatcc ccgtcctcgc caacttcatc 600

gtcaccggcg aggagcaggg cgtccccaag gagaagctca ccggcaccat ccagaacgac 660

atcctcaagg agttcatggt ccgcaacacc tacatcttcc ctcccgagcc ctccatgaag 720

atcatcgccg acatcttcga gtacaccgcc aagcacatgc ccaagttcaa ctccatctcc 780

atctccggct accacatgca ggaggccggc gccgacgcca tcctcgagct cgcctacacc 840

ctcgccgacg gcctcgagta ctcccgcacc ggcctccagg ccggcctcac catcgacgag 900

ttcgcgcccc gcctctcctt cttctggggc atcggcatga acttctacat ggagatcgcc 960

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aactccaagt ccctcctcct ccgcgcccac tgccagacct ccggctggtc cctcaccgag 1080

caggacccct acaacaacat cgtccgcacc gccatcgagg ccatggccgc cgtcttcggc 1140

ggcacccagt ccctccacac caactccttc gacgaggccc tcggcctccc caccgtcaag 1200

tccgcccgca tcgcccgcaa cacccagatc atcatccagg aggagtccgg catccccaag 1260

gtcgccgacc cctggggcgg ctcctacatg atggagtgcc tcaccaacga cgtctacgac 1320

gccgccctca agctcatcaa cgagatcgag gagatgggcg gcatggccaa ggccgtcgcc 1380

gagggcatcc ccaagctccg catcgaggag tgcgccgccc gccgccaggc ccgcatcgac 1440

tccggctccg aggtcatcgt cggcgtcaac aagtaccagc tcgagaagga ggacgccgtc 1500

gaggtcctcg ccatcgacaa cacctccgtc cgcaaccgcc agatcgagaa gctcaagaag 1560

atcaagtcct cccgcgacca ggccctcgcc gagcgctgcc tcgccgccct caccgagtgc 1620

gccgcctccg gcgacggcaa catcctcgcc ctcgccgtcg acgcctcccg cgcccgctgc 1680

accgtcggcg agatcaccga cgccctcaag aaggtcttcg gcgagcacaa ggccaacgac 1740

cgcatggtct ccggcgccta ccgccaggag ttcggcgagt ccaaggagat cacctccgcc 1800

atcaagcgcg tccacaagtt catggagcgc gagggccgcc gcccgcgcct cctcgtcgcc 1860

aagatgggcc aggacggcca cgaccgcggc gccaaggtca tcgccaccgg cttcgccgac 1920

ctcggcttcg acgtcgacat cggcccactc ttccagacgc cccgcgaggt cgcccagcag 1980

gccgtcgacg ccgacgtcca cgccgtcggc gtctccaccc tcgccgccgg ccacaagacc 2040

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tgcggcggcg tcatccctcc ccaggactac gagttcctct tcgaggtcgg cgtctccaac 2160

gtcttcggcc ccggcacccg catccccaag gccgccgtcc aggtcctcga cgacatcgag 2220

aagtgcctcg agaagaagca gcagtccgtc 2250

<210> 734
<211> 2250
<212> DNA
<213> Artificial Sequence

<220>
<223> Codon optimized sequence that encodes an MCM polypeptide with the I671V mutation

<400> 734
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gagagcagcg gcagccggct gatccagcag cggctgctgc accagcagca gcccctgcac 120

cccgagtggg ccgccctggc caagaagcag ctgaagggca agaaccccga ggacctgatc 180

tggcacaccc ccgagggcat cagcatcaag cccctgtaca gcaagcggga caccatggac 240

ctgcccgagg agctgcccgg cgtgaagccc ttcacccggg gcccctaccc caccatgtac 300

accttccggc cctggaccat ccggcagtac gccggcttca gcaccgtgga ggagagcaac 360

aagttctaca aggacaacat caaggccggc cagcagggcc tgagcgtggc cttcgacctg 420

gccacccacc ggggctacga cagcgacaac ccccgggtgc ggggcgacgt gggcatggcc 480

ggcgtggcca tcgacaccgt ggaggacacc aagatcctgt tcgacggcat ccccctggag 540

aagatgagcg tgagcatgac catgaacggc gccgtgatcc ccgtgctggc caacttcatc 600

gtgaccggcg aggagcaggg cgtgcccaag gagaagctga ccggcaccat ccagaacgac 660

atcctgaagg agttcatggt gcggaacacc tacatcttcc cccccgagcc cagcatgaag 720

atcatcgccg acatcttcga gtacaccgcc aagcacatgc ccaagttcaa cagcatcagc 780

atcagcggct accacatgca ggaggccggc gccgacgcca tcctggagct ggcctacacc 840

ctggccgacg gcctggagta cagccggacc ggcctgcagg ccggcctgac catcgacgag 900

ttcgcccccc ggctgagctt cttctggggc atcggcatga acttctacat ggagatcgcc 960

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aacagcaaga gcctgctgct gcgggcccac tgccagacca gcggctggag cctgaccgag 1080

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gagggcatcc ccaagctgcg gatcgaggag tgcgccgccc ggcggcaggc ccggatcgac 1440

agcggcagcg aggtgatcgt gggcgtgaac aagtaccagc tggagaagga ggacgccgtg 1500

gaggtgctgg ccatcgacaa caccagcgtg cggaaccggc agatcgagaa gctgaagaag 1560

atcaagagca gccgggacca ggccctggcc gagcggtgcc tggccgccct gaccgagtgc 1620

gccgccagcg gcgacggcaa catcctggcc ctggccgtgg acgccagccg ggcccggtgc 1680

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atcaagcggg tgcacaagtt catggagcgg gagggccggc ggccccggct gctggtggcc 1860

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aagtgcctgg agaagaagca gcagagcgtg 2250

<210> 735
<211> 2250
<212> DNA
<213> Artificial Sequence

<220>
<223> Codon optimized sequence that encodes an MCM polypeptide with the I671V mutation

<400> 735

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gagtcctccg gctcccggct gatccagcag aggctcctgc accagcagca acccctgcat 120

ccggagtggg ccgccctcgc caagaaacag ttgaaaggca agaaccccga ggatctcatc 180

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aaattctaca aggacaacat caaggcgggc cagcagggcc tgagcgtggc cttcgaccta 420

gccacccacc ggggctatga cagcgacaac ccacgggtca ggggcgacgt gggcatggcg 480

ggcgtggcca tagacaccgt ggaggacacc aagatcctgt tcgacgggat cccacttgag 540

aagatgagcg tgtccatgac catgaacggc gccgtcatcc ccgtgctggc caacttcatc 600

gtgaccggcg aggagcaggg cgtgcccaag gagaagctga ccggcaccat acagaacgac 660

atcctgaagg agtttatggt gcgcaacacc tatatcttcc cccccgaacc cagcatgaag 720

atcatcgccg acatcttcga gtacaccgcg aagcacatgc ccaagttcaa ctccatcagc 780

atcagcggct accatatgca ggaggccggt gcggacgcca tcctggagct tgcctacacc 840

ctggccgacg ggctggagta cagcaggacc gggctccagg ccggtctgac catcgacgaa 900

ttcgccccca ggctgagctt cttctggggc atcggcatga acttctacat ggagatcgcc 960

aaaatgaggg ccggcaggag gctctgggcc cacctgatcg aaaaaatgtt ccagcccaaa 1020

aacagcaaat ccctgctgct gcgggcccac tgccagacca gcggctggag cctcaccgag 1080

caagacccct ataataacat cgtcaggacg gccatcgaag cgatggccgc cgtgttcgga 1140

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gtggccgacc cgtggggtgg cagctacatg atggagtgcc tcacgaacga cgtgtatgac 1320

gccgcgctga aactgatcaa cgagatcgag gagatggggg ggatggccaa ggccgtggct 1380

gagggtattc ccaagctgcg catagaggag tgcgccgcca ggcgccaggc caggatcgac 1440

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gaggtgctgg caatcgacaa caccagcgtg aggaaccggc agatcgaaaa gctgaagaag 1560

attaaaagca gccgggacca agccctggca gagaggtgcc tggccgccct gacggaatgc 1620

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atcaaacgtg tgcacaagtt catggaaagg gagggcaggc gcccgaggct cctcgtcgcc 1860

aagatgggcc aggatgggca cgacagggga gccaaagtca tcgccaccgg gtttgcggac 1920

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aaatgcctgg agaagaaaca gcagtccgtg 2250

<210> 736
<211> 2250
<212> DNA
<213> Artificial Sequence

<220>
<223> Codon optimized sequence that encodes an MCM polypeptide with the I671V mutation

<400> 736
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gagagctccg gaagcaggct catacagcag cgcctgctcc accagcagca gcccctgcac 120

cccgagtggg ccgctctggc taagaaacag ctgaagggca aaaatcccga ggacctgatc 180

tggcataccc ccgagggcat cagcatcaaa cccctgtata gcaaacggga caccatggac 240

ctcccggagg agctgcccgg agttaagccc ttcaccaggg gcccctatcc aacaatgtac 300

accttccggc cctggaccat ccgacagtac gccggcttca gcacggtcga ggagtccaac 360

aagttctata aggacaacat caaggccggg cagcagggcc tgagcgtcgc cttcgacctg 420

gccacccacc gtgggtacga cagcgacaac cccagggtgc ggggcgacgt gggcatggcc 480

ggcgtggcca tagataccgt ggaggacacc aagatcctgt ttgacggcat ccccctggag 540

aagatgagcg tgtccatgac aatgaacggc gccgtgatcc ccgtgctcgc caatttcata 600

gtgaccggcg aggagcaggg cgtgccgaag gagaagttga ccggaacaat ccagaacgac 660

atcctgaagg agttcatggt gcggaacacc tacatcttcc cccccgagcc gtcaatgaag 720

atcatcgccg acatcttcga gtacaccgcc aagcacatgc ccaagttcaa cagcatcagc 780

atcagcggct atcatatgca ggaggccggg gccgacgcca tcctggagct ggcttacacg 840

ctggccgacg gcctggagta ttccaggacc ggcttacaag ccggcctgac catcgacgag 900

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gtggccgacc cctggggcgg ctcctacatg atggagtgcc tgaccaacga tgtctacgac 1320

gccgccctga aactgatcaa cgagatcgag gagatgggag gcatggccaa ggccgtggct 1380

gagggcatcc ccaagctgag gatcgaggag tgcgcagccc gtcgtcaggc ccgcatcgac 1440

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gaagtgctgg ccatcgacaa cacgtccgtc cgcaataggc agatcgagaa actgaagaag 1560

atcaagtcgt ccagggacca ggccctggcc gagagatgcc tggccgccct gacggaatgc 1620

gccgccagcg gggatggcaa tatcctggcc ctggccgtgg acgcctcccg ggccaggtgc 1680

acagtggggg agatcaccga cgcgctcaag aaggtgtttg gcgagcacaa ggccaacgat 1740

aggatggtga gcggcgcgta caggcaggag ttcggcgagt ccaaggagat caccagcgcc 1800

atcaagagag tgcacaagtt catggagcgg gaggggcgga ggccgaggct gctcgtggcg 1860

aagatgggcc aagacgggca cgacaggggc gccaaggtta tcgccaccgg gtttgcagac 1920

ctgggcttcg acgtggacat cggccccctc tttcagaccc cccgagaagt ggcacaacag 1980

gccgtggacg ccgacgtgca cgccgtgggc gtaagcaccc tggccgccgg ccataaaacc 2040

ctggtgccgg agctgatcaa ggagctcaac agcctgggcc gacccgacat cctggtgatg 2100

tgtgggggtg tgattcctcc ccaggattac gagttcctgt tcgaggtggg cgtgagcaat 2160

gtcttcggcc cggggaccag gatacccaag gcggccgtcc aggtgctcga cgacattgag 2220

aagtgcctcg agaagaaaca gcagtccgtg 2250

<210> 737
<211> 2250
<212> DNA
<213> Artificial Sequence

<220>
<223> Codon optimized sequence that encodes an MCM polypeptide with the I671V mutation

<400> 737
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cccgagtggg ccgccctggc caagaaacag ctgaagggga agaatcctga ggacctgatc 180

tggcacaccc ccgagggaat cagcatcaag cccctgtact ccaagaggga caccatggac 240

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acctttcggc cctggaccat caggcagtac gccggcttct ccaccgtgga ggagagcaac 360

aagttctaca aggacaacat caaagcgggc caacagggtc tgagcgtggc cttcgatctg 420

gccacgcaca ggggctacga cagcgacaac cccagggtcc ggggcgacgt gggcatggcc 480

ggcgtggcca tcgacacggt ggaggacacc aagatcctgt tcgacggcat ccccctggag 540

aaaatgtccg ttagcatgac catgaatggg gccgtcatcc cggtgctggc caacttcatc 600

gtgaccgggg aggagcaggg agttcccaag gagaaactca ccgggaccat acagaacgac 660

atcctgaagg aatttatggt caggaacacc tatatatttc cccccgagcc cagcatgaag 720

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atcagcgggt atcacatgca ggaggccggc gccgacgcca tcctggagct ggcgtacacc 840

ctcgccgacg gcctggagta cagccggacc gggctccagg ccggcctcac catcgatgag 900

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gagggcatcc ccaagctgcg gatcgaggag tgcgccgcca ggaggcaggc ccggatagac 1440

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gaggtgctcg ccatcgacaa cacgagcgtg cggaacaggc agatcgagaa actcaagaag 1560

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gcggtggacg ccgacgtaca tgccgtgggc gtgtccaccc tggcggccgg ccacaagacg 2040

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tgcggcggcg tgatcccgcc ccaggattac gagttcctgt ttgaggtggg ggtgtccaac 2160

gtctttggcc ccggcaccag gatccccaag gcggccgtgc aggtgctgga cgatatcgag 2220

aaatgtctcg aaaagaagca gcagtccgtg 2250

<210> 738
<211> 2250
<212> DNA
<213> Artificial Sequence

<220>
<223> Codon optimized sequence that encodes an MCM polypeptide with the I671V mutation

<400> 738
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cccgagtggg cggccctggc caagaagcag ctcaagggca aaaaccccga ggacctgatc 180

tggcataccc ccgagggcat aagcatcaaa cccctgtaca gcaagaggga caccatggac 240

ctcccggagg agctgcccgg tgtgaagccc ttcaccaggg gcccttatcc gaccatgtac 300

accttcaggc cctggaccat caggcaatat gccgggttca gcaccgtgga ggagagcaac 360

aagttctata aggataacat caaggccggc cagcaaggcc tcagcgtagc cttcgacctg 420

gccacccata ggggatacga cagcgacaat ccccgggtgc ggggcgacgt ggggatggcc 480

ggcgtggcga tcgataccgt ggaggacaca aaaatcctct tcgacgggat ccccctggag 540

aaaatgagcg tgtccatgac catgaacggc gcggtgatcc cggtgctggc caattttata 600

gtcaccgggg aggagcaagg cgtacccaag gagaagctga ccgggaccat ccagaacgac 660

atcctgaagg agttcatggt caggaacacc tacatcttcc ccccagagcc gagcatgaag 720

atcatcgccg acatatttga gtacaccgcc aagcacatgc ccaagttcaa cagcatcagc 780

ataagcggct accatatgca ggaggccggc gccgacgcca tcctggagct ggcctacacc 840

ctggccgacg gcctcgagta ttccaggacc gggctgcagg ccggactgac catcgacgag 900

ttcgcgcccc ggctgtcctt cttctggggg atagggatga acttctacat ggagatcgcc 960

aagatgaggg ccggccggcg gctgtgggcc cacctgatcg aaaagatgtt ccagcccaag 1020

aactcaaaaa gcctgttgct gcgcgcccac tgccagacct ccgggtggtc acttaccgaa 1080

caggacccct ataataacat cgtcaggacc gccatcgagg ccatggccgc cgtgtttggc 1140

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agcgcgagga tcgcaaggaa cacccagata atcatccagg aggaaagcgg catccccaag 1260

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gaggtgctgg ccatcgacaa cacctcagtg aggaataggc agatcgaaaa gctgaagaag 1560

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aagatgggcc aggacgggca cgaccgcggc gccaaggtga tcgccaccgg cttcgccgac 1920

ctggggtttg acgtggacat cggccccctg ttccagaccc ccagggaggt agcccagcaa 1980

gccgtggacg ccgacgtgca cgccgtggga gtgagtaccc tggccgccgg ccacaagacc 2040

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tgcggtggcg tcatcccgcc ccaggactac gagttcctgt tcgaagtggg cgtgtccaac 2160

gtgttcggcc cgggcacccg catccccaag gccgccgtgc aggtgctcga cgacatcgag 2220

aaatgtctgg agaagaagca gcagtccgtg 2250

<210> 739
<211> 2250

<212> DNA
<213> Artificial Sequence

<220>
<223> Codon optimized sequence that encodes an MCM polypeptide with the I671V mutation

<400> 739
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gagtcctccg gctccaggct gatccagcag cgactgctgc accagcagca gcccctccac 120

cccgagtggg ccgctctcgc caagaagcag ctgaagggca agaaccccga ggacctgata 180

tggcacaccc cggagggcat ctcgatcaag cccctgtatt ccaaacggga cactatggac 240

ctgccggagg agctgcccgg cgtcaagccc tttacgcggg gcccctaccc caccatgtac 300

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aagttctaca aggacaacat caaggccggc cagcagggcc tgagcgtggc gttcgacctg 420

gccacacaca ggggctacga cagcgacaac cccagggtga ggggcgacgt gggcatggcc 480

ggggtggcca tcgacaccgt ggaggacacc aagatcctgt tcgacggcat ccccctggag 540

aagatgagcg tgagcatgac aatgaatggg gccgtgatcc ccgtgctggc caatttcatc 600

gtcaccgggg aggaacaggg cgtgcctaag gaaaagctga caggcaccat ccagaacgac 660

atcctcaagg agttcatggt gcggaacacc tacatcttcc cccccgagcc cagcatgaag 720

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aactccaaga gcctgctgct gagggcccac tgccagacct ccgggtggag cctgactgag 1080

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gtgtttgggc ccgggacccg gatcccgaag gccgccgtgc aggtgctgga tgatatagag 2220

aagtgcctgg agaagaagca gcagagcgtg 2250

<210> 740
<211> 2250
<212> DNA
<213> Artificial Sequence

<220>
<223> Codon optimized sequence that encodes an MCM polypeptide with the I671V mutation

<400> 740
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gagtccagcg ggtcccgtct gatccagcag aggctgctgc accagcagca gcccctgcac 120

cccgagtggg ccgctctggc taagaagcag ctgaagggta aaaaccccga ggacctgatc 180

tggcacaccc ccgaaggcat ctccatcaag cccctctaca gcaagaggga tactatggac 240

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aagttttaca aggacaacat caaggccggg cagcagggtc tgagcgtggc cttcgacctc 420

gccacccacc gcggctacga ctccgacaac ccccgggtgc ggggcgacgt gggcatggcc 480

ggggtggcca tcgacaccgt ggaggacacc aagatactct tcgatgggat ccccctggag 540

aagatgtcag tctcgatgac catgaacggc gccgtgattc ccgtgctggc caactttatc 600

gtgaccgggg aagagcaggg ggtgcccaaa gaaaaactga ccgggaccat tcagaacgat 660

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aagtgcctgg agaagaagca gcaaagcgtg 2250

<210> 741
<211> 2250
<212> DNA
<213> Artificial Sequence

<220>
<223> Codon optimized sequence that encodes an MCM polypeptide with the I671V mutation

<400> 741
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gagtcctccg gctccaggct gatccagcag cgactgctgc atcagcaaca gccgctgcac 120

cccgagtggg ccgccctggc caagaagcag ctgaagggca agaatcccga ggacctgatc 180

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gccacccaca ggggttacga cagcgataat ccacgggtga ggggcgacgt ggggatggct 480

ggggtggcca tcgacaccgt ggaggatacc aagatcctgt tcgacggcat ccccctggag 540

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gtgaccggcg aggagcaagg ggtgcccaaa gagaagctca ccggaaccat ccagaacgac 660

atcctgaagg agttcatggt ccggaacacc tacatatttc cccccgagcc cagcatgaag 720

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gccgttgatg cggacgtgca cgcggtgggc gtctccaccc tggccgccgg ccacaagacc 2040

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<210> 742
<211> 2250
<212> DNA
<213> Artificial Sequence

<220>
<223> Codon optimized sequence that encodes an MCM polypeptide with the I671V mutation

<400> 742
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cccgagtggg cagccctggc gaagaaacag ctgaaaggga agaaccccga ggatctgatc 180

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gtcaccggcg aggagcaggg cgtgcctaag gagaagctga ccgggaccat ccagaatgac 660

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gccgccagcg gggacggaaa catcctggcc ctggccgtgg atgcctcccg ggccaggtgc 1680

accgtcggcg agatcaccga cgctctgaag aaggtcttcg gcgagcacaa ggctaacgac 1740

cggatggtga gcggcgccta ccggcaggag ttcggcgaga gcaaggagat cacctccgcc 1800

atcaagcggg tgcacaagtt tatggaacgc gagggccgca gacccaggct cctcgtggcc 1860

aagatgggcc aggatggcca cgacaggggg gccaaggtca tcgccaccgg attcgccgat 1920

ctgggcttcg acgtggacat cgggcccctg tttcaaacgc cccgcgaagt agcacagcag 1980

gccgtggacg ccgacgtgca cgccgtgggc gtgtccaccc tggccgccgg ccataagacc 2040

ctggtgcccg agctgatcaa ggagctgaac agcctggggc gcccggatat actcgtgatg 2100

tgcgggggcg tcatcccccc ccaggattac gagtttctct tcgaggtggg ggtgagcaac 2160

gtctttggcc ccggaacccg aatccccaag gccgccgtgc aggtgctcga cgatatagag 2220

aagtgcctgg agaaaaagca gcagtccgtg 2250

<210> 743
<211> 2250
<212> DNA
<213> Artificial Sequence

<220>
<223> Codon optimized sequence that encodes an MCM polypeptide with the I671V mutation

<400> 743
atgctgaggg ccaagaacca gctcttcctg ctgtcccccc actacctgcg gcaggtgaag 60

gagagctccg gcagccgcct gatccaacag cggctgctgc accagcagca accgctgcac 120

cccgagtggg ccgccctggc caagaaacag ctcaagggga agaaccccga ggacctgatc 180

tggcacaccc ccgagggcat ttccatcaaa cccctgtaca gcaagaggga caccatggac 240

ctgcccgagg aactgccggg agtgaagccc ttcacccgcg gcccctatcc caccatgtac 300

accttcaggc cgtggaccat ccgccagtat gccggcttta gcaccgtgga ggagagcaac 360

aagttctaca aagacaacat caaggcaggg cagcagggcc tgagcgtggc cttcgatctg 420

gccacccata ggggctacga cagcgacaac ccgagggtga ggggggacgt gggcatggcc 480

ggcgtggcca tcgataccgt ggaggatacc aagatcctgt ttgacggcat ccccctggag 540

aagatgtccg tgagtatgac catgaacggc gcggtgatcc cggtgctggc caacttcatc 600

gtgaccggcg aggaacaggg cgtgccaaag gagaagctga ccggcaccat ccagaacgac 660

atactcaaag agttcatggt acggaacacc tacatcttcc cccccgagcc ctcgatgaag 720

atcatcgccg acatcttcga gtacaccgcc aagcacatgc ccaagttcaa ctccatctcc 780

atctcgggct atcacatgca ggaagccggg gccgacgcca tcctggaact ggcctacact 840

ctggccgacg gcctcgagta ctccaggacc ggcctgcaag cgggcctgac catcgacgag 900

ttcgcccccc ggctgtcttt tttttgggga atcggcatga acttctacat ggagatcgcc 960

aagatgaggg ccggtcgccg gctctgggcc cacctgatcg agaagatgtt ccagcccaag 1020

aacagcaaga gcctcctgct gagggcccac tgccagacca gcggctggag cctgactgag 1080

caagatccct acaacaacat cgtgcggacg gccatcgagg cgatggctgc cgtcttcggc 1140

ggaacccaga gcctgcatac caacagcttc gatgaagccc tggggctgcc caccgtgaag 1200

tccgcgagga tcgccaggaa cacgcagatc attatacagg aggagagcgg gatccccaag 1260

gtggcagatc cctggggcgg aagctacatg atggagtgcc tgaccaacga cgtgtacgac 1320

gcggcgctga agctgattaa cgagatcgag gaaatgggag gcatggccaa ggccgtggcc 1380

gagggcattc ccaaactccg gatcgaggag tgtgcagcca ggcgacaagc caggatcgac 1440

agtggctccg aggttatcgt cggcgtgaac aagtaccagc tggagaaaga ggacgccgtg 1500

gaggtcctgg ccatcgacaa cacaagcgtg aggaaccggc aaatcgaaaa gctgaagaag 1560

atcaaaagca gccgggacca ggccctcgcc gagcgctgtc tggccgccct caccgagtgt 1620

gctgccagcg gtgacggcaa tatcctggcc ctggccgtgg atgccagccg cgcccggtgc 1680

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cgcatggtgt ccggcgccta tcggcaggag ttcggcgaga gcaaggaaat aaccagcgcc 1800

atcaagcggg tgcacaaatt catggagcgg gagggccggc ggcccaggct gctggtcgcc 1860

aagatgggcc aggacgggca cgacagggga gctaaggtga tcgcgacggg gttcgccgat 1920

ctgggctttg acgtggatat cggacccctc ttccagacac cgcgggaggt ggcccagcag 1980

gccgtggacg ccgacgtgca tgccgtcggc gtgagcacac tggccgccgg acacaagact 2040

ctggtgcccg agctcatcaa ggagctgaac agcctcggac ggcccgatat cctcgtgatg 2100

tgcggtggcg tgatcccccc gcaggactac gaatttctct ttgaggtggg cgtgagcaac 2160

gtgttcggcc ccggcacgag gatccccaaa gccgccgtgc aggtgctgga cgacatcgag 2220

aagtgtttgg agaagaagca gcagtccgtg 2250

<210> 744
<211> 2250
<212> DNA
<213> Artificial Sequence

<220>
<223> Codon optimized sequence that encodes an MCM polypeptide with the I671V mutation

<400> 744
atgctgaggg ccaagaacca gctgtttctc ctgagccccc actacctcag gcaggtgaag 60

gagagctccg gctcaaggct gatccagcaa cgtctgctgc atcagcagca acccctgcac 120

ccagagtggg ccgccctcgc caagaagcag ctgaagggca aaaaccccga ggatctgatc 180

tggcacaccc ccgagggcat cagcatcaag cccctgtact ccaagaggga tacaatggac 240

ctgccggagg agctgcccgg agtgaaaccc ttcaccagag gcccctaccc caccatgtac 300

acctttaggc cctggaccat acggcagtac gccgggttca gcaccgtgga ggagagcaat 360

aaattctaca aggacaacat aaaggccgga cagcagggcc tgtccgtggc cttcgacctg 420

gccacccaca ggggctatga cagcgataac ccccgcgtga ggggggacgt cggcatggcc 480

ggagtagcca tcgataccgt ggaggatacc aagatcctgt tcgacggcat ccccctcgag 540

aagatgagcg tgtccatgac catgaatggc gcagtgatcc ccgtgctggc caacttcatc 600

gtgaccggtg aggagcaggg cgtgcccaag gagaaactga ccgggaccat ccagaacgac 660

atactgaagg agtttatggt gcggaacacg tacatattcc cccccgagcc cagcatgaag 720

atcatcgccg acatcttcga atataccgcc aagcacatgc ccaagttcaa cagcattagc 780

atctcaggct accacatgca ggaggccggc gccgacgcga tcctggagct ggcctacacc 840

ctggccgacg gcctggagta cagccggacc ggcctgcagg caggcctgac catcgacgaa 900

ttcgcccccc ggctctcctt cttctggggg atcggcatga acttttacat ggagatcgcc 960

aaaatgcggg ccggccggcg gctctgggcc cacctgatcg aaaagatgtt ccagcccaag 1020

aacagcaaga gcctgctgct gagggcccac tgccagacga gcggctggag cctgaccgag 1080

caagacccct acaacaacat cgtgcgcacc gccatagagg ccatggccgc cgtgttcggg 1140

ggtacacaaa gcctccacac taacagcttc gacgaggccc tgggtcttcc cacggtgaag 1200

tcagcgcgca ttgcccgcaa cacccagatc atcatccaag aagagtccgg catccccaag 1260

gtggccgacc cctggggcgg gagctacatg atggaatgcc tcaccaacga cgtgtatgac 1320

gcggcgctca agctgatcaa cgagatcgaa gaaatgggcg gcatggcaaa ggccgtggcc 1380

gagggcatcc ctaagctgag aatcgaggag tgcgcagcca gacggcaggc caggattgac 1440

agcggcagcg aggtaatcgt gggagtgaac aagtatcagc tggagaagga ggacgccgtg 1500

gaagtgctgg ccatcgacaa cacctccgtg aggaatcgac agatcgagaa gctgaagaag 1560

atcaagtcca gccgggacca ggccctggcc gagaggtgcc tggccgccct gaccgagtgt 1620

gccgccagcg gggacggcaa catccttgcc ctggccgtgg acgcgtccag ggcccgctgt 1680

accgtgggcg agatcaccga cgccctgaag aaggtgtttg gggagcacaa ggccaatgat 1740

cgcatggtgt ccggcgcgta ccggcaggag ttcggagaga gcaaggagat cacctccgcc 1800

attaagaggg tgcacaagtt catggaaagg gagggccgga ggccccgcct actggtggcc 1860

aaaatgggcc aagacggcca cgacagggga gccaaggtga tcgccaccgg gttcgcggac 1920

ctgggctttg acgtcgacat cggccccctg tttcagaccc ccagggaagt ggcgcagcag 1980

gcggtggacg ccgatgtgca cgccgtgggc gtgagcacac tggcagccgg ccacaagact 2040

ctggtgcccg agctgataaa agagctgaac tctctgggca ggcccgacat cctggtgatg 2100

tgcggcggcg tcatcccccc ccaagactac gagttcctgt tcgaggtggg cgtaagcaat 2160

gtgttcggcc ccggcacccg aattcccaag gcggccgtgc aagtgctgga cgacatcgag 2220

aagtgcctcg agaagaagca gcagagcgtc 2250

<210> 745
<211> 2250
<212> DNA
<213> Artificial Sequence

<220>
<223> Codon optimized sequence that encodes an MCM polypeptide with the I671V mutation

<400> 745
atgctcaggg ccaagaatca gctgttcctg ctcagccccc attacctgag gcaggtgaag 60

gaatcgtccg ggtcccgcct catccagcag cgactcctgc accagcagca gccactacac 120

cccgagtggg ccgccctggc caagaagcag ctgaaaggca agaaccccga ggatctcatc 180

tggcacacgc ccgagggcat cagcatcaaa cccctgtatt ccaagcgtga caccatggac 240

ctgcccgagg agctgcctgg tgtcaagccc ttcacccggg ggccctaccc gacgatgtac 300

acctttcgtc cctggaccat caggcagtac gccggcttca gcaccgtaga ggagagcaac 360

aagttctaca aagacaacat caaagccggt cagcaagggc tgtccgtggc cttcgacctg 420

gccacgcacc gcggctatga cagcgacaac ccccgagtca gaggggacgt ggggatggcc 480

ggggtggcaa tcgataccgt cgaggacacc aagattctgt tcgatggcat tcccctggag 540

aagatgagcg tcagcatgac catgaatgga gccgtgatcc ccgtgctggc caacttcatc 600

gtgactggtg aggaacaggg cgtgcccaag gagaagctga ccgggaccat ccagaacgac 660

atcctgaagg agtttatggt tcgcaatacc tacatattcc cccccgagcc cagcatgaag 720

atcatcgccg atatcttcga atataccgcc aaacacatgc ccaagtttaa tagcatcagc 780

atcagcggct accacatgca ggaagccggg gccgacgcca tcctggagct ggcatacact 840

ctggccgacg gcctggagta cagccgcacc ggcctccaag cagggctcac gatcgacgag 900

ttcgccccac ggctcagctt cttctggggg atcggcatga atttctacat ggagatcgcc 960

aagatgaggg ccggtcggag gctttgggcc catttgatcg aaaaaatgtt ccaacccaag 1020

aatagcaaat ccctgctgct cagggcccac tgccagacca gcggctggtc actgaccgaa 1080

caggacccat acaacaatat cgtgaggacc gccatcgagg ccatggcggc ggtgttcggc 1140

ggcacccaga gcctccacac caacagtttt gacgaggccc tgggactgcc gaccgtgaag 1200

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gtcgccgacc cctggggcgg cagctacatg atggaatgcc tgaccaacga cgtgtacgac 1320

gccgccctca agctcatcaa tgagatcgag gagatgggcg ggatggccaa ggccgtggcc 1380

gagggcatcc ccaagctgcg aatcgaagaa tgcgccgcca ggcggcaggc ccggatcgac 1440

tccggctccg aggtcatcgt cggcgtcaac aagtaccagc tcgagaagga ggatgccgtg 1500

gaggtgctgg ccatcgataa cacgtccgtg aggaaccggc agattgagaa gctgaagaag 1560

atcaagagct cccgagacca ggccctggcc gagaggtgcc tggccgccct gactgagtgc 1620

gccgcctccg gggacgggaa catcctggcc ttggctgtgg acgcgagcag ggccaggtgc 1680

accgtgggcg aaatcaccga cgccctcaag aaggtcttcg gcgagcacaa ggccaatgac 1740

cggatggtca gcggtgccta caggcaggag ttcggtgaat ccaaggagat cacctcggcc 1800

ataaaaagag tccacaagtt tatggagagg gaagggcgta ggccccgact cctggtggcc 1860

aagatgggcc aagacggcca cgaccggggc gccaaggtca tcgccaccgg gttcgccgac 1920

ctggggttcg acgtcgacat cgggcccctg ttccagaccc cacgagaggt ggcccagcag 1980

gccgtcgacg ccgacgtgca cgccgtgggc gtctccacgc tggcggccgg ccacaaaacc 2040

ctcgtgcccg agctgatcaa ggagctgaat tccctcggcc ggcccgacat cctggtgatg 2100

tgcgggggggg tcatcccccc ccaagattac gagttcctgt tcgaggtggg cgtgagcaac 2160

gtgttcggcc ccggcaccag gatccccaag gccgccgtgc aggtgctgga cgacatcgag 2220

aagtgcctcg agaagaagca gcagtccgtg 2250

<210> 746
<211> 2250
<212> DNA
<213> Artificial Sequence

<220>
<223> Codon optimized sequence that encodes an MCM polypeptide with the I671V mutation

<400> 746
atgctgaggg ccaagaacca gctattcctg ctgagcccac actacctccg gcaggtgaag 60

gagagcagcg gaagcaggct gatccagcag cggctgctcc accagcagca accactgcac 120

cccgagtggg ccgccctcgc caagaaacaa ctgaagggca agaaccccga agacctaatc 180

tggcacactc cagagggtat cagcatcaag cccctgtact ccaagagaga caccatggac 240

ctgcccgagg aactgcccgg cgtcaagccc tttaccaggg gcccctaccc caccatgtat 300

accttccgac cctggaccat caggcagtac gccgggttca gcacggtgga ggagtccaat 360

aagttctaca aggataacat caaggccggt cagcagggtc tgtccgtggc cttcgacctg 420

gccacccacc gcggatatga cagcgacaac ccgagggtga ggggcgacgt ggggatggcc 480

ggcgtggcca tcgacaccgt ggaggacaca aagatactgt tcgacggaat cccgctggaa 540

aagatgagcg tcagcatgac catgaacggg gccgtgatcc ccgtgctggc caacttcatc 600

gttaccggtg aggaacaggg ggtgcctaag gagaagctga ccggcaccat acagaacgac 660

atcctgaagg agtttatggt gaggaacacc tatatcttcc cccccgagcc aagcatgaaa 720

atcatcgcag acatctttga gtacaccgcc aagcacatgc ccaagttcaa cagcatcagc 780

atttccggct accacatgca ggaagccggg gccgacgcca tcctcgaact ggcctacacc 840

ctggctgacg gcctggagta cagccggaca gggctgcagg ccgggcttac gatcgacgag 900

ttcgcccccc ggctgtcctt cttttggggg atcgggatga acttctatat ggagatcgca 960

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aactcgaaga gcctgctgct gcgcgcccat tgccaaacaa gcggctggtc actgacagag 1080

caggacccct acaacaatat cgtgaggacc gccatcgagg ccatggccgc cgtgttcggg 1140

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gagggcatcc ccaagctgcg gatagaggag tgcgccgcca ggcgccaggc caggatcgac 1440

agcggttccg aggtgatcgt gggcgtgaac aagtatcagc tggagaagga agacgccgtg 1500

gaggtcctgg ccatcgacaa cacatcggtg agaaataggc agatcgaaaa gctcaaaaag 1560

atcaagtcca gccgtgacca agccctggcc gagaggtgtc tggcggccct gaccgagtgc 1620

gccgccagcg gcgacggcaa catccttgcc ctcgcggtcg atgccagcag ggccaggtgc 1680

accgtggggg aaatcaccga cgccctgaag aaggtgttcg gcgagcacaa agccaacgac 1740

aggatggtga gcggcgccta ccgccaagag ttcggcgagt ccaaggagat caccagcgcc 1800

atcaagcgcg tgcacaagtt catggagagg gaaggcagga ggccgcgcct gctggtggcc 1860

aagatgggcc aggacggcca cgataggggg gccaaagtca tcgccaccgg cttcgccgac 1920

ctgggcttcg acgtggacat cggccccctg tttcagaccc cccgtgaggt cgcccagcag 1980

gccgtggacg cggatgtgca cgccgtgggg gtgtccaccc tggccgccgg acataaaacc 2040

ctggtgccgg aactgatcaa ggaactgaac agcctgggac ggcccgacat actggtgatg 2100

tgcggaggcg tgatcccccc ccaggattac gagttcctgt tcgaggtggg cgtttccaat 2160

gtgttcggac cgggcacgcg gattcccaag gccgcagtgc aggtgctgga tgacatcgaa 2220

aaatgcctgg agaagaagca gcagtcagta 2250

<210> 747
<211> 2250
<212> DNA
<213> Artificial Sequence

<220>
<223> Codon optimized sequence that encodes an MCM polypeptide with the I671V mutation

<400> 747
atgctgcgcg ccaagaacca gctgttcctg ctgtcccccc actacctgcg gcaggtgaag 60

gagagctccg gcagccgtct gatccaacag cggttactgc accagcaaca gcctctgcac 120

ccagagtggg ccgccctggc caagaagcag ctcaaaggga agaaccccga ggacctgatc 180

tggcacaccc ccgaaggcat cagcatcaag cctctctata gcaagcgaga caccatggac 240

cttcccgagg agctgcccgg cgtcaagccc ttcacccgag gcccctaccc caccatgtat 300

accttccgcc cctggacaat caggcaatac gccggcttca gcaccgtgga ggagagcaac 360

aagttctaca aggacaacat caaggccggc cagcaaggcc tcagcgtggc cttcgacctg 420

gcgacccaca ggggctatga cagcgataac cccagggtca ggggggacgt gggcatggcc 480

ggggtggcca tcgacaccgt ggaagacacc aagatcctgt tcgacgggat ccccctcgag 540

aaaatgtcgg tgtccatgac catgaatgga gccgtgatcc ccgtactggc caacttcata 600

gtcaccggag aggagcaagg cgtcccaaag gagaagctga ccggcaccat ccagaacgac 660

atcctgaaag agtttatggt tagaaacacc tatatcttcc cccccgagcc ctccatgaag 720

atcatcgcgg atatcttcga atacaccgcc aagcacatgc ccaagttcaa cagcataagc 780

attagcggct accatatgca agaggccggc gccgatgcca tcctggagct ggcttacacc 840

ctcgccgatg gcctggaata cagccgaacc ggactgcagg ccgggctcac cattgacgaa 900

tttgcacccc gtctaagctt cttctggggc atcggcatga acttttacat ggagatcgcc 960

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aacagcaaga gcctcctgct gagggcccac tgccagacct ccggttggag cctgaccgag 1080

caggacccct acaataacat cgtgcgcacg gccatcgagg ccatggccgc cgtgttcggg 1140

gggacccaaa gcctgcacac caactcgttc gacgaagcgc tgggcctccc gacggtgaag 1200

tccgcccgca tcgcccggaa cacccagatc atcatccaag aggagagcgg cattcccaag 1260

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gccgccctga agctcatcaa cgagatcgag gagatgggcg gtatggccaa ggccgtggcc 1380

gaaggcatcc ccaagctgcg cattgaggaa tgcgccgccc ggaggcaagc ccggatagac 1440

agcggctccg aagtgatcgt gggcgtcaac aaataccagc tggagaagga ggacgccgtc 1500

gaggtgctgg ccattgacaa caccagcgtg aggaacaggc agatcgaaaa gctgaaaaaa 1560

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gccgccagcg gcgatggcaa catcctggcc ctggccgtgg acgccagccg cgcccggtgt 1680

accgtgggcg agattaccga cgccctgaag aaggtctttg gggagcacaa ggccaacgac 1740

cgaatggtga gcggcgccta taggcaggag tttggcgaaa gcaaggagat caccagcgcc 1800

atcaagcgtg tgcataagtt catggagcgg gagggccggc gcccgaggct gctcgtcgcc 1860

aagatgggcc aggatggcca tgacaggggc gccaaggtca tcgccaccgg gtttgccgac 1920

ctgggcttcg acgtggacat cgggcccctc ttccagacgc cgcgcgaagt cgcccagcag 1980

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gtgttcggcc ccggcactag gatccccaag gccgcagtac aggtgctcga cgacatagag 2220

aagtgcctgg agaagaaaca gcagagcgtg 2250

<210> 748
<211> 2250
<212> DNA
<213> Artificial Sequence

<220>
<223> Codon optimized sequence that encodes an MCM polypeptide with the I671V mutation

<400> 748
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gagtcctcgg gcagcaggct gatacagcag aggctgctgc accaacaaca gcccctgcac 120

cccgagtggg ccgccctggc caagaagcag ctgaagggga agaatccgga ggacctgatc 180

tggcacaccc cagagggcat aagcatcaaa cccctgtaca gcaagcggga taccatggac 240

ctgcccgagg agctgcccgg cgtgaagccc ttcacgaggg gcccctaccc caccatgtat 300

acctttaggc cctggaccat caggcagtat gccggcttca gcaccgtgga ggagagcaac 360

aaattctaca aggataacat aaaggccggg cagcaaggtc tcagcgtcgc cttcgatctc 420

gccacccatc ggggctacga ctcggataac ccccgcgtgc gcggcgacgt aggaatggcc 480

ggcgtcgcca tcgacaccgt ggaggacacg aagatactat tcgacggaat ccccctggaa 540

aagatgagcg ttagcatgac catgaacggg gccgtgatcc ccgtgctggc caatttcatc 600

gtgaccggcg aagagcaggg cgtgccgaag gagaagctca ccggtaccat ccagaacgac 660

atcctgaaag agttcatggt gaggaatacc tacatctttc cccccgaacc cagcatgaag 720

atcattgcgg acatcttcga gtataccgct aagcacatgc cgaagtttaa cagcatctcc 780

atcagcggct accatatgca agaggccggc gccgacgcca tcctggagct ggcgtacacc 840

ctcgccgacg gcctcgagta tagccgtacc ggcctgcagg cggggctcac catcgacgag 900

ttcgcccccc gactgagttt cttctggggc atcggcatga acttctacat ggagatcgca 960

aagatgaggg ccggccgaag gctctgggcc cacctgatcg agaagatgtt tcagcccaag 1020

aacagcaaga gcctgctgct gagggcccac tgccagacct ccgggtggtc cctgaccgag 1080

caggacccct acaataatat tgttagaacc gccatcgagg ccatggccgc agtcttcgga 1140

ggcacccaga gcctgcacac caactccttc gacgaggccc tgggcctgcc gaccgtgaag 1200

agcgccagga tcgccaggaa cacccaaatc ataatccagg aggagagcgg catccccaag 1260

gtcgccgacc cctggggcgg atcctacatg atggaatgcc tgaccaacga cgtgtacgac 1320

gccgccctga aactgatcaa tgagatcgag gagatgggcg ggatggcgaa ggccgtggcc 1380

gaggggatcc ccaagctgcg gatcgaggag tgcgccgcca ggaggcaggc ccgcatcgac 1440

agcggcagcg aagtgatcgt gggcgtcaac aagtaccagc tggagaaaga agacgccgtg 1500

gaggtgctcg caatcgacaa caccagcgta aggaatcgcc agatcgaaaa gctgaaaaag 1560

atcaaaagca gccgagacca ggccctggcc gagaggtgtc tggccgccct gaccgagtgt 1620

gccgccagcg gcgacgggaa cattctggcc ctggccgtgg atgcaagcag ggctaggtgc 1680

accgtgggcg agataaccga cgcgctgaag aaggtgttcg gcgagcacaa ggccaacgac 1740

cgcatggtgt cgggggccta tcggcaggag tttggggaga gcaaggagat tacctccgcg 1800

attaagaggg tccacaagtt catggagcgc gaaggcaggc ggccccggct gctggtggcc 1860

aagatgggcc aggacgggca cgatcgtgga gccaaagtga tcgccaccgg cttcgccgac 1920

ctgggcttcg acgtggacat cggccccctc ttccagaccc ccagggaggt ggcccagcag 1980

gccgtggacg ccgacgtcca cgccgttggc gtgtccacac tggccgccgg acacaaaacc 2040

ctggtgcccg agcttatcaa agagctgaac agcctgggca ggcccgacat actcgtgatg 2100

tgcgggggcg tgatcccccc ccaggactac gagttcctgt tcgaagtggg cgtgagcaac 2160

gtctttggcc ccggcaccag gatccccaag gccgccgtgc aggtgctcga cgatatcgag 2220

aaatgccttg agaagaagca gcagagcgtg 2250

<210> 749
<211> 2250
<212> DNA
<213> Artificial Sequence

<220>
<223> Codon optimized sequence that encodes an MCM polypeptide with the I671V mutation

<400> 749
atgctgaggg ccaagaacca gctgttcctg ctgagccccc actacctgag gcaggtgaaa 60

gaaagcagcg gcagcaggct aatccaacag cgtctgctcc accagcagca gcccctccat 120

ccagagtggg cggccctggc gaaaaagcaa ctcaagggca agaatcccga agatctcatc 180

tggcatacgc ccgaggggat cagcataaag ccgctgtaca gcaagaggga caccatggat 240

ctgcccgagg aactgcccgg cgtgaagccc tttacgcggg gcccctaccc gaccatgtac 300

accttccggc cctggaccat ccgacagtac gccgggttca gcaccgtgga ggagagcaat 360

aagttttaca aggacaatat caaagccggc cagcagggcc tgtccgtcgc cttcgacctg 420

gccacccacc gcggatatga cagcgacaac ccccgggtgc ggggcgacgt gggcatggcc 480

ggcgtggcca tcgacaccgt ggaggacaca aagatcctgt tcgacgggat acccctggag 540

aagatgagcg tcagcatgac catgaacggc gccgtgatcc cagtcctggc caacttcatc 600

gtgaccggcg aggaacaggg ggtgcccaag gagaagctga ccggcaccat ccagaatgat 660

atcctgaagg agttcatggt gcggaacacc tacatcttcc cccccgaacc gagcatgaag 720

atcatcgccg acatctttga gtacaccgcc aagcatatgc ccaagtttaa tagcatcagc 780

atcagcgggt accacatgca ggaggccgga gccgacgcca tcctcgagct cgcctacact 840

ctcgccgacg gcctcgagta cagccggacc ggactgcagg ccggcctcac catcgacgag 900

ttcgcacccc ggctgtcctt cttctggggg atcggcatga atttctacat ggagatcgcc 960

aagatgcggg ccggcaggcg cctgtgggcc cacctcatcg agaagatgtt ccagcctaaa 1020

aacagcaaga gcctgctgct gagggcgcac tgccagacct ccggctggag cctgaccgaa 1080

caggacccct ataataatat tgtccggacc gccatcgaag ccatggcagc cgtgttcggc 1140

ggtacccagt ccctgcacac caactccttc gacgaggcgc tgggcctgcc caccgtcaag 1200

tccgccagga ttgcccgtaa cacccagatc atcatacagg aggagtcagg catcccgaag 1260

gtggccgacc cctggggcgg ctcctacatg atggagtgcc tcaccaacga cgtgtacgac 1320

gccgccctga agctgatcaa cgagatcgag gagatgggcg gcatggcaaa ggccgttgcc 1380

gagggcatcc ccaagctgag gatcgaagag tgcgccgcca ggaggcaggc ccggatagac 1440

tccggcagcg aggtgatcgt cggcgtgaac aagtaccagc tggagaagga agatgccgtg 1500

gaagtgctgg ccatcgacaa tacctccgtg cgcaaccgtc agatcgagaa gctcaagaaa 1560

atcaagtcca gccgggacca ggccctggcg gaacgatgtc tggccgccct gaccgagtgc 1620

gccgccagcg gcgatggcaa tatactggcc ctggccgtgg acgccagccg cgcccggtgc 1680

accgtcgggg agatcaccga cgccctgaag aaggtgttcg gggaacacaa ggccaacgac 1740

cggatggtga gcggcgccta caggcaggag ttcggggaga gcaaggagat caccagcgcc 1800

atcaagaggg tccacaagtt catggagagg gagggcaggc ggccgcggct gttggtggcc 1860

aaaatggggc aggacgggca cgaccggggc gccaaggtca tcgccaccgg cttcgccgat 1920

ctgggttttg acgtggacat cggcccccctg ttccaaaccc ccagggaggt ggcccagcag 1980

gccgtcgacg ccgacgtgca tgccgtcggc gtgtccaccc tggccgccgg gcacaagaca 2040

ctggtccccg agctcatcaa ggagctcaat tccctgggca ggcccgacat cttggtcatg 2100

tgcggcggcg tgatcccccc gcaggactat gagttcctct tcgaggttgg ggtgagcaac 2160

gtctttggcc ctgggacaag gatccccaag gccgccgtgc aggtgctgga cgacatcgag 2220

aaatgtctcg agaagaagca acagagcgtt 2250

<210> 750
<211> 2250
<212> DNA
<213> Artificial Sequence

<220>
<223> Codon optimized sequence that encodes an MCM polypeptide with the I671V mutation

<400> 750
atgctcaggg ccaagaacca gctcttcctg ctctcccccc actacctgag gcaggtgaag 60

gaatcctccg ggagcaggct gatacagcag aggctgctgc accaacaaca gcccctccac 120

cccgagtggg ccgccctggc caagaagcag ctgaaaggga agaaccccga agacctcatc 180

tggcacaccc ccgaagggat cagcatcaag ccgctgtaca gcaagcggga cacgatggac 240

ctgcccgagg agctgcccgg ggtcaaacca ttcaccaggg ggccctaccc caccatgtat 300

accttccgcc cctggacgat caggcagtac gccggctttt ccacggtgga ggagagcaac 360

aagttctaca aggataacat caaggccgga cagcagggcc tgagcgtcgc cttcgacctg 420

gccacccata ggggctacga cagcgacaac cccagggtac gtggcgacgt aggaatggcc 480

ggggtcgcca tcgacaccgt ggaagacacc aagatcctgt tcgacgggat ccccctcgag 540

aaaatgagcg tcagcatgac catgaacggg gccgtcatcc ccgtgctggc caacttcatc 600

gtgacgggcg aggagcaagg agtacccaaa gaaaagctga ccggcaccat ccagaacgac 660

atcctgaagg agttcatggt ccggaacacc tacatcttcc ccccggaacc aagcatgaag 720

atcatcgccg atatcttcga gtacaccgcc aaacacatgc ccaagttcaa ttccatcagc 780

atcagcggct accacatgca ggaggccggc gcggacgcca tcctggagct cgcctacacc 840

ctggcggacg gcctcgagta cagcaggacc ggcctgcagg caggactgac catcgacgag 900

ttcgccccca ggctgtcctt cttctggggc atcggcatga acttctacat ggagatcgcc 960

aagatgcggg ccggcaggcg gctgtgggcc cacctgatcg agaagatgtt ccagcccaag 1020

aacagcaagt cgctgctgct gcgcgcgcat tgtcagacca gcggctggtc actcaccgag 1080

caggatccgt acaacaatat cgtgcgaacc gccatcgagg ccatggccgc agtgttcggc 1140

ggcacccaga gcctgcacac caatagcttc gacgaggcgc tggggctgcc caccgtgaag 1200

agcgcccgga tcgcccgaaa cacacagatc atcatccagg aggaaagcgg catccccaag 1260

gtggccgacc cctgggggggg cagctacatg atggagtgcc tgaccaacga tgtgtacgac 1320

gccgccctga agctgatcaa cgagatcgag gagatggggg gcatggccaa agccgtggcg 1380

gaggggattc ccaagctgag gatagaagag tgcgctgcca ggcgccaagc ccggatcgac 1440

agcggctcgg aggtcatcgt gggcgtgaac aagtaccagc tggagaagga ggacgcagtg 1500

gaggtcctgg ctatcgacaa cacgagcgtg aggaaccggc aaatcgaaaa actgaagaag 1560

ataaagagca gccgcgacca ggcgctggcc gagaggtgcc tggccgccct gaccgagtgt 1620

gcggcctccg gcgatggcaa catcctggcc ctcgccgtgg acgcctccag agccaggtgc 1680

accgtggggg agatcaccga cgccctcaag aaggtgttcg gggagcataa ggccaatgac 1740

aggatggtca gtggggccta ccgccaggag ttcggcgagt ccaaggagat aaccagcgcc 1800

atcaagaggg ttcacaagtt catggagagg gaaggcagac gccccaggct gctggtcgcc 1860

aagatgggcc aggacggcca cgaccgaggt gccaaggtga tcgccaccgg cttcgcggac 1920

ctgggcttcg atgtcgacat cggccccctg ttccagaccc cccgcgaggt cgcccagcaa 1980

gccgtcgacg ccgacgtgca cgccgtaggg gtgagcaccc tcgccgcggg ccacaaaacc 2040

ctggtgcctg agctcatcaa agaactcaac tccctgggaa ggcccgacat actggtgatg 2100

tgcggcggcg tgatcccccc acaggactac gagttcctct tcgaggtggg cgtgtccaac 2160

gtgttcgggc ccgggacccg gatccccaag gccgccgtcc aagtgctgga cgacattgag 2220

aaatgcctgg agaagaagca gcagagcgtg 2250

<210> 751
<211> 2250
<212> DNA
<213> Artificial Sequence

<220>
<223> Codon optimized sequence that encodes an MCM polypeptide with the I671V mutation

<400> 751
atgctgaggg ccaagaacca actgttcctg ctgtcccccc actacctcag gcaggtcaag 60

gagtcgagcg gcagcaggct gattcagcaa cggctgctgc accaacaaca gcccctgcac 120

cccgagtggg cggcgctggc gaagaagcag ctgaagggga aaaaccccga ggacctgatc 180

tggcacaccc ccgagggcat cagcataaag cccctgtata gcaaacgcga caccatggac 240

ctcccagagg agctgcccgg cgtgaagccg tttacccgcg ggccctaccc caccatgtac 300

accttcaggc cctggaccat ccgacagtac gccggtttca gcaccgtcga ggagtcaaac 360

aagttctaca aggacaatat caaggccggc cagcaaggtc tgagcgtggc cttcgacctg 420

gcgacccaca ggggctacga ttccgataat ccgagggtga ggggtgatgt gggcatggcc 480

ggcgtggcca tcgacaccgt tgaggataca aaaatcctgt tcgacggcat ccccctggag 540

aagatgtccg tgagcatgac catgaacggc gccgtcatcc ccgtgctggc caacttcatc 600

gtgacaggcg aggagcaagg cgtgcccaaa gagaagctca ccgggaccat ccagaacgac 660

atcctgaaag agttcatggt gcggaacacc tacatattcc cacccgagcc cagcatgaag 720

atcatcgccg acatcttcga gtataccgcc aagcacatgc ccaagttcaa ctccattagc 780

atctccggct atcacatgca ggaggccggc gccgacgcca tcctggagct ggcctacacc 840

ttagccgacg gcctggagta ctccaggacc ggcctccagg ccgggctgac catagatgag 900

ttcgcacccc ggctgtcctt cttctggggc ataggcatga acttctacat ggagatcgcc 960

aagatgaggg ccgggcggag actgtgggcc catctgatag aaaagatgtt ccagcccaag 1020

aacagcaaga gcctcctgct aagggcgcat tgccaaacct ccggttggag cctcaccgaa 1080

caggacccct acaacaatat agtgaggacc gccatcgaag ccatggccgc cgtgtttggc 1140

ggcacccaat ccctccacac caacagcttc gatgaggccc tggggctgcc cactgtaaag 1200

agcgcccgca tcgcacgcaa cacccagatc atcatccagg aggaaagcgg cattcccaaa 1260

gtcgccgacc cgtgggggg gtcctacatg atggagtgcc tgaccaacga cgtgtatgac 1320

gccgccctga agctgatcaa cgagatagaa gagatgggtg gcatggcaaa ggctgtcgcc 1380

gagggcatcc cgaagctgcg gatcgaagag tgcgccgcca ggaggcaagc ccggatagac 1440

tccggcagcg aggtgatcgt gggtgtgaac aagtaccagc tggagaagga ggacgccgtc 1500

gaggtgctgg ccatcgacaa caccagcgtg aggaacaggc agatcgagaa actcaagaag 1560

atcaagagca gccgcgacca agccctggcc gagcggtgtc tggccgccct gaccgagtgc 1620

gccgcttccg gcgacggaaa catcctggcc ctggccgtcg acgccagccg ggcccggtgc 1680

accgtcggcg agatcaccga tgccctgaag aaggtcttcg gggagcacaa ggccaatgac 1740

cggatggtga gtggcgctta caggcaggag ttcggcgaga gcaaggaaat cacgagcgcc 1800

atcaagaggg tccacaagtt catggagcgg gaggggagga ggcccaggct gctggtggcc 1860

aagatgggcc aggacgggca cgacaggggc gcgaaggtca tcgccacggg cttcgccgac 1920

ctggggtttg atgtcgacat cggcccactc ttccagaccc cccgggaggt ggcccaacag 1980

gccgtcgacg ccgacgtcca cgccgtgggg gtgagcaccc tggccgccgg gcacaagacc 2040

ctggtgcctg aactgatcaa ggagctgaac agcctgggca ggccagacat actggttatg 2100

tgcgggggtg tgataccccc gcaggactac gagttcctct ttgaggtggg cgtgagcaac 2160

gtgtttggcc ccggcaccag gatccccaaa gccgccgtgc aggtgctgga tgatatcgaa 2220

aagtgcctgg agaaaaagca acagtccgtg 2250

<210> 752
<211> 2250
<212> DNA
<213> Artificial Sequence

<220>
<223> Codon optimized sequence that encodes an MCM polypeptide with the I671V mutation

<400> 752
atgctgcggg ccaagaacca gctgttcctg cttagtcccc actacctccg tcaagtgaag 60

gagtcctccg ggagccggct catacagcag aggctgctcc accagcagca gcccctgcat 120

cccgagtggg ccgccctggc caagaagcag ctgaagggta aaaaccccga ggatctgatc 180

tggcacaccc ccgagggcat cagcatcaag cccctctaca gcaagcgcga taccatggac 240

ctccccgagg agctccccgg cgtgaagccc ttcacaaggg gcccctaccc caccatgtac 300

acctttaggc cgtggaccat ccggcagtat gccggcttca gcaccgtgga ggaatccaac 360

aagttctaca aagacaacat caaggcgggg caacagggcc tgagcgtggc cttcgacctg 420

gccacccata gggggtacga ctccgacaac ccgagggtga gaggcgacgt cgggatggcc 480

ggcgtggcca ttgacacagt ggaggatacc aaaatcctgt tcgacgggat acccctggaa 540

aagatgtcgg tgtccatgac catgaacggc gccgtaatcc ccgtgctggc gaacttcatc 600

gtgaccggcg aggaacaggg cgtgccaaag gaaaagctga cggggacgat ccagaacgac 660

attctcaagg aattcatggt gaggaacacc tacatctttc cccccgagcc cagcatgaaa 720

atcatcgcag acatctttga atacaccgcc aagcacatgc ccaagttcaa cagcatcagc 780

atctccggct accacatgca ggaggccggc gccgacgcca tactggaact ggcatacacc 840

ctggccgacg ggctcgagta ctccaggacc gggctccagg ccggactgac catagacgaa 900

ttcgccccac ggctgtcctt cttttggggc atcgggatga acttctacat ggagatcgcc 960

aagatgcgag ccggccgcag gctgtgggcc cacctgatag agaagatgtt ccagcccaag 1020

aactccaagt cactgctgct gagggcccat tgccagacca gcggctggag cctcaccgag 1080

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ggcacccagt ccctgcatac caactccttt gatgaggcgc tgggcctgcc cacagtgaag 1200

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gaaggcatcc ccaagctgcg catcgaggaa tgcgccgccc gcaggcaggc caggatcgat 1440

tccggcagcg aggtgatcgt cggcgtgaac aagtaccagc tggagaaaga ggacgccgtg 1500

gaggtgctcg ccattgacaa cacctctgtg aggaatcgcc agatcgagaa actcaagaag 1560

atcaagagct ccagggacca ggcgctggcc gagcggtgcc tggccgcgct gaccgaatgc 1620

gccgcctccg gggacgggaa catcctggca ctcgcggtgg acgcctccag ggccaggtgc 1680

acggtgggcg agatcaccga cgccctgaag aaggtgtttg gcgagcacaa ggccaatgac 1740

cggatggtgt ccggcgccta taggcaagag ttcggggaga gcaaagaaat aaccagcgcc 1800

atcaagcggg tgcacaagtt tatggagagg gaaggccgcc gcccccggct gctggtcgcc 1860

aagatggggc aggacggcca cgaccgcggc gccaaggtga tagcgaccgg cttcgccgat 1920

ctgggcttcg acgtggatat cggccccctc ttccagacgc cccgggaggt ggcgcaacag 1980

gcagtggacg ccgacgtgca tgccgtgggc gtgtccaccc tggccgcagg ccacaagacc 2040

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gtgttcggcc ccggcacccg gatccccaag gccgccgtgc aggtgctgga cgacatcgag 2220

aagtgtctgg agaagaaaca gcagagcgtg 2250

<210> 753
<211> 2250
<212> DNA
<213> Artificial Sequence

<220>
<223> Codon optimized sequence that encodes an MCM polypeptide with the I671V mutation

<400> 753
atgctgcgag ccaagaacca gctgttcctc ctgagccccc actacctccg gcaggtcaag 60

gaaagctccg gttcccggct gatacagcag aggctgctgc accagcaaca acccctgcac 120

cccgagtggg ccgcacttgc caaaaaacag ctgaagggga agaaccccga ggacctgatc 180

tggcatacac ccgagggcat cagcatcaag cccctgtact cgaaacgtga caccatggac 240

ctgcccgagg agctgcccgg cgtgaagccc ttcaccaggg ggccctaccc caccatgtac 300

accttccgac cctggaccat ccggcagtac gccggcttca gcacggttga ggagtcgaac 360

aaattctata aggacaatat caaagccggc caacagggcc tgagcgtggc atttgatctg 420

gccacgcacc ggggatacga tagtgataac ccccgggtca ggggggacgt gggcatggcc 480

ggcgtagcca tcgacacggt ggaggacacc aagatactgt tcgacggcat cccactggaa 540

aagatgtccg tgagcatgac gatgaacggg gccgtgatcc cggtcctggc caacttcatc 600

gtgaccggcg aagagcaggg ggttcccaag gagaagctca ccggcaccat ccaaaacgac 660

atcctgaagg agttcatggt gcgcaatacc tacatctttc ccccggagcc cagcatgaag 720

ataatagccg acatattcga atacaccgcc aagcacatgc ccaagttcaa tagcatctcc 780

atcagcggat accacatgca ggaagccggc gccgatgcca tcctggaact ggcctacacc 840

ctggctgatg gactcgagta cagccggacc gggctgcaag ccgggctgac catcgacgag 900

ttcgccccca ggctgagctt tttctggggg atcggcatga atttttacat ggagatcgcc 960

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gagggcatcc ccaagctgcg gatcgaggag tgcgccgcca ggaggcaggc caggatcgac 1440

agcggcagcg aggttatcgt gggggtcaac aagtaccaac tggagaaaga agacgccgtg 1500

gaggtgctcg ccatcgacaa caccagcgtg aggaaccggc agattgagaa actgaagaaa 1560

atcaagagct ccagggacca ggccctggcc gagaggtgtc tggccgccct gaccgaatgc 1620

gcggccagcg gcgacggcaa catcctggcc ttggccgtgg atgccagccg agccaggtgc 1680

accgtgggag aaatcaccga cgccctgaag aaggtgttcg gcgagcataa ggccaatgac 1740

aggatggtgt ccggcgccta ccgccaggag ttcggtgagt cgaaagagat caccagcgcc 1800

atcaagcgcg tgcacaagtt catggagagg gaaggcaggc ggccgcggct gctcgtggcc 1860

aagatgggcc aagatggcca cgaccgcggt gccaaagtca tcgccaccgg gttcgcggat 1920

ctgggcttcg acgttgacat cggccccctg ttccagaccc cccgggaggt ggcccagcag 1980

gccgtggatg ccgacgtgca cgccgtgggc gtgtccaccc tggccgccgg gcacaaaacc 2040

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gtgttcggcc cggggaccag gatccccaag gcggccgtgc aggtcctgga cgacatcgag 2220

aagtgcctgg agaagaagca gcaatccgtc 2250

<210> 754
<211> 2250
<212> DNA
<213> Artificial Sequence

<220>
<223> Codon optimized sequence that encodes an MCM polypeptide with the I671V mutation

<400> 754
atgctgaggg ccaaaaatca gctgttcctg ctgagccccc actacctccg gcaggtgaag 60

gaatcctcgg ggtccaggct gatccagcag aggctgctgc accagcagca gcccctgcat 120

ccggagtggg ccgccctggc caagaagcag ctcaagggca agaaccccga ggacctgatc 180

tggcacaccc cagaaggcat ctcgatcaaa cccttgtact ccaagaggga caccatggac 240

ctacccgagg agctgcccgg ggtgaagccc ttcacccgcg gcccctatcc cacgatgtac 300

acgttcaggc cctggaccat ccgccagtac gcgggcttca gcaccgtgga ggagagcaac 360

aagttttata aagacaacat caaggccggc cagcagggcc tgagcgtggc cttcgacctc 420

gccacccacc gcggctacga cagcgacaac ccccgcgtga ggggcgacgt ggggatggcc 480

ggcgtggcga tcgacaccgt ggaggacacg aagatcctgt tcgacgggat ccccctggag 540

aagatgagcg tctccatgac catgaatggc gccgtgatcc cagtgctggc caacttcatc 600

gtgaccggcg aggagcaggg ggtcccgaaa gagaaactca ccggcaccat ccagaacgac 660

atcctgaagg agttcatggt gaggaacacc tacatcttcc ccccggaacc cagcatgaaa 720

atcatagccg acatcttcga gtacaccgcc aagcatatgc ccaaattcaa cagcatcagc 780

atatccggct accacatgca ggaggccggc gccgacgcga tcctggaact ggcctacacc 840

ctggccgacg gtctggagta cagcaggacc ggcctgcagg cgggtctcac cattgacgag 900

ttcgcgccga ggctgtcctt cttctggggc atcggcatga acttctatat ggagatagcc 960

aagatgaggg ccggcagaag gctgtgggcc catctgatcg agaaaatgtt ccagccgaag 1020

aatagcaagt ccctgctgct gagggcccac tgtcagacca gcgggtggtc cctaaccgag 1080

caggacccct acaacaacat cgtgcggacc gcgatcgaag ccatggcggc cgtgttcggg 1140

ggcacccaga gcctgcacac gaacagcttc gacgaggccc taggcctgcc aacggtgaag 1200

tccgccagga tcgcgaggaa cacgcagatc atcatccaag aggaaagcgg gatccccaaa 1260

gtggccgacc cctggggcgg tagctacatg atggagtgcc tcaccaacga tgtgtacgac 1320

gcggccctga aactcattaa tgagatcgaa gagatgggcg gcatggccaa agccgtggcc 1380

gagggcatcc ccaagctgag aatcgaagag tgcgccgcta ggcggcaagc ccggatcgac 1440

agcggcagcg aggtgatagt gggcgtcaac aagtaccaac tggagaagga agacgccgtg 1500

gaggtgctgg cgatcgacaa cacttcggtg cggaatcgtc agatagagaa gctgaagaag 1560

atcaagtcca gccgagacca ggccctggcc gagaggtgcc tggccgccct gacagagtgc 1620

gccgcctccg gcgacggcaa catcctcgct ctcgccgtag atgccagcag ggcgcgctgt 1680

accgtgggcg agatcaccga cgccctgaaa aaggtgttcg gggaacacaa ggccaacgac 1740

cggatggtgt ctggcgccta ccgccaggag ttcggggagt ccaaggagat caccagcgcc 1800

atcaagcgcg tacacaagtt catggagagg gagggcaggc gccccaggct gctcgtggcc 1860

aaaatgggac aggacgggca cgacaggggc gccaaggtga tcgcgaccgg attcgcggac 1920

ctgggcttcg acgtggacat aggacccctg ttccagaccc ccagggaggt cgcccagcag 1980

gccgtggatg cggacgtgca tgccgtgggc gtctccaccc tggccgccgg tcacaagacc 2040

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tgcggcggcg tgatcccccc ccaggattac gagttcctgt tcgaagtggg tgtatccaac 2160

gtgttcggac ccggcacccg catcccgaag gccgccgtgc aggtcctgga tgacattgag 2220

aagtgcctgg agaagaagca gcagagcgtg 2250

<210> 755
<211> 2250
<212> DNA
<213> Artificial Sequence

<220>
<223> Codon optimized sequence that encodes an MCM polypeptide with the I671V mutation

<400> 755
atgctgaggg ccaagaacca gctgttcctg ctgagccccc actatctgcg ccaggtaaag 60

gagagcagcg ggtccaggct gatccagcag aggctgctgc accagcagca gcccctccac 120

cccgagtggg ccgccctcgc caaaaagcag ctcaagggga agaaccccga agacctgata 180

tggcacaccc ccgaggggat ctccatcaaa cccctctatt ccaagaggga caccatggat 240

ctgccggagg agctgcccgg agtgaagccc tttacaaggg gcccctaccc caccatgtat 300

accttccggc cctggaccat ccgtcagtac gccggcttct cgaccgtcga ggagagcaac 360

aagttctaca aggacaacat caaggccggg cagcagggac tcagcgtggc gtttgacctg 420

gccacacata ggggctacga ctccgacaat ccccgggtga ggggcgatgt ggggatggcc 480

ggcgtggcca tcgacaccgt cgaggacacc aaaatcctgt ttgacggcat ccccctggaa 540

aagatgagcg tgtccatgac catgaacggc gccgtgatcc ccgtgctagc caacttcatc 600

gtgaccggcg aggaacaagg cgtgcccaag gagaagctca ccggcaccat ccagaacgac 660

atcctcaagg agttcatggt ccgtaatacc tacattttcc cccccgaacc cagcatgaaa 720

atcatcgccg acatcttcga gtacacggcc aaacacatgc ccaagttcaa ctccatcagc 780

atcagcggct accacatgca ggaggccggg gccgacgcca tcctggagct ggcctacacc 840

ctggccgacg ggctggagta cagcaggacc ggtctccagg ccgggctgac catcgacgag 900

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aagatgcgcg ccgggcgtcg gctgtgggcc cacctgatcg agaagatgtt tcagcccaag 1020

aactcgaaaa gcctgcttct gcgggcccac tgtcagacca gcggctggtc cctgaccgag 1080

caggacccct acaataacat cgtgagaacc gcgatcgagg ccatggcggc cgtcttcggc 1140

gggacccaaa gcctgcacac taacagcttc gacgaggccc tgggtctccc caccgtgaag 1200

agcgccagga tcgcacgtaa cacgcagatc atcatccagg aggagagcgg gatccccaag 1260

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gagggcatcc ccaagctgag gatcgaggaa tgtgccgcca ggcggcaagc ccggatcgac 1440

agcggcagcg aagtgatcgt cggcgtgaat aagtaccagc tggagaaaga ggacgccgtg 1500

gaagtgctcg ccatcgacaa cacctcagtc cgtaacaggc agatagagaa actgaagaag 1560

ataaagagct cccgcgacca ggccctggcc gagcgttgcc tggccgccct gactgagtgc 1620

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atcaagcgcg tgcacaagtt catggagagg gagggcagga ggccgagact gctggtggcc 1860

aagatgggcc aggacggcca cgaccgcggc gccaaggtca ttgccaccgg cttcgccgac 1920

ctcgggtttg acgtggacat cggccccctg ttccagacgc cccgggaagt ggcccagcag 1980

gccgtggacg ccgatgtgca cgccgtgggc gtgtcgaccc tggccgccgg ccacaagacc 2040

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tgcggtggag tcattccccc ccaggactac gagttcctgt tcgaggtcgg ggtgagcaac 2160

gtgttcggcc ccggaacccg catccccaaa gccgccgtgc aggtgctgga cgacatagag 2220

aagtgtctgg aaaagaaaca gcaaagcgtg 2250

<210> 756
<211> 2250
<212> DNA
<213> Artificial Sequence

<220>
<223> Codon optimized sequence that encodes an MCM polypeptide with the I671V mutation

<400> 756
atgcttaggg ccaagaacca gctgttcctc ctctcccccc actatctcag acaggtgaag 60

gagagcagcg gcagcaggct gatccaacag aggctcctcc accagcagca gcccctccac 120

ccggagtggg cagccctggc taagaaacag ctgaaaggga agaatcccga ggatctgatc 180

tggcacaccc cggaggggat atccataaag cccctgtatt cgaagaggga caccatggac 240

ctgcccgagg agctgcccgg cgtgaagccc tttacccgcg gaccctaccc caccatgtat 300

accttcaggc cctggaccat ccggcagtac gccggtttct ctaccgtgga ggagtccaac 360
aagttctaca aggacaacat caaggccggt cagcagggcc tcagcgtggc cttcgatctg 420
gccacccacc ggggctatga ttccgacaac ccgagggtcc gcggcgacgt ggggatggcc 480
ggcgtggcaa ttgataccgt ggaagacacc aagatcctgt ttgacggcat ccccctggag 540
aagatgagcg tgagcatgac catgaacggc gcagtgatcc ccgtgctggc aaatttcatc 600
gtcaccgggg aggagcaggg cgtgccaaag gagaagctga ccggcaccat ccagaatgat 660
atcctgaagg agttcatggt caggaatacc tacatcttcc cacccgagcc cagcatgaaa 720
atcatcgcgg acatcttcga gtacaccgcc aagcacatgc ccaagttcaa ttccatcagc 780
atctccgggt accacatgca ggaggccggc gccgacgcca tcctggagct cgcctacacc 840
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ttcgccccga ggctgagctt cttctggggc atcgggatga acttctatat ggaaatcgcc 960
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caggacccct acaataacat cgtcaggacc gccatcgagg ccatggccgc cgtgttcggc 1140
gggacccagt ccctccacac caacagcttc gacgaggcac tgggtctccc cacagtgaaa 1200
agcgccagga tcgccaggaa cacccaaatc atcatccagg aagaaagcgg catcccgaag 1260
gtggccgacc cctggggcgg cagctacatg atggagtgcc tgaccaacga tgtgtacgat 1320
gccgccctga agctcatcaa cgagatcgag gagatggggg gcatggccaa agccgttgcc 1380
gaaggaatac caaagctgcg tatcgaggag tgcgccgcga ggaggcaggc gcgcatcgac 1440
agcgggtccg aggttatcgt gggcgttaac aagtatcagc tggagaagga ggacgccgtg 1500
gaggtgctgg ccatcgacaa cacctccgtg aggaacaggc agatagagaa gctgaagaaa 1560
atcaagagct ccagggacca agcgctggcc gagaggtgcc tcgccgcgct gacggagtgc 1620
gccgccagcg gcgatggcaa catcctggcc ctggccgtgg acgccagcag ggcccggtgt 1680
acagtgggcg agatcaccga cgccctcaag aaggtgtttg gggagcacaa ggcgaacgac 1740
aggatggtgt ccggcgccta ccggcaggag tttggcgagt caaaagaaat aacctccgcc 1800
atcaagcggg tgcacaagtt catggagagg gaggggagga ggcctaggct gctggtggcc 1860
aagatgggcc aggatggcca cgacaggggc gccaaagtaa tcgccacggg cttcgccgac 1920
ctcgggttcg acgtggacat aggacccctg ttccagaccc cccgggaggt ggcccagcag 1980
gccgtcgacg ccgacgtaca tgccgtcggc gtgtccaccc tggccgcagg ccacaagacc 2040
ctggtgcccg agctgatcaa ggagctcaac agcctgggca ggcccgacat tctcgtcatg 2100
tgcggcggtg tgatcccccc ccaggactac gagtttctgt tcgaggtggg cgtcagcaac 2160
gtattcgggc ccggcacgag gatccccaag gctgccgtgc aagtgctgga cgacattgag 2220
aaatgcctgg agaagaagca gcagtccgtg 2250

<210> 757
<211> 2250
<212> DNA
<213> Artificial Sequence

<220>
<223> Codon optimized sequence that encodes an MCM polypeptide with the I671V mutation

<400> 757
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gagtccagcg gcagccggct catccagcaa aggctgctgc atcagcagca gcccctgcac 120

cccgagtggg ccgcccttgc caagaaacag ctgaagggca aaaaccccga agacctgatc 180

tggcacaccc ccgaaggcat cagcatcaag cccctgtaca gcaagcgcga caccatggac 240

ctgcccgagg aactgcccgg cgtgaaacct ttcacgaggg gcccgtaccc caccatgtat 300

accttccgcc cgtggacgat caggcagtat gctggcttca gcaccgtgga ggagagcaac 360

aagttttaca aagacaacat caaggccggg cagcaggggc tgagcgtcgc cttcgacctc 420

gccacccacc gcggctatga cagcgataat ccccgggtga ggggggacgt gggcatggcc 480

ggcgtcgcga tcgacacggt ggaggacacc aagatcctct tcgacgggat ccccctggag 540

aagatgagcg tgagcatgac tatgaacggc gccgtgatcc ccgtgctcgc caatttcatc 600

gtgacgggcg aggagcaagg cgtgccgaaa gagaagctga ccggcacgat ccagaacgat 660

atcctgaagg agtttatggt gaggaacacc tacatcttcc ccccggagcc cagcatgaag 720

atcatcgcgg acatcttcga atacaccgcg aaacacatgc ccaagtttaa tagcatcagc 780

atttccggct accacatgca ggaggccggc gccgatgcca tcctcgaact ggcctacacc 840

ctcgccgacg gtctggagta ctccaggaca gggctccagg ccggactgac catcgacgag 900

ttcgccccca ggctgagttt cttttggggc atcggcatga acttctacat ggagatcgcc 960

aaaatgaggg ccggcaggag gctgtgggcg cacctgatcg aaaagatgtt ccaaccgaag 1020

aatagcaaaa gtctgctgct ccgcgcccat tgccagacat ccggctggag cctgaccgag 1080

caggatccct acaacaacat cgtgagaacc gccatcgagg ccatggccgc cgtgttcggc 1140

ggcacccagt ccctgcacac taacagcttc gacgaagccc tgggcctccc caccgtgaaa 1200

agcgccagga tcgcccggaa cacccagatc ataatccaag aggagtctgg catcccgaag 1260

gtggcggacc cgtggggcgg ctcctatatg atggagtgcc tgaccaacga cgtgtacgac 1320

gccgccctga aactcatcaa cgagatagaa gaaatgggcg gcatggcgaa ggccgtcgcc 1380

gagggcatcc ccaagctgag gatcgaagag tgcgccgcca ggaggcaggc caggatcgat 1440

agcggctccg aggtgatcgt gggcgtgaat aagtaccaac tggagaagga ggacgccgtg 1500

gaggtgctgg ccattgacaa cacctccgtc aggaacaggc agatcgagaa actgaagaag 1560

atcaagagct cacgggacca ggcgctggcc gaacgatgcc tggccgccct gaccgaatgc 1620

gcggccagcg gggacggcaa catcctggcc ctggccgtgg atgcgtccag ggcgaggtgt 1680

accgtgggcg agatcaccga cgccctcaag aaggtgttcg gcgagcacaa ggccaacgac 1740

cggatggtct ccggcgccta caggcaagag ttcggggagt ccaaggagat taccagcgcc 1800

atcaagaggg tccacaagtt catggagagg gagggcaggc gcccccggct cctagtggcc 1860

aagatgggcc aggacggcca cgacaggggg gccaaggtga tcgcgacggg atttgccgat 1920

ctgggcttcg acgtggacat cggccccctg ttccagacgc ccagggaggt ggcccaacag 1980

gccgtggacg ccgacgtgca cgccgtgggc gtctccactc tggctgccgg ccataagacc 2040

ctggtgcccg aactcattaa ggaactgaat agcctcgggc gtcccgacat actggtgatg 2100

tgcggcgggg tgatcccccc acaggactac gaattcctgt tcgaggtggg ggtctccaac 2160

gtgttcggcc ccggtacccg gatccccaag gcagccgtgc aggtactcga cgacatcgag 2220

aagtgtctgg agaagaagca gcagagcgta 2250

<210> 758
<211> 2250
<212> DNA
<213> Artificial Sequence

<220>
<223> Codon optimized sequence that encodes an MCM polypeptide with the I671V mutation

<400> 758
atgctaagag cgaagaatca gctgttcctc ctgagccccc attacctgag acaggtgaag 60

gaatccagcg gctcccgcct gatacagcag aggctgctcc accagcagca gcccctgcac 120

cccgagtggg ccgccctggc caaaaagcag ctcaagggca aaaaccccga agacctgatc 180

tggcacaccc cagaggggat ctccatcaaa ccgctgtaca gcaagaggga caccatggac 240

ctgcccgagg aactgcccgg ggtgaagccg ttcaccaggg gcccctaccc caccatgtat 300

acgttcaggc cctggaccat caggcagtac gccggattca gcacggtgga ggaaagcaac 360

aagttctaca aggataacat aaaggccggg cagcagggcc tgagcgtggc cttcgacctg 420

gccacccacc gaggctacga cagcgataac cccagggtgc ggggcgatgt cggaatggcc 480

ggcgtggcca tcgacacggt cgaggacacc aagatcctct tcgacgggat ccccctcgag 540

aaaatgtccg tgtccatgac catgaacggc gccgtgatcc ccgtgctggc caatttcatc 600

gtgaccgggg aggagcaggg cgtgcccaag gagaagctga ccggcaccat ccagaacgac 660

atcttgaagg aattcatggt gcgaaacacc tacatcttcc cccccgagcc aagcatgaag 720

atcatcgcgg acatcttcga atacaccgcc aagcacatgc ccaaatttaa tagcatctcc 780

atctccggct atcacatgca ggaggccggt gccgacgcga tcctggagct ggcctatacc 840

ctcgccgacg gtctggagta cagccggacc ggcctccagg ccggcctcac catcgacgaa 900

ttcgccccgc ggctgagctt cttctggggc atcggcatga acttctacat ggagatcgcc 960

aagatgaggg ccggccgcag gctgtgggct catctcatcg agaagatgtt ccagcccaag 1020

aactcgaaga gcctgctcct gagggcccat tgccagacca gcgggtggtc cctgaccgag 1080

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gccgccctca agctcatcaa cgagatcgaa gagatgggcg gcatggctaa ggccgttgcc 1380

gagggcatcc ccaagctgag gatcgaggag tgcgcagccc ggaggcaggc caggatcgat 1440

agcggctcgg aagtgatcgt gggggtgaac aagtaccagc ttgagaagga ggacgccgtg 1500

gaggtgctgg ccatcgacaa tacctccgtg agaaacaggc agatcgaaaa gctgaagaaa 1560

atcaagagct ccagggacca ggcgctcgcg gagcgatgcc tcgccgccct gaccgagtgt 1620

gccgcctcgg gtgacgggaa catcctggcc ctcgccgtcg acgcctccag ggcccggtgc 1680

accgtgggcg agatcaccga cgccctgaag aaggtgttcg gcgagcataa agccaacgac 1740

aggatggtga gcggcgccta caggcaggag tttggcgaga gcaaggagat caccagcgct 1800

atcaagaggg tgcacaagtt catggaaagg gaggggagga ggccccgcct gctggtcgcc 1860

aagatgggcc aagacgggca cgataggggc gccaaggtga tcgcgaccgg cttcgccgac 1920

ctgggatttg acgtggacat cgggccactg ttccagacgc cccgggaggt cgcccagcag 1980

gccgtcgacg ccgacgtgca cgcggtgggc gtgagcacac tggcagccgg ccacaaaacc 2040

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tgcggcggag ttatcccccc ccaggactac gaattcctgt tcgaggtggg cgtcagcaac 2160

gtgttcgggc ccggtaccag gatccccaag gccgccgtcc aggtgctgga cgacatcgag 2220

aaatgcctgg aaaagaaaca acaaagcgtg 2250

<210> 759
<211> 2250
<212> DNA
<213> Artificial Sequence

<220>
<223> Codon optimized sequence that encodes an MCM polypeptide with the I671V mutation

<400> 759
atgctgcgcg ccaagaatca gctgttcctg ctgagccccc actacctgcg ccaggtgaag 60

gaatcgagcg gatcgaggct gatccagcag aggctgcttc accagcagca acccccttcac 120

cccgagtggg ccgcactggc gaagaagcaa ctgaagggta agaaccccga agacttaatc 180

tggcacaccc ccgaagggat cagcatcaag cccctgtaca gcaaaaggga caccatggac 240

ctgccggagg agctgcccgg ggtgaagccc ttcaccaggg gcccctaccc cacgatgtac 300

accttccggc cctggactat ccgtcagtac gccggctttt ccacagtgga ggagagcaac 360

aagttttata aggacaacat caaggccggc cagcaaggcc tgagcgtggc gtttgacctg 420

gccacccaca ggggctacga ctccgacaac ccacgggtga ggggcgacgt cggcatggcc 480

ggggtggcca tcgacaccgt ggaggacacc aagatcctgt tcgacggcat ccccctcgag 540

aaaatgagcg tgtccatgac catgaacggc gccgtgattc cggtgctggc caacttcatt 600

gtcaccggag aggagcaagg cgtgccaaag gagaagctga ccgggaccat ccagaacgac 660

attctgaaag agttcatggt gcgcaacacg tacatattcc cccccgagcc cagcatgaag 720

atcatcgctg acatcttcga gtacaccgcc aagcatatgc ccaagttcaa cagcatcagc 780

atctccggct accacatgca agaagccggc gccgatgcca tactcgagct cgcctacacc 840

ctggccgatg gtctggaata ctccaggacg ggcctgcagg cgggcctcac catcgacgag 900

tttgcgccca ggctgagctt cttttggggc atcggcatga acttctacat ggaaatcgcc 960

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gccgccagcg gggacggcaa catcctggcg ctggccgtgg atgccagccg cgccaggtgc 1680

accgtcggcg agatcacgga cgccctgaag aaggtcttcg gagagcacaa ggccaacgac 1740

cggatggtca gcggcgcgta caggcaggag ttcggcgagt ctaaggagat cacctccgcc 1800

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aagtgcctgg agaaaaaaca acagagcgtg 2250

<210> 760
<211> 2250
<212> DNA
<213> Artificial Sequence

<220>
<223> Codon optimized sequence that encodes an MCM polypeptide with the I671V mutation

<400> 760
atgcttcggg cgaagaacca gctgttcctg ctgtccccgc actacctcag gcaggtgaag 60

gagagctccg gcagccgcct gatccagcag aggctgctgc accagcagca gcccctgcac 120

ccggagtggg ccgcgctggc caagaagcag ctgaagggca agaaccccga ggacctgata 180

tggcacaccc ccgagggcat ctccatcaag ccgctgtatt cgaagaggga caccatggac 240

ctgcctgagg agctgcctgg ggtaaagccc ttcaccaggg ggccctaccc caccatgtac 300

acctttcggc catggaccat ccggcaatat gccgggttct caaccgtgga ggagagcaac 360

aagttctaca aggacaacat taaggcgggg cagcaggggc tgtccgtggc gttcgacctg 420

gccacccacc ggggctatga cagcgacaat ccccgggtga ggggggacgt gggcatggcg 480

ggcgtggcca tcgatacagt cgaggacacg aagatactgt ttgacggcat ccccctggag 540

aaaatgtcgg tgtcgatgac gatgaacggc gccgtgatcc cggtgctggc caacttcatc 600

gtgaccggcg aggagcaggg ggtgcctaag gagaaactga ccgggaccat ccagaacgac 660

atcctgaagg agttcatggt gcgcaacacc tacatatttc cccccgagcc cagcatgaag 720

atcatcgccg acatcttcga atacaccgcc aagcatatgc ccaagttcaa cagcatcagc 780

atctccgggt accacatgca ggaggccggc gccgacgcca tcctggaact ggcctacacc 840

ctggccgacg gcctggagta cagcagaacc gggctccagg caggcctgac catcgacgag 900

ttcgccccac ggctgtcctt cttctggggg atcggcatga acttctatat ggagatcgcc 960

aagatgaggg ccgggcggag gctctgggcc catctgatcg agaagatgtt ccagccaaag 1020

aacagcaaga gcctcctgct gagggcccac tgccagacca gcggctggtc cctgaccgag 1080

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gtggcggacc cttggggtgg ctcctacatg atggaatgcc tcacaaatga tgtgtacgac 1320

gccgccctca aactgatcaa cgaaatcgag gagatgggtg gcatggccaa agccgtagcg 1380

gagggcatcc ccaagctccg gatcgaggag tgcgccgcca ggcgacaggc ccggatcgac 1440

agcggctccg aggtcatcgt cggggtgaac aagtaccagc tcgaaaagga ggacgccgtg 1500

gaggtgctgg cgatcgacaa caccagcgtg cggaacaggc agatagagaa gctgaagaag 1560

atcaagagca gtagggacca ggccctcgcc gagaggtgtc tggccgccct gaccgagtgc 1620

gccgcctccg gcgatggcaa catcctggcc cttgccgtgg acgcgagccg cgccaggtgc 1680

accgtgggcg agatcaccga cgccctgaag aaggtgtttg gcgaacacaa ggccaacgac 1740

aggatggtgt ccggcgccta ccgtcaggag ttcggcgaga gcaaggagat caccagcgcc 1800

atcaagaggg tgcacaagtt tatggaacgc gaagggaggc gccccaggct gctggtggcc 1860

aagatggggc aggacgggca cgacaggggc gccaaagtca tcgccaccgg ctttgccgac 1920

ctgggattcg atgtggacat cggccccctg tttcagaccc ccagagaggt cgcccaacag 1980

gcggtcgacg ccgacgtcca tgccgtcggc gtgagcaccc tggccgccgg gcacaagacg 2040

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tgcgggggg tgattccccc ccaggactat gagttccttt tcgaagtggg tgtcagcaac 2160

gtgttcggcc cgggcacccg catccccaag gctgcggtcc aggtgctgga cgacatcgag 2220

aagtgcctgg agaagaaaca gcaatccgtg 2250

<210> 761
<211> 2250
<212> DNA
<213> Artificial Sequence

<220>
<223> Codon optimized sequence that encodes an MCM polypeptide with the I671V mutation

<400> 761
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gagtcctccg gcagcaggct cattcagcag aggctgttgc accagcagca gcccctgcac 120

ccagagtggg ccgccctcgc caagaagcag ctgaagggga agaaccccga ggacctgatc 180

tggcatacgc ccgagggtat ctccataaaa cccctctaca gtaagaggga caccatggac 240

ctgcccgagg aactgcccgg cgtgaagccg ttcacgcggg gcccataccc caccatgtac 300

accttccggc cgtggaccat caggcaatac gccggcttca gcaccgtgga ggagagcaac 360

aagttctaca aagacaacat caaagccggt cagcaagggc tgagcgtagc cttcgacctg 420

gccacccaca ggggctacga ctccgacaac cccagggtgc gcggcgacgt gggcatggcc 480

ggcgtggcca tcgacaccgt ggaagacacc aagatcctct tcgacggcat ccccctggaa 540

aagatgtccg tgtccatgac catgaacggg gccgttatac cggtgctggc caacttcata 600

gtcaccggcg aggagcaggg ggtcccgaag gagaagttaa ccggcacgat tcagaacgac 660

atcctgaaag agttcatggt gaggaacacc tatatcttcc cccccgagcc ctccatgaaa 720

atcatcgccg acatcttcga gtacaccgcg aagcacatgc ccaagttcaa ctccatcagc 780

atctccggat atcacatgca ggaagccggc gccgacgcca tcctggagct ggcctacacc 840

ctggcggacg gactggagta cagccgcacg ggcctgcagg cgggcctgac catagacgaa 900

tttgccccgc ggctgagctt tttctggggg atcggcatga atttctacat ggagatcgcc 960

aagatgcggg ccggcagacg gctgtgggcc catctgatcg aaaaaatgtt ccagcccaaa 1020

aacagcaagt ccctgctgct gcgggcccac tgccagacca gcggctggag cctgaccgag 1080

caggacccgt acaataacat cgtgaggacc gccatcgagg ccatggccgc cgtgttcggc 1140

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gtggccgacc cctggggcgg ctcctacatg atggagtgcc tgacgaacga cgtgtacgac 1320

gccgccctga agctgatcaa cgagatcgag gagatgggcg gcatggccaa ggccgtcgcc 1380

gagggcatcc ccaagctgcg catcgaggag tgcgccgcca ggcgccaagc ccggatcgat 1440

agcggcagcg aggtgatcgt gggggtgaac aagtaccagc tggagaagga ggacgcggtc 1500

gaggtcctgg ccatagacaa cacgagcgtg cggaacaggc agatcgagaa gctcaagaaa 1560

atcaagagca gccgggacca ggccctggcc gaaaggtgcc tcgccgccct cacggaatgc 1620

gccgccagcg gcgacggcaa tatcctggcc ctggcggtcg atgccagccg cgctcggtgc 1680

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atcaagcggg tccataagtt catggagagg gagggccgga ggcccaggct gctcgtggcc 1860

aaaatgggcc aggacggcca tgacaggggc gccaaggtga tcgccaccgg gttcgccgac 1920

ctcggcttcg acgtggacat cgggccgctg ttccagacgc cgcgggaggt cgcccagcaa 1980

gcggtggacg ccgacgtgca cgccgtcggg gtgagcaccc tcgccgctgg gcataagacc 2040

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tgcggcggcg tcatcccgcc ccaggactac gagttcctgt ttgaggtcgg cgtctccaac 2160

gtgttcggcc caggcaccag gatccccaag gccgccgtgc aggtgttgga cgatatcgag 2220

aaatgcctcg agaaaaagca gcagagcgtc 2250

<210> 762
<211> 2250
<212> DNA
<213> Artificial Sequence

<220>
<223> Codon optimized sequence that encodes an MCM polypeptide with the I671V mutation

<400> 762
atgctgaggg cgaagaatca gctgtttctg ctgagccccc actacctcag gcaggtgaag 60

gagagcagcg gcagcaggct gatccagcag aggctgctgc accagcagca acccctgcac 120

cccgagtggg cggccctggc caagaagcag ctcaagggca agaaccctga agacctgatc 180

tggcacaccc ccgagggaat cagcatcaag ccgctgtact ccaagaggga caccatggac 240

ctgcccgagg agctccccgg cgtcaagccc ttcacccggg gcccctaccc caccatgtac 300

accttcaggc cctggaccat ccgccagtac gcgggcttct ccaccgtgga agagtccaac 360

aagttctaca aggacaacat caaggccggg caacagggcc tctccgtggc cttcgacctg 420

gccacgcacc ggggttacga ttctgacaac ccgcgcgtgc ggggcgacgt cgggatggcc 480

ggggtcgcga tcgacaccgt cgaggatacc aagatcctgt tcgacggcat ccccctcgag 540

aagatgagcg tcagcatgac catgaacggc gccgtgatcc ccgtgctggc caacttcatc 600

gtcaccggcg aggagcaggg ggtccccaaa gagaagctaa ccggcaccat ccagaacgac 660

atcctgaagg agttcatggt gaggaacacc tatatcttcc cgcccgagcc cagcatgaag 720

atcatcgccg acatcttcga gtacaccgcc aagcacatgc ccaagttcaa cagcataagc 780

atcagcgggt accacatgca ggaggccggt gcggacgcca tcctcgagct cgcctatacc 840

ctggcagacg gtctggagta cagcaggacc ggactgcaag ccgggctgac gatcgacgaa 900

ttcgccccca ggctgagctt cttctggggt attggcatga acttctacat ggagatcgcc 960

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aacagcaagt ccctgctgct cagggcccac tgccagacaa gcgggtggag cctcaccgag 1080

caggacccgt acaacaacat cgtgcgcacc gccatcgaag ccatggcggc cgtcttcggc 1140

ggcacccaga gcctgcatac caacagcttc gacgaggctc tgggcctgcc cacggtgaag 1200

tccgccagga tcgcccggaa cacccagatt ataatccagg aagagagcgg cattcccaag 1260

gtggcggacc catggggtgg cagctacatg atggaatgcc tcaccaatga cgtgtacgac 1320

gcggccctga agctgatcaa cgagatcgag gagatggggg ggatggccaa ggccgtggcc 1380

gagggcatcc ccaagctgag gatcgaagag tgcgccgccc gaaggcaggc ccggatcgac 1440

agcggcagcg aagtcatcgt gggcgtgaac aagtaccaac tcgagaagga ggacgcagtc 1500

gaagtgctcg ccatcgacaa caccagcgtg aggaaccggc agatcgagaa gctgaagaag 1560

atcaagtcct ccagagacca ggccctggcc gagaggtgcc tggccgccct gacggaatgc 1620

gccgccagcg gcgacggaaa catcctggcc ctggccgtag acgccagcag ggccaggtgt 1680

accgtgggcg agatcacgga cgcgctgaaa aaggtctttg gcgagcacaa agccaacgac 1740

aggatggtga gcggcgccta tcgccaggag ttcggcgagt ccaaggaaat caccagcgcc 1800

atcaagcggg tccacaagtt catggagagg gagggacgcc gcccccggct gctggtggcc 1860

aagatgggcc aggacgggca tgacaggggg gccaaggtga tcgccacggg ctttgccgat 1920

ctgggcttcg atgtggacat cggccccctg tttcagacgc ccagagaggt ggcccaacag 1980

gccgtggacg ccgacgtgca cgccgtgggt gtctccaccc tggccgccgg ccacaagacg 2040

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tgcgggggg tgatcccccc ccaggactac gagttcctgt ttgaggtggg cgtgtccaac 2160

gtgttcgggc ccggcaccag gatccccaag gccgccgtgc aggtgctgga cgacatcgag 2220

aagtgtctgg aaaaaaagca acagagcgtg 2250

<210> 763
<211> 2250
<212> DNA
<213> Artificial Sequence

<220>
<223> Codon optimized sequence that encodes an MCM polypeptide with the I671V mutation

<400> 763
atgctgaggg ccaagaacca gctgtttctg ctgagccccc actacctgcg gcaggtgaag 60

gaaagctccg gcagccggct gattcagcag cgcctgctgc accagcagca gcccctgcat 120

cccgagtggg ccgccctggc caagaagcag ctgaagggca agaaccccga ggacctgatc 180

tggcataccc ccgaagggat ctccatcaag cccctgtact ccaagaggga tacgatggac 240

ttgcccgaag agctccccgg cgtgaaaccc ttcacccggg gcccttaccc gactatgtac 300

accttcaggc cctggaccat caggcagtac gccggcttct ccaccgtgga ggagagcaac 360

aagttctaca aggataatat caaggccggc cagcagggcc tcagcgtggc cttcgacctg 420

gccacccacc gtggctacga cagcgacaac ccccgcgtcc ggggcgatgt gggaatggcc 480

ggcgtggcca tcgataccgt ggaggatacg aagatactat tcgacggtat ccccctggag 540

aagatgagcg tgagcatgac catgaacggc gcggtgatac ccgtgctggc caacttcatc 600

gtcacggggg aggagcaagg cgtgcccaaa gaaaagctga ccggcaccat ccagaacgac 660

atcctcaagg aattcatggt gcggaacacc tacatcttcc cccccgagcc ctccatgaag 720

attatcgccg atatcttcga gtacaccgcc aagcacatgc ccaagttcaa tagcatctcc 780

atctccggct accacatgca agaggccggc gccgacgcaa tcctggagct ggcctacaca 840

ctcgccgatg gcctggagta ttccaggacc ggcctgcagg ccggcctgac catcgacgag 900

ttcgccccca ggctgagctt cttttggggc attggcatga atttctacat ggagatcgcg 960

aagatgaggg ccggccggcg gctgtgggca cacctgatcg aaaagatgtt ccaacccaag 1020

aacagtaaga gcctgctgct gagggcccac tgccagacca gcggctggag cctgaccgag 1080

caggacccct acaataacat tgtgcggacc gccatcgagg cgatggccgc cgtgttcggc 1140

ggcacacaga gcctgcacac caacagcttt gatgaggccc tcggcctgcc cacggtgaag 1200

tccgccagga tcgccaggaa cactcagatc atcatccagg aggaaagcgg catccccaaa 1260

gtggccgacc cctggggcgg cagctacatg atggagtgcc tgaccaacga cgtctacgat 1320

gccgccctga aactcatcaa cgagattgag gagatgggcg gcatggccaa ggccgtggcc 1380

gaggggatcc ccaaactgag gatcgaagag tgcgccgccc ggaggcaggc ccgtatcgac 1440

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atcaagaggg tgcacaagtt catggagagg gaggggcggc gaccccgcct gctggtggcc 1860

aagatgggtc aggacgggca cgataggggc gccaaggtga ttgccaccgg attcgccgac 1920

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gtgttcgggc ccggcacccg gattcccaag gcggccgtgc aggtgctgga cgacatcgag 2220

aagtgtctgg aaaagaagca acagagcgtg 2250

<210> 764
<211> 2250
<212> DNA

<213> Artificial Sequence

<220>
<223> Codon optimized sequence that encodes an MCM polypeptide with the I671V mutation

<400> 764
atgctgaggg caaaaaacca gctcttcctg ctcagccccc actacctcag gcaagtgaag 60

gagtcctccg gctcccgtct gattcagcag aggctgctgc accagcagca gcccctgcac 120

cccgagtggg ccgccctcgc gaagaaacag ctcaagggga agaacccgga ggacctcatc 180

tggcacaccc ccgagggaat cagcatcaag cccctctact ccaagaggga taccatggac 240

ctgcccgagg agctgcccgg cgtgaaaccc ttcacccgtg gcccctaccc cacgatgtac 300

accttcaggc cctggaccat ccgccagtac gccggcttct ccaccgtgga ggagtccaac 360

aaattctaca aagacaatat caaggccgga caacagggcc tctccgtggc attcgatctg 420

gctacacaca gggggtacga ctccgacaac cccagggtgc ggggcgacgt cggtatggcc 480

ggggtcgcca tcgacacggt ggaagacacc aagatcctgt ttgacggcat ccccctggag 540

aaaatgagcg tgtccatgac catgaacggc gccgtgatcc ccgtcctggc caacttcatc 600

gtgaccggcg aagagcaggg cgtgcccaaa gagaagctga ccggtaccat ccaaaacgac 660

atcctgaaag agtttatggt ccggaacacc tacatcttcc cccccgagcc cagcatgaaa 720

atcattgcag atatattcga gtacaccgcc aaacatatgc ccaagttcaa cagcatctcc 780

atatccgggt atcacatgca ggaggccggg gccgacgcca tcctggagct ggcctacacc 840

ctggccgacg gcctggagta ttcccgaacg ggcctccagg ccgggctgac aatcgacgag 900

ttcgccccca ggttgagctt cttctggggc ataggaatga acttctacat ggaaatagcc 960

aagatgaggg ccggcaggag actgtgggcc cacctgatcg agaagatgtt ccagcccaag 1020

aacagcaaga gcctgctgct gcgggcccac tgccagacca gtggctggtc cctgaccgag 1080

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gagggaatcc cgaagctgag gatagaggag tgcgccgcga ggcgccaggc caggatcgat 1440

tccggctccg aggtgatcgt gggcgtgaac aagtaccagc tcgagaagga ggacgccgtg 1500

gaggtgctgg ccatagacaa cacctccgtg cggaaccgcc agatcgagaa actgaagaag 1560

atcaagtcca gccgcgacca ggccctggcc gagcggtgtc tggccgcgct cactgagtgc 1620

gccgccagcg gcgacggaaa catactggcc ctggccgtgg acgcctcccg cgccaggtgc 1680

acggtgggag agatcaccga cgccctgaag aaggtgttcg gggaacacaa ggccaacgat 1740

cggatggtct ccggcgccta ccgacaggag ttcggcgaaa gcaaggagat taccagcgcc 1800

atcaagcggg tgcacaagtt tatggagagg gagggccgga ggccccggct gctcgtggcc 1860

aagatgggcc aggatggaca cgatcgaggg gccaaagtca tcgccaccgg gttcgccgac 1920

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gtgttcggcc cgggcacccg gatccccaaa gccgccgtgc aggtgctcga tgacattgaa 2220

aagtgtctgg agaagaaaca gcaatccgtg 2250

<210> 765
<211> 2250
<212> DNA
<213> Artificial Sequence

<220>
<223> Codon optimized sequence that encodes an MCM polypeptide with the I671V mutation

<400> 765
atgctgaggg ccaagaacca gctgttcctg ctgtctcccc actatctaag gcaggtcaag 60

gagagcagcg gcagcaggct gatccagcag cgtcttctgc accagcagca gccactgcat 120

cccgagtggg ccgccctggc caagaagcag ctgaagggca agaaccccga ggacctgatc 180

tggcacaccc ctgagggcat cagcatcaag cccctgtact caaaacgcga caccatggac 240

ctgcccgaag agctgcccgg ggtgaagccc ttcacccggg gcccataccc cacgatgtac 300

acctttaggc cgtggaccat caggcagtat gccggcttct caaccgtgga ggagagcaac 360

aagttttaca aagacaacat caaggccggc cagcagggcc tgtccgtggc cttcgacctg 420

gccacacacc gggggtacga cagcgacaac ccccgcgtgc gtggtgatgt cgggatggcc 480

ggagtggcca tagacacggt ggaggacacc aagatcctgt tcgacggcat ccccctggaa 540

aagatgagcg tgagcatgac catgaacggc gccgtcatcc ccgtgctggc aaacttcatc 600

gtgaccggcg aggagcaggg cgtgccgaag gagaagctga ccggcaccat ccagaacgac 660

atcctgaagg aatttatggt caggaatacc tacatcttcc cacccgagcc ctccatgaag 720

atcatcgccg acatcttcga atacaccgcc aagcatatgc ccaaattcaa tagcatcagc 780

atcagcggtt accacatgca ggaagccggc gcggacgcca tcctggagct ggcctacacc 840

ctggcagatg gcctggagta ctcccgaacg ggactgcagg ccgggctgac catcgacgag 900

ttcgccccca ggctgagctt cttttggggc atcggcatga acttctacat ggaaatcgcc 960

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aacagcaagt ccctcctgct cagggcccac tgtcaaacca gcgggtggtc gctgaccgag 1080

caggacccct acaacaacat cgtccggacc gccattgagg cgatggccgc cgtgtttggg 1140

ggcacccagt ccctgcacac caacagcttc gacgaggccc tggggctgcc aaccgtcaag 1200

agcgcccgga tcgcgaggaa cacccagatc ataatccagg aggagtccgg catccccaag 1260

gtcgccgacc catggggcgg ctcctacatg atggagtgcc tcaccaacga cgtgtacgac 1320

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gagggcatcc cgaagctgag gattgaggag tgcgccgcca ggcggcaggc ccggatcgac 1440

agcggcagcg aggtgatcgt gggcgtgaac aagtatcagc tggagaaaga ggacgcggtg 1500

gaggtcctgg ccatcgacaa tacctcggtg aggaaccgcc agatcgagaa gctgaaaaag 1560

atcaagtcct ccagggacca ggccctggcc gagcgatgcc tcgccgccct gaccgagtgc 1620

gccgcctccg gcgacgggaa catcctggcc ctggcggtgg acgccagccg ggccaggtgt 1680

accgtgggcg agatcaccga cgccctgaag aaggtgttcg gcgagcataa ggccaacgat 1740

cgcatggtca gcggcgccta caggcaggag ttcggagaga gcaaggagat taccagcgcc 1800

atcaagaggg tgcacaagtt catggaacgg gaggggaggc ggcccaggct gcttgtggcg 1860

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gtcttcgggc ccggcacccg gatcccgaag gccgccgtcc aggtgctgga cgacatcgag 2220

aagtgcctgg agaagaaaca gcagagcgtg 2250

<210> 766
<211> 2506
<212> DNA
<213> Artificial Sequence

<220>
<223> mRNAs encoding human MCM

<400> 766
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tgctgagccc ccactacctg cggcaggtga aggagagcag cggcagccgg ctgatccagc 180

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agctgaaggg caagaacccc gaggacctga tctggcacac ccccgagggc atcagcatca 300

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gcgccgacgc catcctggag ctggcctaca ccctggccga cggcctggag tacagccgga 960

ccggcctgca ggccggcctg accatcgacg agttcgcccc ccggctgagc ttcttctggg 1020

gcatcggcat gaacttctac atggagatcg ccaagatgcg ggccggccgg cggctgtggg 1080

cccacctgat cgagaagatg ttccagccca agaacagcaa gagcctgctg ctgcgggccc 1140

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ccgccatcga ggccatggcc gccgtgttcg gcggcaccca gagcctgcac accaacagct 1260

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tcatcatcca ggaggagagc ggcatcccca aggtggccga cccctggggc ggcagctaca 1380

tgatggagtg cctgaccaac gacgtgtacg acgccgccct gaagctgatc aacgagatcg 1440

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agtgcgccgc ccggcggcag gcccggatcg acagcggcag cgaggtgatc gtgggcgtga 1560

acaagtacca gctggagaag gaggacgccg tggaggtgct ggccatcgac aacaccagcg 1620

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<223> mRNAs encoding human MCM

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tgctgagccc ccactacctg cggcaggtga aggagagcag cggcagccgg ctgatccagc 180

agcggctgct gcaccagcag cagcccctgc accccgagtg ggccgccctg gccaagaagc 240

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ccggcctgca ggccggcctg accatcgacg agttcgcccc ccggctgagc ttcttctggg 1020

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cccacctgat cgagaagatg ttccagccca agaacagcaa gagcctgctg ctgcgggccc 1140

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tcatcatcca ggaggagagc ggcatcccca aggtggccga cccctggggc ggcagctaca 1380

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ttgaataaag tctgagtggg cggc 2484

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<212> DNA
<213> Artificial Sequence

<220>
<223> mRNAs encoding human MCM

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cccgagtggg ccgccctcgc caagaagcag ctcaagggca agaaccccga ggacctcatc 180

tggcacaccc ccgagggcat ctccatcaag cccctctact ccaagcgcga caccatggac 240

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gccacccacc gcggctacga ctccgacaac ccccgcgtcc gcggcgacgt cggcatggcc 480

ggcgtcgcca tcgacaccgt cgaggacacc aagatcctct tcgacggcat ccccctcgag 540

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gtcaccggcg aggagcaggg cgtccccaag gagaagctca ccggcaccat ccagaacgac 660

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gtcttcggcc ccggcacccg catccccaag gccgccgtcc aggtcctcga cgacatcgag 2220

aagtgcctcg agaagaagca gcagtccgtc 2250

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<212> DNA
<213> Artificial Sequence

<220>
<223> mRNAs encoding human MCM

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tgctgagccc tcactacctg cggcaggtga aggagagcag cggcagccgg ctgatccagc 180

agcggctgct gcaccagcag cagcccctgc accccgagtg ggccgccctg gccaagaagc 240

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<211> 2483
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<213> Artificial Sequence

<220>
<223> mRNAs encoding human MCM

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tgctgagccc ccactacctg cggcaggtga aggagagcag cggcagccgg ctgatccagc 180

agcgcctcct ccaccagcag cagcccctcc accccgagtg ggccgccctc gccaagaagc 240

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tgaataaagt ctgagtgggc ggc 2483

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<212> DNA
<213> Artificial Sequence

<220>
<223> mRNAs encoding human MCM

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tgctaagccc ccactacctg cggcaagtga aggaaagcag cggttcacgg ctgatccagc 180

agcgcctcct ccaccaacag cagcccctcc accccgagtg ggccgccctc gccaagaagc 240

aacttaaagg caagaacccc gaggacctca tttggcacac gcccgagggc atctccatca 300

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<210> 772
<211> 2250
<212> DNA
<213> Artificial Sequence

<220>
<223> Codon optimized sequence that encodes an MCM polypeptide with the I671V mutation

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<400> 773
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<210> 774
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<213> Artificial Sequence

<220>
<223> 3 prime UTR

<400> 774
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