

MODULATION OF GENE TRANSCRIPTION USING ANTISENSE OLIGONUCLEOTIDES TARGETING REGULATORY RNAS

CROSS REFERENCE TO RELATED APPLICATIONS

[0001] This application claims the benefit of U.S. Provisional Application No. 63/292,920, filed December 22, 2021, and U.S. Provisional Application No. 63/308,373, filed February 9, 2022, both of which are hereby incorporated in their entirety by reference.

SEQUENCE LISTING

[0001] The instant application contains a Sequence Listing which has been submitted via EFS-Web and is hereby incorporated by reference in its entirety. Said ASCII copy, created on December 21, 2022, is named CTC-028WO_140628340009.xml, and is 925,586 bytes in size.

FIELD OF THE INVENTION

[0002] The disclosure relates to methods of upregulating or downregulating gene transcription using antisense oligonucleotides (ASOs) targeting regulatory RNAs (*e.g.* CPS1 regulatory RNAs), such as promoter-associated RNAs and enhancer RNAs.

BACKGROUND

[0003] Transcription factors bind specific sequences in promoter and enhancer DNA elements to regulate gene transcription. It was recently reported that active promoters and enhancer elements are themselves transcribed, generating noncoding regulatory RNAs (regRNAs) such as promoter-associated RNAs (paRNAs) and enhancer RNAs (eRNAs) (*see* Sartorelli and Lauberth, *Nat. Struct. Mol. Biol.* (2020) 27, 521–28). Unlike coding RNAs, regRNAs are transcribed bi-directionally. Various models have been proposed for the functions of regRNAs, including nucleosome remodeling (*see* Mousavi *et al.*, *Mol. Cell* (2013) 51(5):606–17), modulation of enhancer-promoter looping (*see* Lai *et al.*, *Nature* (2013) 494(7438):497–501), and direct interaction with transcription regulators (*see* Sigova *et al.*, *Science* (2015) 350, 978–81).

[0004] Gene expression has been generally known as an undruggable biological process. Despite on-going efforts into understanding the biology of gene transcription and regRNAs, clinically suitable methods of modulating gene expression are limited. There remains a need for new and useful methods for treating diseases associated with aberrant gene expression.

SUMMARY

[0005] In one aspect, provided herein are antisense oligonucleotides (ASO) complementary to at least 8 contiguous nucleotides of a regulatory RNA (regRNA) of Carbamoyl-Phosphate Synthetase 1 (CPS1), wherein the regRNA has a nucleotide sequence selected from the group consisting of SEQ ID NO: 49, 50, 69-79 and 89-90.

[0006] In some embodiments, the ASO is complementary to a sequence in the regRNA that is no more than 200 nucleotides from the 3' end of the regRNA.

[0007] In some embodiments, the ASO is complementary to a sequence in the regRNA that is no more than 200 nucleotides from the 5' end of the regRNA.

[0008] In some embodiments, the regulatory RNA has a nucleotide sequence of SEQ ID NO: 49, and the ASO comprises a nucleotide sequence of SEQ ID NO: 1.

[0009] In some embodiments, the regulatory RNA has a nucleotide sequence of SEQ ID NO: 49, and the ASO comprises a nucleotide sequence of SEQ ID NO: 2.

[0010] In some embodiments, the regulatory RNA has a nucleotide sequence of SEQ ID NO: 49, and the ASO comprises a nucleotide sequence selected from the group consisting of SEQ ID NOs: 1-3.

[0011] In some embodiments, the regulatory RNA has a nucleotide sequence of SEQ ID NO: 50, and the ASO comprises a nucleotide sequence selected from the group consisting of SEQ ID NOs: 4-15.

[0012] In some embodiments, the regulatory RNA has a nucleotide sequence of SEQ ID NO: 89, and the ASO comprises a nucleotide sequence selected from the group consisting of SEQ ID NOs: 487-574.

[0013] In some embodiments, the regulatory RNA has a nucleotide sequence of SEQ ID NO: 90, and the ASO comprises a nucleotide sequence selected from the group consisting of SEQ ID NOs: 575-662.

[0014] In some embodiments, the ASO is no more than 50, 40, 30, or 25 nucleotides in length.

[0015] In some embodiments, the ASO comprises a polynucleotide comprising one or more chemical modifications. In some embodiments, the ASO comprises an RNA polynucleotide comprising one or more chemical modifications. In some embodiments, the ASO comprises an RNA and DNA polynucleotide comprising one or more chemical modifications.

[0016] In some embodiments, at least 3, 4, or 5 nucleotides at the 5' end and at least 3, 4, or 5 nucleotides at the 3' end of the ASO comprise ribonucleotides with one or more chemical modifications.

[0017] In some embodiments, the one or more chemical modifications comprise a nucleotide sugar modification comprising one or more of 2'-O—C1-4alkyl such as 2'-O-methyl (2'-OMe), 2'-deoxy (2'-H), 2'-O—C1-3alkyl-O—C1-3alkyl such as 2'-methoxyethyl ("2'-MOE"), 2'-fluoro ("2'-F"), 2'-amino ("2'-NH₂"), 2'-arabinosyl ("2'-arabino") nucleotide, 2'-F-arabinosyl ("2'-F-arabino") nucleotide, 2'-locked nucleic acid ("LNA") nucleotide, 2'-amido bridge nucleic acid (AmNA), 2'-unlocked nucleic acid ("ULNA") nucleotide, a sugar in L form ("L-sugar"), 4'-thioribosyl nucleotide, constrained ethyl (cET), 2'-fluoro-arabino (FANA), or thiomorpholino.

[0018] In some embodiments, the one or more chemical modifications comprise an internucleotide linkage modification comprising one or more of phosphorothioate ("PS" or (P(S))), phosphoramidate (P(NR₁R₂)) such as dimethylaminophosphoramidate (P(N(CH₃)₂)), phosphonocarboxylate (P(CH₂)_nCOOR) such as phosphonoacetate "PACE" (P(CH₂COO-)), thiophosphonocarboxylate ((S)P(CH₂)_nCOOR) such as thiophosphonoacetate "thioPACE" ((S)P(CH₂COO-)), alkylphosphonate (P(C1-3alkyl)) such as methylphosphonate —P(CH₃), boranophosphonate (P(BH₃)), or phosphorodithioate (P(S)₂).

[0019] In some embodiments, the one or more chemical modifications comprise a nucleobase modification comprising one or more of 2-thiouracil ("2-thioU"), 2-thiocytosine ("2-thioC"), 4-thiouracil ("4-thioU"), 6-thioguanine ("6-thioG"), 2-aminoadenine ("2-aminoA"), 2-aminopurine, pseudouracil, hypoxanthine, 7-deazaguanine, 7-deaza-8-azaguanine, 7-deazaadenine, 7-deaza-8-azaadenine, 5-methylcytosine ("5-methylC"), 5-methyluracil ("5-methylU"), 5-hydroxymethylcytosine, 5-hydroxymethyluracil, 5,6-dehydrouracil, 5-propynylcytosine, 5-propynyluracil, 5-ethynylcytosine, 5-ethynyluracil, 5-allyluracil ("5-allylU"), 5-allylcytosine ("5-allylC"), 5-aminoallyluracil ("5-aminoallylU"), 5-aminoallylcytosine ("5-aminoallylC"), an abasic nucleotide, Z base, P base, Unstructured Nucleic Acid ("UNA"), isoguanine ("isoG"), isocytosine ("isoC") a glycerol nucleic acid (GNA), glycerol nucleic acid (GNA), or thiophosphoramidate morpholinos (TMOs).

[0020] In some embodiments, the one or more chemical modifications comprise 2'-O-methoxyethyl, 5-methyl cytidine, locked nucleic acid (LNA), and phosphorothioate internucleotide bond.

[0021] In some embodiments, the ASO comprises 8 or more contiguous nucleotides of unmodified DNA flanked by at least 3 nucleotides of modified ribonucleotides at each of the 5' end and the 3' end.

[0022] In some embodiments, the ASO comprises the nucleotide sequence and/or chemical modification of any one of SEQ ID NO: 16, 22-27, 31-39, 403-412, 414-415, 417-432, 435-480, or 482-486.

[0023] In some embodiments, the ASO comprises the nucleotide sequence and/or chemical modification of SEQ ID NO: 409.

[0024] In some embodiments, the ASO further comprises at least one phosphorothioate internucleotide bond.

[0025] In some embodiments, the ASO comprises the nucleotide sequence of SEQ ID NOs: 403-406, 409-415, 417-424, 470, 473, 477, 480, or 486.

[0026] In some embodiments, the chemical modification is cET.

[0027] In some embodiments, the ASO comprises the nucleotide sequence of SEQ ID NOs: 425-432 or 435-442.

[0028] In some embodiments, the chemical modification is LNA.

[0029] In some embodiments, the ASO comprises the nucleotide sequence of SEQ ID NOs: 443-458.

[0030] In some embodiments, the chemical modification is LNA and 2'-O-methoxyethyl.

[0031] In some embodiments, the ASO comprises the nucleotide sequence of SEQ ID NOs: 400, 408, 460, 462, 464-466, 468, 469, 471, 472, 475, 476, or 479.

[0032] In some embodiments, the ASO does not comprise 8 or more contiguous nucleotides of unmodified DNA.

[0033] In some embodiments, the ASO does not comprise an unmodified ribonucleotide.

[0034] In some embodiments, the ASO does not comprise a deoxyribonucleotide.

[0035] In some embodiments, the length of the ASO is $2 \times n + 4$ nucleotides (n is an integer of 8 or greater), wherein the nucleotides at positions $2 \times m$ are ribonucleotides modified by LNA (m is an integer from 1 to n) and the remaining nucleotides are ribonucleotides modified by 2'-O-methoxyethyl.

[0036] In some embodiments, the ASO comprises the nucleotide sequence of SEQ ID NOs: 393 or 394.

[0037] In some embodiments, the length of the ASO is $3 \times n + 2$ nucleotides (n is an integer of 4 or greater), wherein the nucleotides at positions $3 \times m$ are ribonucleotides modified by LNA (m is an integer from 1 to n) and the remaining nucleotides are ribonucleotides modified by 2'-O-methoxyethyl.

[0038] In some embodiments, the ASO comprises the nucleotide sequence of SEQ ID NOs: 392 or 395.

[0039] In some embodiments, the length of the ASO is $3 \times n + 2$ nucleotides (n is an integer of 6 or greater), wherein the nucleotides at positions $3 \times m$ are ribonucleotides modified by LNA (m is an integer from 1 to n) and the five nucleotides at the 3' and 5' positions are ribonucleotides modified by 2'-O-methoxyethyl.

[0040] In some embodiments, the ASO comprises the nucleotide sequence of SEQ ID NO: 19 or 20.

[0041] In some embodiments, the length of the ASO is $4 \times n$ nucleotides (n is an integer of 3 or greater), wherein the nucleotides at positions $4 \times m$ are ribonucleotides modified by LNA (m is an integer from 1 to n) and the five nucleotides at the 3' and 5' positions are ribonucleotides modified by 2'-O-methoxyethyl.

[0042] In some embodiments, the ASO comprises the nucleotide sequence of SEQ ID NO: 21.

[0043] In some embodiments, the length of the ASO is $4 \times n + 4$ nucleotides (n is an integer of 3 or greater), wherein the nucleotides at positions $4 \times m$ are ribonucleotides modified by LNA (m is an integer from 1 to n) and the remaining nucleotides are ribonucleotides modified by 2'-O-methoxyethyl.

[0044] In some embodiments, the ASO comprises the nucleotide sequence of SEQ ID NOs: 396 or 397

[0045] In some embodiments, each ribonucleotide of the ASO is modified by 2'-O-methoxyethyl.

[0046] In some embodiments, the ASO comprises the nucleotide sequence of any one of SEQ ID NOs: 17, 28-30, and 40-48.

[0047] In some embodiments, each nucleotide of the ASO is a ribonucleotide modified by 2'-O-methoxyethyl.

- [0048] In some embodiments, the ASO comprises the nucleotide sequence of any one of SEQ ID NOs: 17, 28-30, and 40-48.
- [0049] In some embodiments, each cytidine in the ASO is modified by 5-methyl.
- [0050] In some embodiments, the length of the ASO is $5 \times n + 5$ nucleotides (n is an integer of 3 or greater), wherein the nucleotides at positions $5 \times m$ are ribonucleotides modified by LNA (m is an integer from 1 to n) and the nucleotides at the remaining positions are ribonucleotides modified by 2'-O-methoxyethyl.
- [0051] In some embodiments, the ASO comprises the nucleotide sequence of SEQ ID NOs: 398 or 399.
- [0052] In some embodiments, the ASO further comprises a GalNAc moiety, optionally a GalNAc3 moiety.
- [0053] In some embodiments, the ASO further comprises a biotin or cholesterol moiety.
- [0054] In some embodiments, each cytidine in the ASO is modified by 5-methyl.
- [0055] In some embodiments, the regRNA is an enhancer RNA (eRNA).
- [0056] In another aspect, provided herein are pharmaceutical compositions comprising the ASO disclosed herein and a pharmaceutically acceptable carrier or excipient carrier.
- [0057] In another aspect, provided herein are methods of increasing transcription of CPS1 in a human cell, the method comprising contacting the cell with the ASO disclosed herein or the pharmaceutical composition disclosed herein.
- [0058] In some embodiments, the cell is a hepatocyte.
- [0059] In some embodiments, the ASO increases the amount of the regulatory RNA in the cell as compared to a cell that has not been contacted with the ASO or the pharmaceutical composition.
- [0060] In some embodiments, the ASO increases the stability of the regulatory RNA in the cell as compared to a cell that has not been contacted with the ASO or the pharmaceutical composition.
- [0061] In another aspect, provided herein are methods of treating a urea cycle disorder, the method comprising administering to a subject in need thereof an effective amount of the ASO disclosed herein or the pharmaceutical composition disclosed herein.
- [0062] In some embodiments, the urea cycle disorder is CPS1-deficiency.
- [0063] In some embodiments, the urea cycle disorder is hyperammonemia.

[0064] In some embodiments, the ASO increases the amount of the regulatory RNA in a cell of the subject (e.g., as compared to a cell (e.g., a similar cell from the subject) that has not been contacted with the ASO or the pharmaceutical composition).

[0065] In some embodiments, the ASO increases the stability of the regulatory RNA in a cell of the subject (e.g., as compared to a cell (e.g., a similar cell from the subject) that has not been contacted with the ASO or the pharmaceutical composition).

[0066] In some embodiments, the cell is a hepatocyte.

BRIEF DESCRIPTION OF THE DRAWINGS

[0067] **FIG. 1** shows an illustrative schematic of eRNA, paRNA, mRNA, and natural antisense transcript (NAT) of a gene on the chromosome. The eRNA, paRNA, and NAT are all non-coding RNAs. The eRNA is transcribed bidirectionally from an enhancer of the gene. The paRNA is transcribed from the promoter of the gene, same as the mRNA, but in the antisense direction. The NAT is transcribed from a downstream promoter of its own in the antisense direction, such that the transcript overlaps at least partially with the mRNA. Generally, eRNAs and paRNAs upregulate gene expression whereas NATs downregulate gene expression.

[0068] **FIG. 2** shows analysis of mouse and human CPS1 ATAC-seq and H3K27Ac ChIP-SEQ for identification of regRNAs.

[0069] **FIG. 3** shows relative CPS1 mRNA expression in hepatocytes treated with an ASO and non-targeting control (NTC).

[0070] **FIG. 4A** shows a schematic of various human CPS1 ASOs with chemical modifications. Light gray indicates a 2'-O-(2-methoxyethyl) (2'-MOE) modification. Dark gray indicates a locked nucleic acid (LNA) modification. *C indicates a 5-methyl on the cytidine.

FIG. 4B shows relative CPS1 mRNA expression in hepatocytes treated with the ASOs.

[0071] **FIG. 5A** shows a schematic of various human CPS1 ASOs with chemical modifications. Light gray indicates a 2'-O-(2-methoxyethyl) (2'-MOE) modification. Dark gray indicates a locked nucleic acid (LNA) modification. Line brackets indicate a phosphodiester (PO) linkage. *C indicates a 5-methyl on the cytidine. Unique sequence identifiers are assigned to nucleotide sequences having the specific chemical modifications shown in this figure. **FIG. 5B** shows a schematic of various mouse CPS1 ASOs with chemical modifications.

[0072] FIG. 6A shows CPS1 mRNA levels in wildtype and OTC-deficient hepatocytes treated with CPS1 ASOs. Heatmaps of CPS1 and OTC mRNA levels are shown in FIG. 6B and FIG. 6C.

[0073] FIG. 7A shows OTC mRNA levels in wildtype and OTC-deficient hepatocytes treated with CPS1 ASOs. Heatmaps of CPS1 and OTC mRNA levels are shown in FIG. 7B and FIG. 7C.

[0074] FIG. 8 is a schematic depiction of the *in vivo* ammonia challenge for mice treated with CPS1 ASOs.

[0075] FIG. 9A shows relative CPS1 mRNA expression in the mouse liver. FIG. 9B shows plasma ammonia levels of treated mice. FIG. 9C shows relative mRNA expression of other urea cycle genes in the treated mice. FIG. 9D shows mRNA expression of genes neighboring the CPS1 locus following ASO treatment.

[0076] FIG. 10 shows ammonia levels in OTC deficient mice treated with a CPS1 ASO.

[0077] FIG. 11A shows a dose dependent effect on plasma ammonia *in vivo* in male OTC-D mice (*Otc^{spf/ash}*) after the ASO treatment. FIG. 11B, there was a dose dependent effect on urea *in vivo* in male OTC-D mice (*Otc^{spf/ash}*) after the ASO treatment. FIG. 11C shows that the reduction in ammonia correlated with the total ASO administered.

[0078] FIG. 12A shows that CPS1 ASO treatment increased mouse OTC and CPS1 mRNA expression in the OTC deficient mice (1.26 FC of CPS1 and 1.43 FC of OTC). FIG. 12B shows that ASO treatment increased additional urea cycle genes, such as Nags, Ass1, Asl, and Arg1. In both figures WT C57 mice mRNA is shown on the left bar, *Otc^{spf-ash/J}* treated with PBS is shown in middle bar, and *Otc^{spf-ash/J}* treated with ASO is shown on the right.

[0079] FIG. 13 shows that mouse *Otc* deficient livers showed hyperammonia 30 min after ammonia treatment. Treatment with mouse CPS1 ASO decreased ammonia to WT levels.

[0080] FIG. 14 provides shows a schematic of various human CPS1 ASOs with chemical modifications. Unique sequence identifiers are assigned to nucleotide sequences having the specific chemical modifications shown in this figure.

[0081] FIG. 15A shows that hCPS1-ASO-1x decreased *in vivo* plasma ammonia in the OTC^{def} mice with humanized liver. FIG. 15B shows that hCPS1-ASO-1x increased *in vivo* urea in the OTC^{def} mice with humanized liver. FIG. 15C shows that hCPS1-ASO-1g also increased OTC protein levels after treatment with 5 mg/kg and 20 mg/kg ASO.

[0082] FIG. 16 shows that the indicated ASOs increased CPS1 mRNA and ureagenesis in both healthy and OTC^{def} primary human hepatocytes

[0083] FIG. 17 shows that hCPS1-ASO-1x decreased ammonia production in NHPs by a statistically significant amount as compared to PBS only treatment by Day 27. FIG. 17 also provides the ammonia AUC both over time and per dose in the NHP experiment.

[0084] FIG. 18 shows that hCPS1-ASO-1x decreased ammonia in NHPs after a single dose of 5 mg/kg for up to 5 weeks

[0085] FIG. 19 provides the NHP study ammonia AUC quantification on Days 22, 29 and 36.

[0086] FIG. 20 shows that combination of hCPS1-ASO-1x with ¹³C-sodium acetate treatment enhanced ureagenesis in NHPs at day 43 as compared to hCPS1-ASO-1x alone.

DETAILED DESCRIPTION

[0087] The present disclosure provides antisense oligonucleotides (ASOs) targeting regulatory RNAs, such as promoter-associated RNAs and enhancer RNAs, and methods using these ASOs to regulate gene expression. These methods are useful for modulating the levels of gene products, for example, modulating expression levels of disease-causing genes such as Carbamoyl-Phosphate Synthetase 1 (CPS1), thereby to treat diseases associated with aberrant gene expression such as a urea cycle disorder. Urea cycle disorders are reviewed in Haberle et al., 2012, Orphanet J. Rare Dis. 7:32, hereby incorporated by reference in its entirety. Urea cycle disorders result in the accumulation of ammonia and other precursor metabolites, causing development of hyperammonia and related symptoms, such as cerebral edema and the related signs of lethargy, anorexia, hyper- or hypoventilation, hypothermia, seizures, neurologic posturing, and coma. Milder or partial urea cycle enzyme deficiencies cause ammonia accumulation and elevations of plasma ammonia concentration. CPS1 deficiency is the most severe of the urea cycle disorders. Individuals with complete CPS1 deficiency rapidly develop hyperammonemia and are at risk for additional hyperammonemia events.

I. DEFINITIONS

[0088] To facilitate an understanding of the present application, a number of terms and phrases are defined below.

[0089] The terms “a” and “an” as used herein mean “one or more” and include the plural unless the context is inappropriate.

[0090] As used herein, the term “Carbamoyl-Phosphate Synthetase 1” or “CPS1” refers to the protein of UniProt Accession No. P31327 as set forth in the applicable database as of the priority date of the instant application and related isoforms and orthologs, the gene encoding the protein (e.g., NCBI Entrez Gene: 1373), or the mRNA encoding the protein (e.g., Accession Nos. NM_001122633.3, NM_001369256.1, NM_001369257.1, and NM_001875.5).

[0091] As used herein, the terms “regulatory RNA” and “regRNA” are used interchangeably to refer to a noncoding RNA transcribed from a regulatory element of a gene (e.g., a protein-coding gene), wherein the gene is not the noncoding RNA itself. Exemplary regulatory elements include but are not limited to promoters, enhancers, and super-enhancers. A noncoding RNA transcribed from a promoter, in the antisense direction, is also called “promoter RNA” or “paRNA.” A noncoding RNA transcribed from an enhancer or super-enhancer, in either the sense direction or the anti-sense direction, is also called “enhancer RNA” or “eRNA.” It is understood that a natural antisense transcript (NAT) complementary with at least a portion of the transcript of the gene is not a regulatory RNA as used herein.

[0092] As used herein, the term “nascent RNA” refers to an RNA that is still being transcribed or has just been transcribed by RNA polymerase and remains tethered to the DNA from which it is transcribed. An RNA that has dissociated from the DNA from which it is transcribed is also called an “untethered RNA.”

[0093] As used herein, the term “antisense oligonucleotide” or “ASO” refers to a single-stranded oligonucleotide having a nucleotide sequence that hybridizes with a target nucleic acid under suitable conditions or a conjugate comprising such single-stranded oligonucleotide.

[0094] As used herein, the stability of a regRNA is reversely correlated with the degradation rate of the regRNA. Where an ASO increases the stability of a regRNA, it reduces the degradation rate of the regRNA. Where an ASO decreases the stability of a regRNA, it increases the degradation rate of the regRNA. The degradation rate of a regRNA can be measured by blocking synthesis of new regRNA and assessing the half-life of the existing regRNA.

[0095] As used herein, the terms “subject” and “patient” refer to an organism to be treated by the methods and compositions described herein. Such organisms preferably include, but are not

limited to, mammals (*e.g.*, rodents, primates, simians, equines, bovines, porcines, canines, felines, and the like), and more preferably include humans.

[0096] As used herein, the term “effective amount” refers to the amount of a compound (*e.g.*, a compound of the present application) sufficient to effect beneficial or desired results. An effective amount can be administered in one or more administrations, applications or dosages and is not intended to be limited to a particular formulation or administration route. As used herein, the term “treating” includes any effect, *e.g.*, lessening, reducing, modulating, ameliorating or eliminating, that results in the improvement of the condition, disease, disorder, and the like, or ameliorating a symptom thereof.

[0097] As used herein, the term “pharmaceutical composition” refers to the combination of an active agent with a carrier, inert or active, making the composition especially suitable for diagnostic or therapeutic use *in vivo* or *ex vivo*.

[0098] As used herein, the term “pharmaceutically acceptable carrier” refers to any of the standard pharmaceutical carriers, such as a phosphate buffered saline solution, water, emulsions (*e.g.*, such as an oil/water or water/oil emulsions), and various types of wetting agents. The compositions also can include stabilizers and preservatives. For examples of carriers, stabilizers and adjuvants, *see e.g.*, Martin, *Remington's Pharmaceutical Sciences*, 15th Ed., Mack Publ. Co., Easton, PA (1975).

[0099] Throughout the description, where compositions are described as having, including, or comprising specific components, or where processes and methods are described as having, including, or comprising specific steps, it is contemplated that, additionally, there are compositions described in the present application that consist essentially of, or consist of, the recited components, and that there are processes and methods according to the present application that consist essentially of, or consist of, the recited processing steps.

[0100] As a general matter, compositions specifying a percentage are by weight unless otherwise specified. Further, if a variable is not accompanied by a definition, then the previous definition of the variable controls.

II. ANTISENSE OLIGONUCLEOTIDES

[0101] The antisense oligonucleotides (ASOs) disclosed herein hybridize with a regRNA transcribed from a regulatory element of a target gene. It is understood that both eRNAs and

paRNAs are regRNAs facilitating or upregulating gene expression (**FIG. 1**). In certain embodiments, the target regRNA is an eRNA. In certain embodiments, the target regRNA is a paRNA. eRNAs can be identified using methods known in the art, such as Assay for Transposase-Accessible Chromatin using sequencing (ATAC-seq), global run-on sequencing, precision run-on sequencing, cap analysis gene expression, and histone modification analysis (see, *e.g.*, Sartorelli & Lauberth, *Nat. Struct. Mol. Biol.* (2020) 27:521–28; PCT Application Publication No. WO2013/177248). paRNAs are RNAs transcribed from promoters of target genes in the antisense direction (transcripts in the sense direction are mRNAs of the target genes). They can be identified by similar methods, taking into account their specific location and orientation. In the human CPS1 gene, multiple, distinct eRNAs have been identified to transcribe from the same enhancer region. The nucleotide sequences of exemplary regRNAs are provided in **Table 1** below. Any of these regRNAs are contemplated as a target regRNA of an ASO disclosed herein.

Table 1. Exemplary regRNAs

regRNA	Nucleotide Sequence
Human CPS1 RR44_v1 SEQ ID NO: 49	GCCTGATGTGTGTGCCTGCATTGCCTGTCACTCTGCTCAGCTGCGTGCAGACAG CTTATATGAAGGAGGACTGTGTACATGTGGTCAGAGAAGAAAAAATGCTTATTTT TAAAAATGTTTTGAAAAATAATCTGTCCTAAAAGTGTAACATTTCCACTAAATTTTT TCATGTCTGACTTTAACATTCCTACCAACCAACTCTTATAGCCTCAACTCCTTTGA TCTATCCTAATGTAAACTCCCTCACTAATGTGTAATATATTTTTTCCAGTTTGGTTA TAGATTTTCAGTCTAGCCTGAACACTCAAGTATGAACTAGCCACTATTTTTATTAT GGCTGTTCCAACCTCCATTGTGGAATTATAATTGATGGATTTTCCAAGTCTCTAATT CAGAATATTTAATCAAATTTTCCAAAATTTCTGCCTTCTCCTCCTCATTCTGATGA CTAAAGACATGGACCATAAAATATATATACATATATACATACATATGTATATGTAT GTATATACACATATATATATGTATGTATATATACATACATATATATATGTATATATA CACACACATATACATATGTATGTATATATACACACACACATATATATATGTATGTA TATATATACACACACATATATATATGTATGTATATATATACACACACATATATATAT GTATGTATATATATACACACACACACACCGTAGTTTGCAAGTCTGCATCTGGGACCCT TACTGATAAAAAATGAAAGCCCATTAATACTCTCATGCCACATTTCTCTCTAGACT TTAGAGTAGGAGAATTCTATCCTAGAATTGTTGATTGTTGACATTTCTATGGAAAA ACATGTTTAATTCATCATGCTTTGTAGTCAACTGCTATAAATGGTGATGAAGTCTTT TCCTTGGTCAAGCTCTGGACTCCTCAGTACTTCCACTGTCATTTTGATTAAAAACAT AAGTGATGAAGGGAGGAAATATATTATAGTATTCATTGCATGGGTACCTTAGGGTA ATGGGACTATGACTGATTTAAATTTATTTTGCATCCTAAAAAGTTTCCATTAGTGGG TGCAGCACACCAGCATGGCAGATGTATACATATGTAACCTAACCTGCACAATGTGCA CATGTACCCTAAACTTAAAGTATAATAATAAAGAAAAAAGCTTAAAAAGAA AAGTTTCCATAATGAGGATTGAGTTTATATCGTTTTCTTAATTAAGGAAAGACAAC CCTCACTACACACACACACACACACACACACACATAAAAAAGACAAGAGGTG AGATCAAGGCGTAACTAGTATTGGACTAAGCCAGTAAGTACTGCTTCTCAGTCCT CAGTTCTCTAGGTTGGGAGTTTTCTTTTGTATTTTCAATTCCTCCTCCAATTCATTT TCAATGATCTTCAACACAAATTTGCGCTTATTTCTTGTTCAAAATACTTCCATGAC TATTATGAATACTATTTATGGATGAAGGCTGAACATTTAAGGCATACTAAGTCTC CCATGATATGGTACCTTTTCATTTTCCATTCTATACCCTGCATCTAGGCTTTTAAA

	AAATATACCACATGACTTCATGCCTCTAGGCTATTGCTCATGCCACGGCATCCCTTC TGGGTTTTTTCCCCTCTTTATCTACTTGGTGAATTTGCATCCTTCAGTATAACACAGC TCAACATAATTCTATGCTTAACTTTACTGAAAATGCACAAGGAACCTTGATCTTTCT TTCTTATTTTCCCCTTTTATTTATTTTCCCATTGCATTTGGGCAACCTTCATGGCAC CAGTTATTTTATTAATTTATTTGTATAAACTAGTATGAGCCTATTTTGTTTAGCTTTCT ATCACCAGGAGCCATGAAGCACTTTGAAATCAAATACTGTTTGTACTTGAATATAT TAAGTAAGCGTGAGGACTTAAATTAACTTTGTTCCCTTTAAAAAAATCCTTACCC CAACTCTAGCACTGA
Human CPS1 RR44_v2 SEQ ID NO: 50	ATGAAAATGGAATATTTTGTAAATCATTTAAAGTAATGTTTTAAAAAGAACTTTGTAA TAACATCAAAAATACATTTAACATAATATTGCCTCCAAAAAGCATTATGCAAGTCAA TGGCAATTTTCAAAACTATGTTCTGAGCATTGACATAAATGCTAGAAGATAAATCT TTAGTGTTAAACAGAGATTATGTTTGTGTGGTGGGTATTATCTATTATTCTGTATTTT CACATTTCTTTAAATATCAAATGAAAGTGAATACAACCTAGTACTTGACATTTTAA CATTTTCAATACCAGATATGTCAATAAGGAATTCATAAAATAAAGTGCCCTGAGGG ATTTACAGGGCTAAATGCTTCTATTTTTTAAATGTATTAATAGAAAAGAAGACTA AATCTAAAAAATAATTCATTTTATCAGAGAGTGACTCATAAGTTTAGAAAACCT TTGATGACCTGGCTCAGAAAGAATGTACTTCCAAGTACACAGGGTCCCCAGCCTGA TGTGTGTGCCTGCATTTCATGCCTGTCACTCTGCTCAGCTGCGTGACAGACAGCTTA
Human CPS1 RR7_v1 SEQ ID NO:69	TAGATAGAAAGGAGCAGCCAGAGATGTGCCTCAGGCTGAAGCCAGTGCTGCAAAAT GGGACAGCGCTCTCAAGCTACATTATATGCATTTTATTATCCAACAATTTGTTCTGG GAGGACAGTTTGATTGGCCAGGCAAGAAATTCAAAATGAGAGACTTTTAAATATC ACAACCTCAGCTAAAAGAGCTTCTGTTTTCTGACCTGAGAAATTCATTCTATCAG TCTCAATAAAGATGCTTGTAAATATTAGGTGATGCAGACTCTGAACATTTGTCCCTCT GGACTGAGTGCACTCCCGATGATCTGAGTCTTGGGGCTATGCCTCAGGCTTCACAA TTCTAGTGTGAAAGCTACTTGCATATCCACCCCTCCATCCAGCTGGGTTTTGTCT GCTTTTCTTGTGTAATAATGACTGTGAGTCAAAAAGATGGGAGGTCAACTACTTG CCTTTGACCATTAAATAGGTGTTTAACTAAGCTAACTAAGGAATAACATTGTTTTT CCATTTCTGTGATATCGTTTTCCATTTTATCCTAGATTCTTAACTAGGATGTGAAGAA AATAATAGTAGTCAATATTATAAAGTTTAAATAATACAAAGTAGTCGATATTATA AACACAGACATATTTCTAGAATGGAACAATAAGATAGTAGGCTTCTATGTTTTATT TTAAAAAGGTTCCGAAATTACCCACTTACCATTTGTGTGACCTTGAACAAGTTGCTTT AACTCCGAACCTCAGTTTCTTCATATACAAAATGGGAATACACCTACTATGGAGGT TTGCTGATAGAATTTAAACAGAATAAGTTACGCAAAATATCTGGTGTAGTAAAGA ATTCTCTCAGTGACTCATAGCAAGAGTATAAATTTGGTCTAGTCACTTTGTAGCATG ATTTGTCAATTATACAGTGAAATGTAAAATGTGCATACCTTACAGCAATTACATTTT TCAGGATGAAACTCAGAAAAATACTAAAAACATGTGCACAAAAATGATAGATACATA CATAGATATATAGATATTCATTGCAGCATAAATGAACCAGTGGGAATAATATTTAA ATGCATGAATGTTCTTTTCCCCTTTTGAATTTATTTTACTGACCTTCTCCACAACTCA CCTATTTCTTTTGGGTGGTTTGAATTTATACAACAGGAAGGCAAGAGAGAAAAGAA AAGTTAATATTTATCTTCTGGCAAGGCAACGGGATTTGCAGTAAGAACACAGTGCT AACAAGTAGATTTAATCAGGGAGAGGGGAGTTTCGTTAAATTCTTAACTGCTTTAA CTTATCATAACTCAAACCTAGAGGATTAGATTATATGAATTTTTCACATCTGGTGAA GTGGTAGGAAGAAGAAATGGAACACAGACGTCACATCAGCGTCTTTATTTCCACT TCCACTTTCAACCCCTGATCCAGGACCACTCTTAAAGGCAGTAAAGGAGCAATGTA GTAGAAATGACAGCAGCAGGCCAGCAGATACCTATTCTGAGACAGAGCCCATGG CATTTCAGGGCCTGGAAACTGGGGACCCAAAATAACCCAAGTCTGGTTGTGACAAC ACAGAGGTTCTGAGAGTACAGGAAGAATTAAGAAGCCTGGGGACAAGGTAGAAA ACCACTGCAGGTAGATCATAACAGACAAGGGACAAATGACCAGACCCCTAACGC CCCAAAGAGCAGATGTCAACAGCACAGAGAGCAGACCAGCTCAGCTGCTCTGCAG ATATCAAGGAGGACTCAGAGGATACATCAATCTGATTACCTTTCTTCTGCACCA CTAAATCATGTAACTAAACAACCAGATGCCCTCTTGAAGAGGAATAGGGTAAGC AGGTCAAACCTTGGAAAAAGTGGAAACAAATTGACCAAGCAAGGACAGGGTTACCTAA ATGGAGTATTGGACTGCATTACTGGACTCAAGACAAAACCTTACCAGATTAGACTCG TAGATCAGATCAGTTATTTAAAAAATAAATAAATAAAGGTA

Human CPS1 RR8_v1 SEQ ID NO:70	GTCCATCCTGACTCCTGGCAGGGACCAGGGCCATCCAGTTATACTACGGTGTCTTT CACCACCTCAGTGATGGCAGCTGGCTGGAGTCCAAAGCGTTTCAGTACTCCCAAGC TCTGACTACTTTTTCTCTTCTTTCTTCATCTTGGCCCTACACATTTATCCAAAGAAA ATATTTAGGATGTGAAAAGAGGGGTGTAGATAAGAAATGAATCAAAGGAGAAATG TGTGATTATAAAACAATAAAATACGTAACCTGAACCTTACTGTGGCTTAACACACAG CCAATAGTGCCAAAGATCATATAACTTCTGTCTGCTGAAGTTTCTCTTTATTAAT GGCATTGACAGAGAAAACTATAAAAGAATAATTAATTGAAATAGACTGCAAAATCA CTTAGCCAACATAAAATGATGCAATATTTATCTGATGAAGAAACCTAAAGTTAAA TATTGGTTAGATCAATTTTATCAATTTGTCTATATCCTATCAATCCTTCAAAGCCAT ATGAAATCATACTCTTTTAATGAACCTTATGTATGTATATCTTGTGTGTATCATACA ATTAATATACTGTCCACGTACTCTTATTTACACATTAATATCTTCTCGGTTGAAAT CATTAAATAGCTCCACACTGCTTAACTACAGTGCGAAGTTAAAAATATAATATATT CATTTTTCTAAAGCTTTAGGCTTTTGTGTGCTTCATTACAGTTGTGTGATCTAAATTA GTATCTTCACTGTCTCTGTTAATATCGACAAATTAGAAAGAGTAACAACCATGAC CTCTCATAGTCCATAAGTAATAATTAATTTCTCAATTCCTTCTATAAATACTTATTA AAGCCCTTTTACATGCCAAGCATGGTGCTAGATCCGAGAATAAAAAATAAGTCTGGA ACACAGACTTGTCCCTCAAAAGCTCCCTCTTGAGAAGCCTTTCAGTTTATTCTTAG AAGTGGACAAAAATGTGTATTTCTACTCTCAAGATTGAA
Human CPS1 RR9_v1 SEQ ID NO:71	AAATTAACATATTTGAGGATCACAGAGAAGCATGTGGTGCAACATGTCTTGAAGT TACCGACTTCGTGAAGTGTAAGGGGCGAGTAGTTTACACTGGAATGACGTAGAGAA CAGGTCACCTACGCACATTCCTACTCCACCCCTTTTGTAGAAAATTTGTTATACTG AACCTGATTTCTTCCATGGCCTCCTATTTTCAGCGGAATGTGATTCAGGAAGATACA TTCCACCTCCTGGAAATCGGAAATAGGACCCGTGCTTTCACAAACATTAAGTTCC ATCTTCCCTAAACCTTTATTGCAATTCCTCAGGAATGGATCACAGAGCTATTTCTTC CTCCAGGTTTGTAGATTTGTAAGTTGAGTCATAGGGCAGGAGTACCTTTTTTTATTT TATATAGGCTAAAAATTTGTTGGAGAAGATTAGTGATCTGGAGAGGGGAAAAAAA AGAAGAACAAGAAGGAGATGAAGAAGGGGAGGAAGAAGAGAAAGAAAGACAAA AGGAAGCCAACCCTAATCCTTGAATTCTACAACTACTAACAATTAGTCAAAAGTG CCTACTTGGATTTCAATACCTGACATGCCTTTGAGTGTTGAAGAATTAATGTTTTA TTCTGGTATTGTTTTTTGATGTCAATTTATTTTAACTATACTTGCCCTATCAAGAT CATTCTCAGTTGATAGTAAGAAAAATATGTAATGTTGTTGCTAATTTATCTTGCATT AGGTAATTGATTATTTCAAAGAGCATTCTTGAACATCTTGTAACATAAAAAAGCA AAGAATCTGGTATGAGGAAGTTAAAAACTCTGTCAAGATTTCAAAAAATTTGTGTAT AAAAATTAATTGCCATGTTAGAAGTCGAGGTCAAGCAGTAATGATAGAAATTTGT GAAATGATGATTAGACATAAAATGTAAGACAAATGAGAGAAACAAAGGTACACAA TAGAAAAAGTATTATTAGTACTATATTAGTGACTCTGAATGGCATAA
Human CPS1 RR21_v1 SEQ ID NO:72	GTGCAGAAGGAAAGGGTAATCAGATTGATGTATCCTCTGAGTCTCCTTGATATCT GCAGAGCAGCTGAGCTGGTCTGCTCTCTGTGCTGTTGACATCTGCTCTTTGGGGCGT TAGGGGGTCTGGTCATTTGTCCCTTGCTGTTATGATCTACCTGCAGTGGTTTTCTA CCTGTCCCCAGGCTTCTTAATTTCTCTGACTCTCAGAACCTCTGTGTTGTGACA ACCAGACTTGGGTATTTTTGGGTCCCCAGTTCCAGGCCCTGAATGCCATGGGCTCT GTCTCAGGAATAGGTATCTGCTGGCCTGCTGCTGTCATTTCTACTACATTGCTCCTT TACTGCCTTAAAGAGTGGTCTGGATCAGGGGTTGAAAGTGGAAGTGGAATAAAA GGACGCTGATGTGACGCTCTGTGTTTCCATTCTTCTCTACCCTTACCAGATGTG AAAAATTCATATAATCTGAATCCTCTAGTTTGAGTTATGATAAGTTAAAGCAGTTT AAGAATTTAACGAACTCCCTCTCCCTGATTAAATCTACTTGTAGCACTGTGTTCT TACTGCAAAATCCCCTTGCTTGCAGAAAGATAAATATTAACCTTTTTCTTCTCTTTG CCTTCTGTGTAATAATTCCAAACCACCCAAAAAGAAATAGGTGAGTTGTGGAGA AGGTCAGTAAAAATAATTTCAAAGGGGAAAAAGAACATTCATGCATTTAAATATTATT CCCCTGGTTTCATTTATGCTGCAATGAATATCTATATATCTATGTATGTATCTATCA TTTTGTGCACATGTTTTAGTATTTTCTGAGTTTCATCCTGAAAAAATGTAATTGCT GTAAGGTATGCACATTTTACATTTCACTGTATAATGACAAATCATGCTACAAAAGTG ACTAGACCAATTTATACTCTTGCTATGAGTCACTGAGAGAATTCTTTACTAACACCA GATATTTGCGTAACTTATTCTGTTTAAATTCTATCAGCAAACCTCCATAGTAGGTG TATTCCTATTTGTATATGAAGAACTGAGGTTCCGAGTTAAAGCAACTTGTTCAA

	GGTCACACAAATGGTAAGTGGGTAAATTCGGAACCTTTTAAAAATAAAACATAGAA GCCTACTATCTTATTGTTCCATTCTAGAAATATGTCTGTGTTATAATATCGACTAC TTTGTATTATTTTAACTTTATAATATTGACTACTATTATTTCTTCACATCCTAGTT AAGAATCTAGGATAAAAATGGAACGATATCACGAAATGGAAAAACAATGTTATT CCTTAGTTAGCTTAGTTTAAACACCTATTTAATGGTCAAAGGCAAGTAGTTGACCTC CCATCTTTTGGACTCACAGTCATTAGTTACACAAGAAAAAGCAGAACAAAACCCAGC TGGATGGAGGGGTGGATATGCAAGTAGCTTTCACACTAGGAATTGTGAAGCCTGA GGCATAGCCCCAAGACTCAGATCATCGGGAGTGCACCTCAGTCCAGAGGGACAAAT GTTCAGAGTCTGCATCACCTAATATTACAAGCATCTTTATTGAGACTGATAGAAGT GAATTTCTCAGGTCAGAAAAACAGAAGAGCTCTTTAGCTGAGTTGTGATATTTAAA AGTCTCTCATTTTGAATTTCTTGCCTGGCCAATCAAAGTCTCCTCCAGAACAAATT GTTGGATAATGAAATGCATATAATGTAGCTTGAGAGCGCTGTCCCATTGCGAGCAC TGGCTTCAGCCTGAGGCACATCTCTGGCTGCTCCTTTCTATCTATAAGTTAAAGCAA TGGCCTCAGCAAGCAGTACACTCTGTACAGCAGCTGCAACTCGTTATCGGCTTTGT CCAGAATAACAAACAGAACAAACACATTTTGCAAGGGCTTTTACCCCTCTTATGTA GAGAAGGAGGAATTAAGCAATCAGTGAAATGCTGATTGATCAGTTGTGCTGACTA AGAGAAGTCCAAGGCCACATTAGTACTATTAAGCCCTAAAAAACAAAGCAAAAAAG AAAATGTTCTTAGAACTTTATTTAAACCAAGTATTTCTGTGATGTGAAGTACATTTCC CCCAAAGGGAAAAATGGGAAAAATTTGCATTTCACTTAGTACACTTTACTCATCC AGACTGCTTTGTAATGTAATGATGGTTAAGTATTTTACAAAGATAATTCATTTT TTGGCAGATTTTGGTTGATCATGGAGTATCAGGGTTGTGTGAACCAAAAGGTGTGAT GCAGAGCAGCTTAGTAAACCATCCCATTCCTATGCCACCCGTTTGATTTCAGTACC AACTGCTGTGGCCACATCTAGACCACTCTTACCAGAACTGTGCCACCTTCAAAA TTCCAGCATCCTTTTCCCTCCTCCCTTATTTTGTATCTCATATACTCAAGTATTCT TAGTGTAACAATTCTTTGAGCATTCTTCTTATCTAGCTTAAATCTAGGGTCTACC ATTATAATCATTCTTTTCAAGATAACCTTAACCTTCCACACCCCAATTTCTAAGTGGC CTGGCAAAACTCAGACCTTTGGTGCAAAATCCTCCATCTCTATGCCTGAGCCCTTGT GTTTGAGAATGGCTGAAGAAAACCATGTGCATGGACATTCTGATGTCACTATAAAT TCATGGTACGGATCTCAAATGGGAGCCCAAGACTACTGGCTTTCCTGCTGTGGTT GTCTAATGACAGCATGATCTTACTCTTACAGATATTAGTTTAAACTCTCCAACCTT CAATTGAAAAGTCTACATCTTACTTTATTAGAAAAGTAGAAACAATCAAGGGTTATG CTCCCATTTTACACTACCAAGTAAACAAACCTTCAGTAAGAGAAAGATATATTTCC TATATCTCCTCCTACCCTCCTGTAAAAAGGGTGCAACGTCCTCCCTCCTAACAAAA ACCAATCCTTCTTCATGCTCTTTAGATGCCGTGTTGTCTCTTTCTCAAAGTCTTCA TTTTTGGTTATACTCTTTCTCTCATGCAAAATTTTCTCTCTTTTCAAGTAGAGCAG GCTCAGCAGCTACAAACGTGTCTTGGGCACCTTTCATCAAAAAATAAAAAACATA AAAACAACAAACGAAACCTTCTTGGCTCCACATTCTCATCCAGTTTCTATTCTTTC ACTTAGCTGCTTTTCTCTCATGTTTTGTCTATTTTTTAACATCCTAGTCACTCTCTG ATCTACTTCAGTTTGACTTCTACCTCCATCACTTGAGTAAATTCAATACATGGTTTC AAGTATATTCTAGCCCTAGCCTGATCCACAGGGAAGGTTCTGGACCACAAGCAACA TGGCAGAGTTGTTCACTCTTGAGGTAAAGGAGTTTGGCACCTCATGCCCTATAAT GGATTAAGAAACACTCCTTAATCGGGGTTAGTCCCTGGGAAAGGTTTTAGGTGTG AGCAATTAGCAACCATCACCCACAGTGGCTGGGAGAGGGGGGCATAGCCCAATA AAGAGGATCTAAGTAGTGCACCCAAGCAGGTCTACCACAGTTAGCTTCTATGTGG GCTCAGTTGCATGCAGTGCATCTCTATACAGCAATTAATCTATTTTATAATATTAA TAAAAATAATTTCACTTTCCATGTTAAAAATCCTTCAATGACTTCCTATTGCACTATAA ATGGCAAATCAATATGTTAATGCCCCTGCCAACACCTACAGGGTCTGGGGTCTGA TTGCCTTTCAGATCTCTC
Human CPS1 RR22_v1 SEQ ID NO:73	GAAAGAACACCGTAGTATAAAGTGGATGGCCCTGGTCCCTGCCAGGAGTCAGGATG GACTTTCAGTGTTGAAGAGCCATCTTGGCCTGTACTAGCGCTGCCCCACACCATTG TGTTTGCCTAAGAGCTGAGCCAAAGAATTTACATATGTATGAGCCAAGGTCTGAAA ATAGAAGTTAAAAAAATGGTGCTAAATTGACATATTTGCTATTTTATTTTTTGGTC AGTTAATATGATAAACTTTTATTTAAATGTAAACATTATTTTAAAAAGCACTTTGTT TAAAAAAGTATTTTCAATTGAAATTAATTTCTGGCCTCTAAGCAGAGTTAGCTACAA AGACAATTTGTAATAATGCAGAAAAATTCAGAGTTTAACTTGGAGTTGTTTAAAGTT

	TATTTTCATATTTGAGTCTGATATTTTCAGTTCAGTGAATATTTCAATTTATTTAAAA TATTATCAAGACAAATATTTGGGTACCTTCACAATATTTTTCATTTTCTTACCCC ATATATTA AAAAATGAACAAAAATGAAAGAATTATATAGTCTAGTGGATGGCAATTC TCTTGGTACAGTACTCACAGGATGTCAGAAGTGCTTTGATTTGCATGCAAAATAGAA ACTGCATTTCCTAAAAGACCCCTTAATTGAAGATATTAATAATTTTCATTAGGTTTTAA GTCTTTTAACTTATCATATGGATAGAAAAAGTAAAAGATGTGTTTAATAAAATGTC TTTTACTTATTTTATTTTGTCTATTTTAAAGGTTTATTAGTGAATCTGTTTACCTG GAAAATGTGCAATTCTATTTGCAAATTTGGAGCACTACATATTTAAGAGAATCC TTAGTTTCTGTTGGGAGTGGCAATATTTTATACTGGGCCTTCATATTCCTATGTTA CAGCCCTGGTCCCTGAAAGTCCTACAGCTATCTTTGTTTCAAGTGTGTATGTGTTAT AATAAGATAAGTGTTAATTAGTTAATCAAGTACTAATTAACCTTTTAAATTTATAGA AAAAACAGACATTTATGGACAAGTAAATTTTGGGGTCAAAGTCTTTAATAAATTTGA AGAATGCAGTATTTTTTATGACACAAATATTTCAATGTGAAAAGAATTTCTTTCTGA GTTATATATTTTTATGCCATTACAGAGTCACTAATATAGTACTAATAATACTTTTTCT ATTGTGTACCTTTGTTTCTCTCATTGTCTTACATTTTATGTCTAATCATCATTTTAC AAAATTTCTATCATTACTGCTTGACCTCGACTTCTAACATGGCAATTAATTTTATA CACAAATTTTTGAAATCTTGACAGAGTTTTTAACTTCCTCATACCCGAGTTCTTTGCT TTTTAGTTTACAAGATGTTCAAGAATGCTCTTTTGAATAATCAATTAACCTAATGC AAGATAAAATTAGCAACAACACATTACATATTTTCTTACTATCAACTGAGAATGATCTT GATAGGGGCAAGTATAGGTTAAAAATAAATGACATCAAAAAACAATACCAGAATA AAACATTTAATTCTTCAACACTCAAAGGCATGTCAGGTATTGAAATCCAAGTAGGC ACTTTTACTAATTGTTAGTAGTTTGTAGAATTC AAGGATTAGGGTTGGCTTCCTTT TGCTTTCTTCTCTTCTTCTCTCCCTTCTTCATCTCTCTTCTGTTCTTCTTTTTTTCC CTCTCCAGACTCACTAATCTTCTCCAACAATTTTACGCTATATAAAATAAAAAA AGGTA CTCTGCCCTATGACTCAACTTACAAATCTACAAACCTGGAGGAAGAAATA GCTCTGTGATCCATTCCTGGGGAATTGCAATAAAGTTTTAGGGAAGATGGAACCTTA ATGTTTGTGAAAGCACGGGTCTATTTCCGATTTCCAGGAGGGTGGAATGTATCTT CCTGAATCACATTCCGCTG
Human CPS1 R23_v1 SEQ ID NO:74	CATTCCGCTGAAAATAGGAGGCCATGGAAGAAATCAGGTTACGTATAACAAATTTT CTACAAAAGGGGGTGGAGTAGGAATGTGCGTAGGTGACCTGTCTCTACGTCAATTC CAGTGTA AACTACTGCCCTTACACTTACGGAAGTCGGTAACCTCAAGACATGTTG CACCACATGCTTCTCTGTGATCCTCAAATATGTTAATTTAAAGAGGGTCCAGTAGT GTCCTGGCACATGATCTGGATTGCCATAGATAACCATCTACCTCACAGCTAGGGTT GCTCTTTAGAATCTTGCAAAATCATTTGTTTACTCTTGACAAAAGTTAAGAAAACA AGCCCATCAGAGTTGTTTGTCTGTGATGTTAGAGATGTTTGTGCAATGA TAATCGTTGTGCAAGAAGACTGATGATGATTTTTTTTTTACATTTTCTTAAACAGTAT TTGCTATTTGAAATGAATGATGTTGTTCTAATTATTTAGCCATTTTATTTGTAAATTTAT GTTGTAGGCATATTTAGACCAAGTTATAAGAAAATGCTTCAGCCAAAATTAAGTGT TGAGTTTGATTTGTGTAATTGTTAGTTTCTTTACTAGTTGTTCCATCATTTACACAAT TATTTCTATTTGAAATGCAGTAATTGTTGAGAACTTATATTTCTATACTGATGTCTA CTAACAGCTTTAGATCAAATATTTAAATAACTCAAGAATAATGAGATGATCTTGGCT TACTTAGATATTTGGTTTTTATATCTATAGAACAAGGAATTAGAAAAATTTTGA AGATTCATCCAGCTATGTAAAACTATCTAGGGAATACATTTTACTAGGTTTTCATTT TTCTACAAAACATCTTTCAGCAGAAAAGCAATCCTGTTTCTGATATACAATGTCTGA TACATAGAACTACTCAGTACATAATTCCTGAATTGATTATTTCTTTGGAAATCCTA GATTTGATTTCTGAACAATCATAAACATTTAATGGCATGAAATTACCCAGATTCCA TGGTTCTGGAATACATAACTTCAAGCAATAAGATGCAAGATAGAAACATATAAGA CATTCCTTTGCTATTTTAGTGAAGTCCAGCTGAATCGATTAATCAGCTAGAAAACGTG GCTCAGATGTAATTAGTTTTATTATTAGGTGGATTACTGAAAAATTAATAGCTTTA TTTCCGTATTACCTTATCATTTATTTAATATAAAACATAATAAACCAGAGAAGTTGT GGTACTTTCTTCTGTCTCATTTGTTGAGTTTACTGAAAGTTATGTTTACTGATTTT CACGAAATGCAAAATTTTCTGAGCATCAGAAATCCAGCTTTTGTACCTCCCACTC ATGTATTTCTCCCATCAAATGAATCTTAACAGGTCACCTTTCTCTGTTCATTCAT GCTGTTGCCCTGTTTCTCCAGATATAATTGACATGCTCCAAGAGGATGAACATTG CCTAAGACTTGATTTCTGGTCTTGGCTTTGCAACTTACTAGCTGTGTGACCTTGAAC

	AAGCTACTTAATTCTCTGAGACTCATCATTATTGTTTATAAAAATAGGGATAGCATTAGCTTATTTTCAAGAATTGTTTTAAAAATTAGCAAGGAAGGCATACCAATGCCTAGCTCAGGGGATCAACAAGTGGCAAGTACCTCAACTTTCAGGCAAGATCATACTTATCATCAGTGGAGCCAATAGAACAGATTATTTAAATACCCTATTTTCACTTACTGGCATAACAGCAAGTGGTGTACATATTTATATATCTCTCTATATAGATGCAGATAATATACTAATATATTGTGGTTATATCTTCCAATGTTTTAGTTTCTATTGAGGG
Human CPS1 RR43_v1 SEQ ID NO:75	TCATATAAGCTGTCTGCACGCAGCTGAGCAGAGTGACAGGCATGAATGCAGGCACACACATCAGGCTGGGGACCCTGTGTACTTGGAAGTACATTCTTTGTGAGCCAGGTCATCAAAGGTTTTCTAAACTTATGAGTCACTCTCTGATAAAAATGAATTTTTTTTTTTA GATTTAGTCTTCTTTTCTATTAATACATTTTAAAAAATAGAAGCATTAGCCTGTGA AATCCCTCAGGGCATTATTTTATGAATTCCTTATTGACATATCTGGTATTGAAAA TGTTAAAAATGTCAAGTACTAGGTTGTATTCACCTTTCATTTGATATTTAAAGAAATGT GGAAATACAGAATAATAGATAATAACCCACCACACAAACATAATCTCTGTAAACA CTAAAGTATTATCTTCTAGCATTATGTCAATGCTCAGAACATAGTTTTGAAAATTG CCATTGACTTGACATAATGCTTTTTGGAGGCAATATTATGTTAAATGTATTTTGATGT TATTACAAAGTTCTTTTAAAAACATTACTTTAAATGATTACAAAATATCCATTTTCA TTGCTGCTACAATGCATGTCAATATTGCCATATTTGATTACTATTTACAAATTTCTC TCCAAAGAGAGTGTACTCACCTACATAACAGTGCAATATATGGGTGTCCCTTTAAA AATGTCCTCACCAACATTATGTATTATCTTTCATTTTATTTGCTCCGCTGTAGAAAA TATTATTTTGTCTTCATTTCTATTTTAAATCACTGGTGAAAGTTGAATACTTCACAGTA TGTTTTTAATTGATACTATTCTTTTATCAACTACTGTTTACATTTTGTTCATTAA CTCATTTATATTAATCATTACGAAAATGTCTTTAAAGGAAACATAAAGAAACACTG ACAGCCTGTGTCTATACTGATTTAAACAGTCCACTTCTCAAAACAGTCCACTTTCAT TTAAACAGTCCACTGACATAAGCAAGGGAAGACCTGCTACAGATTGAAAAAAAAA ATGAGAACAGGATGTCTTAGAGATAAAGGTCTTAGGTTTTGGAATGAAGAGAAA ATAAGGGTGTTAGTAATTCCTTTGAAGGTACAGAGACTTCCAACCTGCCCTCTTGAA ATGTTCTAAGTAATGAATCAGAAACAACCTCTAAGAAGTTGGTGCATCTATCAAAA AGTCTCTAACATAGCAAGCATGCAAGAGATGCTTCTGGAAAAATGACTGAATGAA TGGATTGCTGTGTGCTTAATTCCTGCCTGATCAGTGATGATTATTTAAGCAGGAACA AATAAAATTACATCAGTTAAGCATGAGAGGAAAATAAGGATGCTTAGGAGTCATGA AAAAAAAAAACCTGGCAATCAATAATTCTATAAAGTCTATTTTGAAGAGATACATT AAAGCAAGGAGTAAGGTATGACTGGAGAGCAAAACAAATTCAGAGTAAAAGGAGG TGCAATAACTCCCTGAAGAAAGTTCTACTGTTTTGTGTTTGACCAGAAATGTGTGA AAATAGAAATATAAAAGGTAGAAGTAATTGGGTTCAAGTTCTATGATTTTATTAGCC TTAGTATCATAACAAGGAACACGGTCACAATTAAGATATGGATGAAGAAGGCAT CTCTGAGGAAAAGTGGTGTGGATTGTACCATGTAAAAGGCACACATTTTCTCCTA TCACAGAACTAGGACAAGCTGGTAGGAGGATTCCTCAAAAGTTTGCCAGGAAGA AGACTTAAAGTTGTTTGAAGAACCTTCCCAATATGTCAAGGATTGAAAATGACAGAC AGATATCATGTTGTTAGATGATGAGGGTTCAAACCTAACAGATATCCTTGGAAATC CAATCAAGTAAAACCTATTCATTAAGATCCAATTGGCATTTTGAGGAATAGAAAGT GAGGATCAAATTATGATGAATATGCTTATCAATCTAACATTTGATAACATAAAGTT TGGAGTGATACAAAAGAAGGTGAAAAATGAAGCTG
Human CPS1 RR21_v2 SEQ ID NO:76	GCCTGATGTGTGTGCCTGCATTATGCCTGTCACTCTGCTCAGCTGCGTGACAGACAG CTTATATGAAGGAGGACTGTGTACATGTGGTCAGAGAAGAAAAAATGCTTATTTT TAAAAATGTTTTGAAAAATAATCTGTCCTAAAAGTGTAACATTTCCTACTAAATTTT TCATGTCTGACTTTAACATTCCCTACCAACCAACTCTTATAGCCTCAACTCCTTTGA TCTATCCTAATGTAACTCCCTCACTAATGTGTAATATATTTTTTTCCAGTTTGGTTA TAGATTTCACTAGCCTGAACACTCAAGTATGAACTAGCCACTATTTTATTTATT GGCTGTTCCAACCTCCATTGTGGAATTATAATTGATGGATTTTCCAAGTCTCTAATT CAGAATATTTAATCAAATTTTCCAAAATTTCTGCCTTCTCCTCCTTCATTCTGATGA CTAAAGACATGGACCATAAAATATATATACATATATACATACATATGTATATGTAT GTATATACACATATATATATGTATGTATATATACATACATATATATATGTATATATA CACACACATATACATATGTATGTATATATACACACACACATATATATATGTATGTA TATATATACACACACATATATATATGTATGTATATATATACACACACATATATATAT GTATGTATATATATACACACACACACCGTAGTTTGCAAGTCTGCATCTGGGACCT

	T T A C T G A T A A A A A T G A A A G C C C A T T A A A A C T C T C A T G C C C A C A T T T C T C T A G A C T T T A G A G T A G G A G A A T T C T A T C C T A G A A T T G T T G A T T G T T G A C A T T T C T A T G G A A A A A C A T G T T T A A T T C A T C A T G C T T T G T A G T C A A C T G C T A T A A A T G G T G A T G A A G T C T T T T C C T T G G T C A A G C T C T G G A C T C C T C A G T A C T T C C A C T G T C A T A T T T G A T T A A A A C A T A A G T G A T G A A G G G A G G A A A T A T A T T A T A G T A T T C A T T G C A T G G G T A C C T T A G G G T A A T G G G A C T A T G A C T G A T T T A A A T T T A T T T T G C A T C C T A A A A A G T T T C C A T T A G T G G G T G C A G C A C A C C A G C A T G G C A C A T G T A T A C A T A T G T A A C T A A C C T G C A C A A T G T G C A C A T G T A C C C T A A A A C T T A A A G T A T A A T A A A A A G A A A A A A A A C T T A A A A A G A A A A G T T T C C A T A A T G A G G A T T G A G T T T A T A T C G T T T T C T T A A T T A A G G A A A G A C A A C C C T C A C T A C A C A C A C A C A C A C A C A C A C A C A C A C A T A A A A A G A C A A G A G G T G A G A T C A A G G C G T A A A C T A G T A T T G G A C T A A G C C A G T A A G T A C T G C T T C T C A G T C C T C A G T T C T C T A G G T T G G G A G T T T T C C T T T T G C T A T T T T C A T T C T C C T C C A A T T C A T T T T C A A T G A T C T T C A A C A C A A A T T T C G C C T T A T T T T C T T G T T C A A A A T A C T T C C A T G A C T A T T A T G A A T A C T A T T T A T G G A T G A A G G C T G A A C A T T T T A A G G C A T A C T A A G T C T C C C A T G A T A T G G T A C C T T T T C A T T T T C C C A T T C T A T A C C C T G C A T C T A G G C T T T T A A A A A A T A T A C C A C A T G A C T T C A T G C C T C T A G G C T A T T G C T C A T G C C A C G G C A T C C C T T C T G G G T T T T T C C C C T C T T A T C T A C T T G G T G A A T T T G C A T C C T T C A G T A T A A C A C A G C T C A A C A T A A T T C T A T G C T T A A A C T T T A C T G A A A A T G C A C A A G G A A C T T G A T C T T T C T T T C T A T T T T C C C C A T T T T A T T T A T T T T C C C A T T G C A T T T G G G C A A C T T T C A T G G C A C C A G T T A T T T T A T T A A T T A T T T G T A T A A A C T A G T A T G A G C C T A T T T T G T T T A G C T T C T A T C A C C A G G A G C C A T G A A G C A C T T T G A A A T C A A A T A C T G T T T G T A C T T G A A T A T A T T A A G T A A G C G T G A G G A C T T A A A T T A A A C T T T G T T C C T C T T A A A A A A A T C C T T A C C C C A A C T C T A G C A C T G A
Human CPS1 RR7_v2 SEQ ID NO:77	T C T T C C T A T G G G A A A A A A T A A T T T C C T C T A T C A G A G G A A A A A T T T A T T A C T A T T A T G A T A A T A C C C C T T C A G A C C T T T T T C T A G T C A C T T A C A G G T A A A A A T T G T A G T A C T G G T T G G T A C A T A G T G T A T T T T A T T A A T G T T T T A C T G C G T A T A T T G T T G T A T A A A T T G C T T T C C G C A C T C A T T G G C A T G C C T T A G A A T T C T T T T A T T T A G G C T T C A T G A C T A A T T T G T A G T G G A A C C T C A A G A A G A T C A C T T A T G T G C T T C A C T T T C C A C A T A T G T A A A A T G G G A A T A A C A C A G A A T C T G C C T C A T A G T A C T G C T G A A G G G T G A C A T G G G G A A C A C C T G T G A G G C A T T C A G A A C A G A G C C T G T C A T A C A A T A A A T G C C A T G T C A G T G T T T G C T C T T A T T C T C A G T A T A C A G A G A T C T G C T T G A T C T T T T C A T C T T C T G C A A A A T A T T C C A C A A A T T G G C A T A T T G T G T T T T G T A A A T C T C T A T T G A T T A T T T T C A A G C A A G A T T T G G A A T T A T C C G C A G T A G T T T C A A A T G T A C A A A A A A G T A C C T A T T T A T T T A T T T T T T A A A T A A C T G A T C T G A T C T A C G A G T C T A A T C T G G T A A G T T T T G T C T T G A G T C C A G T A A T G C A G T C C A A T A C T C C A T T T A G G T A A C C C T G T C C T T G C T T G G T C A A T T T G T T C C A C T T T T C C A A G T T T G A C C T G C T T A C C C T A T T C C T C T T C A A G A G G G C A T C T G G T T G T T A G T T T A C A T G A T T T A G T G G T G C A G A A G G A A A G G G T A A T C A G A T T G A T G T A T C C T C T G A G T C C T C C T T G A T A T C T G C A G A G C A G C T G A G C T G G T C T G C T C T G T G C T G T T G A C A T C T G C T C T T T G G G G C G T T A G G G G G T C T G G T C A T T T G T C C C T T G T C T T A T G A T C T A C C T G C A G T G G T T T T C A C C T T G T C C C C A G G C T T C T T A A T T C T T C C T G T A C T C T C A G A A C C T C T G T G T T G T C A C A A C C A G A C T T G G G T T A T T T T G G G T C C C C A G T T T C C A G G C C C T G A A T G C C A T G G G C T C T G T C T C A G G A A T A G G T A T C T G C T G G C C T G C T G C T G T C A T T T C T A C T A C A T T G C T C C T T T A C T G C C T T A A G A G T G G T C C T G G A T C A G G G G T T G A A A G T G G A A G T G G A A T A A A G G A C G C T G A T G T G A C G T C T G T G T T C C A T T C T T C T C T A C C A C T T C A C C A G A T G T G A A A A A T T C A T A T A A T C T G A A T C C T C T A G T T T G A G T T A T G A T A A G T T A A A G C A G T T T A A G A A T T T A A C G A A C T C C C C T C T C C C T G A T T A A A T C T A C T T G T T A G C A C T G T G T T C T T A C T G C A A A T C C C G T T G C C T T G C C A G A A G A T A A A T A T T A A C T T T T T C T T T C T T T G C C T T C C T G T T G T A A A T T C C A A A C C A C C A A A A G A A A T A G G T G A G T T T G T G G A G A A G G T C A G T A A A A T A A T T T C A A A G G G A A A A G A A C A T T C A T G C A T T T A A A T A T T A T T C C C A C T G G T T C A T T T A T G C T G C A A T G A A T A T C T A T A T A T C T A T G T A T G T A T C T A T C A T T T T G T G C A C A T G T T T T A G T A T T T T T C T G A G T T T C A T C C T G A A A A A A T G T A A T T G C T G T A A G G T A T G C A C A T T T T A C A T T T C A C T G T A T A A T G A C A A A T C A T G C T A C A A A G T G A C T A G A C C A A T T T A T A C T C T T G C T A T G A G T C A C T G A G A G A A T T C T T T A C T A A C A C C A G A T A T T T T G C G T A A C T T A T T C T G T T T A A A T T C T A T C A G C A A A C C T C C A T A G T A G G T G T A T T C C C A T T T T G T A T A T G A A G A A C T G A G G T T C G G A G T T A

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Human CPS1 RR23_v2 SEQ ID NO:78	TGTTTGTCTGTTTGTATTCTGGACAAAGCCGATAACGAGTTGCAGCTGCTGTACA GAGTGTACTGCTTGCTGAGGCCATTGCTTTAACTTATAGATAGAAAAGGAGCAGCCA GAGATGTGCCTCAGGCTGAAGCCAGTGCTGCAAATGGGACAGCGCTCTCAAGCTA CATTATATGCATTTTCATTATCCAACAATTTGTTCTGGGAGGACAGTTTGATTGGCCA GGCAAGAAATTCAAAATGAGAGACTTTTAAATATCACAACTCAGCTAAAAGAGCT CTTCTGTTTTCTGACCTGAGAAATTCATTCTATCAGTCTCAATAAAGATGCTTGTGA ATATTAGGTGATGCAGACTCTGAACATTTGTCCCTCTGGACTGAGTGCATCCCGA TGATCTGAGTCTTGGGGCTATGCCTCAGGCTTCACAATTCCTAGTGTGAAAGCTACT TGCATATCCACCCCTCCATCCAGCTGGGTTTTGTTCTGCTTTTCTGTGTAACATAATG ACTGTGAGTCAAAAAGATGGGAGGTCAACTACTTGCCTTTGACCATTAAATAGGTG TTTAAACTAAGCTAATAAGGAATAACATTGTTTTTCCATTTCTGTGATATCGTTTTTC CATTTTATCCTAGATTCTTAACTAGGATGTGAAGAAAAATAAGTAGTCAATATTA TAAAGTTTAAAAATAATACAAAGTAGTCGATATTATAAACACAGACATATTTCTAGA ATGGAACAATAAGATAGTAGGCTTCTATGTTTTATTTTAAAGGTTCCGAAATTAC CCACTTACCATTTGTGTGACCTTGAACAAGTTGCTTTAACTCCGAACCTCAGTTTCT TCATATACAAAATGGGAATACACCTACTATGGAGGTTTGCTGATAGAATTTAAACA GAATAAGTTACGCAAAATATCTGGTGTTAGTAAAGAATTCTCTCAGTGACTCATAG CAAGAGTATAAATTGGTCTAGTCACTTTGTAGCATGATTGTGCATTATACAGTGAA

	ATGTAAATGTGCATACCTTACAGCAATTACATTTTTTCAGGATGAAACTCAGAAA AATACTAAAAACATGTGCACAAAAATGATAGATACATACATAGATATATAGATATTCA TTGCAGCATAAAATGAACCAAGTGGGAATAATATTTAAATGCATGAATGTTCTTTTCC CTTTTGAAATTATTTTACTGACCTTCTCCACAACTCACCTATTTCTTTTGGGTGGTT TGGAATTATTACAACAGGAAGGCAAGAGAAAAGAAAAGTTAATATTTATCTTCT GGCAAGGCAACGGGATTTGCAGTAAGAACACAGTGCTAACAAAGTAGATTTAATCA GGGAGAGGGGAGTTCTGTTAAATTCTTAAACTGCTTTAACTTATCATAACTCAAAC AGAGGATTCAGATTATATGAATTTTTACATCTGGTGAAAGTGGTAGGAAGAAGAAT GGAAACACAGACGTCACATCAGCGTCCTTTATTTCCACTTCCACTTTCAACCCCTGA TCCAGGACCACTCTTTAAGGCAGTAAAGGAGCAATGTAGTAGAAATGACAGCAGC AGGCCAGCAGATACCTATTCTGAGACAGAGCCCATGGCATTACAGGGCCTGGAAA CTGGGGACCCAAAATAACCAAGTCTGGTTGTGACAACACAGAGGTTCTGAGAGT ACAGGAAGAATTAAGAAGCCTGGGGACAAGGTAGAAAACCACTGCAGGTAGATCA TAACAGACAAGGGACAAATGACCAGACCCCTAACGCCCCAAAGAGCAGATGTCA ACAGCACAGAGAGCAGACCAGCTCAGCTGCTCTGCAGATATCAAGGAGACTCAG AGGATACATCAATCTGATTACCTTTTCTTCTGCACCACTAAATCATGTAACTAAA CAACCAGATGCCCTCTTGAAGAGGAATAGGGTAAGCAGGTCAAACCTTGGAAAAGT GGAACAAATTGACCAAGCAAGGACAGGGTTACCTAAATGGAGTATTGGACTGCAT TACTGGACTCAAGACAAAACCTTACCAGATTAGACTCGTAGATCAGATCAGTTATTT AAAAATAAATAAATAAGGTACTTTTTGTACATTTGAACTACTGCGGATAATT CCAAATCTTGCTTGAAAATAATCAATAGAGATTATTACAAAACACAATATGCCAAT TTGTGGAATATTTGCAGAAGATGAAAAGATCAAAGCAGATCTCTGTATACTGAGA ATAAGAGCAAACACTGACATGGCATTATTGTATGACAGGCTCTGTTCTGAATGCC TCACAGGTGTTCCCATGTACCCCTTCAGCAGTACTATGAGGCAGATTCTGTTGTTA TTCCCATTTTACATATGTGGAAGTGAAGCACATAAGTGATCTTCTTGAGGTTCCAC TACAAATTAGTCATGAAGCCTAAATAAAAAAGAATTCTAAGGCATGCCAATGAGTG CGGAAAGCAATTTATACAACAATATACGCAGTAAACATTAATAAAATACACTAT GTACCAACCAGTACTACAATTTTTACCTGTAAGTGACTAGAAAAAGGTCTGAAGGG GTATTATCATAATAGTAATAAATTTTTCTCTGATAGAGGAAATTATTTTTCCCAT AGGAAGATCTTAACTTATTTGTAATGTTTCAATTTTTTACATGATGAACAAAGCA ATACACTGCTCATGTTACTGAACTCGATAAAATATATGAAGCTAAAATGGTCAT CTAAAAGTATGATAATATATAATTTATTTTCTACTTTATCTCCAATATGCTTATC ATACAGAAATTATAACAAAATGCAAGCAAATGTTTTGGATAATTTGAAAGTTAATA AGTTGTACACTGTAGCCCTACCATCCCCACTGATGTCAAAGGGCTGATTTTAATTA TGCAATAGTAATTAATAGGGATCAATGTCATTACCTGAGAAAAAC
Human CPS1 RR9_v2 SEQ ID NO:79	AATTCTAAGTCAGGTGGTCCAACAAGGCCTCTCATCCTATTGGTATTACAGTATGA CCTGTCTCCTGAACCTTTGAAGCCATTTCTTTCTTCAGAGGAGATAAGAAAATGTGT CTTATCTTAAGTCTGGAAGAAACACGGAGCCAGTATCAAGGGAGTGGAGTAGTTC TTTTCCAGACGTAGCACAGGGTTTTCAAGCCTGAAGAAAAAGATTAATCTCCTT AAAACAAGGCTTTGTTGACTTGGGTCTGGTCAATGGCAATCCTGTTTCCAGCCATCCT GTGTATAAGCTCTAACGGTCAGAAGTTTGTGTTGCTTTGATTTTGATGTGGCTCATCT TTTCTTAGCTGCTCATATTCAAGATTTGGAAAAAGAAAGGACGGTGGTGAGCTGAGC AATTAATTGGATTCTGATAAGGAGTTCTGGAGAAATTTTATTATCTGAGTTTTAA ACCCGTGTAACCTTAATATAACTTTGGTATGAGCCTTTACATTTTTTCTCTGTGTTT TGTAATTATATTGTGGCATTCTTATTGGGTGTGGTAGTAGCAATAAATTATAAATGT ATGAATTTATACATTATGGATTTATAATTTTATAAGTTTTTGGAGTTTTAAGACTTA CTATTTTTTACACGATGCCTTATGTATTTATAGCATTTAATATTAATCTAAATTCATT TTGAGATATATTTTATCATGCTTTTATCTTTTATATGTTATTAGAAAGCACTTGGTAT TTTAAAAATATATATTAATGTGAGATTTTACAATTTATACCTTGTCTTTGTAGTCAC ATGCGTAGAGGATATTTACAATTTTACTCAAGTTAATTTGCTCAGTGTTGATCATCA GACCTTTTAGCCAGTATTGGCTGGGAAAAAAAGTGAATTTCTTTTTGTTCTCTTGAG AATTTTTTGGATCTAAAGTGATTCTAGGGTGTGGGTCAACTTCTATGATATGAAA GATGACATGGAGGTTTTTTATTTGTGAAGTGCATTAATAGGTGATCATTTCATC CTGGGAGAGCTGCTGGAGAGGAATATTGATTTAGCCTGTTATGGTTGAGTCTTTGG GGTCTTGAGCTTCTTAGATTTTATGTTCTTTTGTATTCTTTATTGTTCAATCTTGA

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Mouse CPS1 RR52_v1 SEQ ID NO:80	CACTGCTGGTTCACCTCCTTCTCTCACCATGGGGAGAAAAAGGTGACCTCTTCTG GCATTGCAAGCACAACTGACTCACAGGGCAATGCTTTTGTATCTGAGTGCTTTTC ACAATCCATTTACTATCTGTAAGTACTGTTCTGTACTAACCTTTAAAAAACTGCTC CCATGCCCTTCAATGACAATTATGTAAATATACTCTAATGACTTTTAACTATCTTTA AAATACTGTGCCCACATCAAAAAAGAAATTAATTTGGATGTGTATTTCTTAGAAAAAT GAGTTTTTAAAGAGAAAGGCAAAAAAATCATACATAAAGGACTATTTCAAAAT AAGTGACTAAGAACACAGGTCCCCCTTGGACTCTGTGGGACTTTAATTCATACCA TGAAGCTTAAGAACTTCCATTTTTCATGCCTGGCATTCTCCAAAGTTCTGGCCAGT AATGACTGTATGTGAGTAATGGCTTTTGCACCTTGAAATGATGGCTTATTCCTCCTG AAAATTGTCAATTCTTAGCTATGAACTATGGAAGACCCTTGAAACAGATCTACCAC CATGAGCTAGAACTGCTTTCCAGGGGTCGGTCCACATAATTAGCTCATGTTGTTGT GTGGTAATTGCTGTGTAGAGTGCTTGCTGAGTCTAGGGATCTGATTTATAATTATTG TGGCCTCCACTATTCAATTGCTCTGTTTTTGGTATTTAACAGAGACCTGCTCATCCTT AGCTACCCACTTCTGTGAGAATAAAGTGGTCCAGGTGACACAGTTCAGAAATATGA CAAAGCACTTAACTGTAGATGGTACTGTTGTCCTTACAGTTTCTTCTTCAAGAT GGCATGTGATGTCTTCAAGGCATTGAAACACTTAACTAAAGCTAAACCACCATTCT CTGTATATCAAGGTACTATGTCCTTATTGATGCTTTAGAATATCCATTCTCCTTTCTG GCTTCCATCTTATTATCAAAATGAATCCAACATGGCTTTCTTAGGCTTTGTAATAAA TTCTCAGGGTAGCAGGCTCAAGTTGGTATCATGTCATTGATGTAAGCATAAAGTGT TCTCTCCCTTTCCCTCCCACTCCTCCTCCCTTCCCCATCCTCCTCTCCTCTCCCTAC CCTCCATGCCACCATCCTTTCCCTCCACCCTCTTTTCTCTCCACCAGTCTTCTTAT GTCTCTCTCCTGTCCCTGGAATCTATAAGAACCTATAGAAATTGCCTGTTCCACAC ATGCCAGAATCCAAAGCCCCTGAAATCCTGACCAAGGCATTATAAGCAAAAGAAT CTCTTTTGGTATAGCATTGGAAATGTAAATGAGCTAAATACCTAATAAAAAATGGA AAAAAAAAAAGAGTCAAATGTCAAAAAAAAAAAAAAAAAAGGAATCTAAGGAGCACC
Mouse CPS1 RR34_v1 SEQ ID NO:81	ACTTCTTTTGCTTCATAATCATGTTACAAGAGGCCCTTGACCTGAGGTACCCTCCAC TAAATACACATTTGATTTGCACAGTGGGGTCAATTGGCTCTGGCAAACAGCAGTGTC AACATTGCTAATCTGAAACAACAATCTCTCATGCCCTCTCTGCCCCACCTTCAAAC ACACCCACAGCAAGTTCTGACAAACACTTTATATGTGCCGAAGTACGATTTCTTTA TCACTTGAGTAGACATGACAACCAGCTAACCTTGACAGGAACGTCCCTCTCTCCTGG CTTCTTTCTAGTGAGAATGGAATCCAGCTCACCTTATCCTAAAATACTTGGTGTAGA ACATGAAATTGTTTTGGAGTTTTCTTCATATATATTTAGATCTAGATAGAGCCCCATG CTTATCTTAAGTTAACGAAAGAGAAATTCAAATTAACAAAAAACAACAAACAAAC AAACAAACAATTGCTCAATCCCTCACACTTGTTAGCTCTGGGCCTGGTCTTTAACCC CGGTTTTCCATTTCTACTTTAGTTCTTTTCTCAGTCAGCAGGGTTTGCTAAGATTCAT GCTTGCTTTACATTTTCTACAAAAGCCCAGAGACTGAAACCATGTGTTTTAAGTGGT TTTAACTCAAAATGTTCTTTTTGCTTGTTGAGAACTCATAACCCAAGTTGATAGAA

	TGTCTTTCTAATTATAAAGTATTGTAATGAGGTCCCTGTATCCAAGAAGCACCATT TAATGTCCGCTCTGATCTCTGAGGGTTTATTTTTACATCAATCCAGTTCTGACCAC CCAGACATGAAAGTGCCTTGGTCACTGAGCCAGCAGCACCCTCCAGTTGGCAAAA GCAAGGTCATGAGAAATGGTGACAAATTCAGAGCTTCTTACTCCTCATTTGGATT CAAAGTCCCTAAAAATGGAATATAATTCCTTTTACCCTTCTTGAAGTACTCTATCAG GCAGGGTCAAAAAATAAAATCCACTTTGAGAGTTTCTTTAAATAGTAACACCCTT AATAATATCAAAACATGATTTGCATAATTGCACTCTATTAATAATATGAGTGTATT TCTTGTGAATAGTTATGTTGAAAAGACGTTCTTGGAAAGCATCAAAAAATATTAATA AAATATTTAAAGAATGATTTAAGCTCCATCAAAATTTTAAATGTTTACTCAAAAG ATACTGTTAAGAAAAGTGAAAAATAAGGCATAGACTTAAAAAGCAAATATTACAAAA TGATATTATTGGTAAAAAAAAAAAAAAAAATTGTATCCAGGCCAGATCAAGAGCTTTTA GAAGTAGATAGCAAGATGAATGAGCCAACCTAAAAATAAGCAGAATAGGAGCTGGA AAATGCTCAGTGGGAAAAATGCTTGCTATGCAAAACATGAGGATCAGATCTCAGATAC CCAACACCCCTATAGCTCACAGCCAACAATTGGACTGAGCTCCAGGGGACCTGGAT GGAGGAGATGGAGAAGGGATTGAAGGAGCTAGGGGTTTGCAGCCCCATGGAGGG AGCAAGAAGTGTCAACAGGCCAGATACCCTAGAGCTTCCAGGGACTGGATCAACC ACCAAAGAATACACATGGAGCAGCCCATGGCGCTGGCCACATATGTGGCAGAAGA TGGCCTGGTTGAACATCAGTGAGAGGAGAGGCCCTTGGGCCTGAAGGTGTTCAATG TCCAGTGTAGGAGAATGCCAGGGAGGGAGAATGGGAGTGAGGGAGTCGGGGAG CACCTCATAGAGGCATGGGAGGGGGAATGGGATAGGG
Mouse CPS1 RR35_v1 SEQ ID NO:82	AGTTTTGGCACACCATTTTAAATGAGACAGCAGATGCAAAAGTGCTTACAACAGCTG CCTAAGTAGACATTTTATCATCCTCCCTCACAGCAGCCATTCTGTGCCTTCTCTG CATGGCTATTTAGCAATTGTAAGTCTCTAGAACCATTCAATGGTATTCTGTACAGTT AATGTTTTTAATTATATTCTGCTTCAGACTTTGATTCTTTTGAAGCTTTTTCTTTAC ATAAAAATTACCAACTGCTTCTTTTCTTCTTGGACTTACACATGTCTATCATAACC AACTGACTTTATTTGGAGACAAAGTAATAAGGTAACCTTAACTTTACTTACTCATT ATAGTGTTAAGGAATCAACCTCATGTCTCACACAGACTAGGTAACCTGTCTGTAC TGAGCTGATTCCTAGCCTTTCTAATGTTCTATGAGTGATTATTATAATCTACGAAAG ACTAAGGGCACAGTAAGGAACAACACAAAATTTTCTGCCTCCACTGAACCTGTATT GTAAATGTTATAATGAAATGTAGGGACCATGAATGAATAATGGATATGGTATCTCC AAATCTTATGCATCGTCATTTTCTAATTCCTGTATCCTGATATTTGTGGGAAACTT GCTACCCTGTTGACTGATGTCTTGGTGGGACAGTCTTTGATCTTACTCCAATCTCG TTCTCTTTGCCAAGTGTAGACACCTGATCATGCTTGTCCAATCAGACTCAGAGTAA AACTGAATATAATTGGACTATGTTCAACTCAAAGATGGCTCTTTGACAAAAGGCCAT TGACTCCTGCCACCTAGTCCTCAGGGACTCATTGTCTTATTTGTTCCAAAGGCCCT CTTTCTTGGCTACTCCTGTATGCAAAATCTTCACTGTTCTTGCAAGTTATTTTAA GTGTAATTTTGTGTTGGCTGGAATCCAGTTATTCTAATACATTAAATTTGGCAAAGG AAAGAGCATAGCATTCTTTATTTCTCCAAGTCAACTGTCTTATCCTTTTATCCACT GGGCTTGTAAGAAATTAATTTGAACTTTAGTGGGGATTCCCTCTATGATTCCGT GGCTGAGAACCAGTAGCCAGTTTCTGAGGTGTCCACTGTGGCCGCCTTTGTTCTAT GCCAGGGATAAGAAGATCGTTAGAGAGACTGGTTATCAGGGAGCTAAGGTTCTGCT TCTACAGGTGCAACGTGCAAAAGCCTACTGTATGTAAGTCTGTATTATGCCTGGGAG ACTTTGTACCATCGGGCTGATTACTCTGATGCAAAAGCCTCCCTCAGACAGTTAACTT ATCTTAAAGCCTCTGTTATCGTTCATGAACAGAGGGCAAACCTCATGTCCATTCTGTC TTGTTCTCCACCTGTCTCTTAAGTTGCTCTGGATTGCTACATTAAACTCTGAGGAA CAATGAACCCATTCTTCCATTTAGTATGAATTTAGTAAGTGTCTGATCCATTCCAAA TTCTCTATGAGACTCTGAAAAGACAAAGGGAAACTCCATTTAGTTATTGTTCTACA GGAGTACATTTTGGGTTGGAGAAAGGGAAGATTAAGTAAGCTAGTGGCTAAGCAA CAGGGCAGTGATGAACCTGACAAGAACCATGACAACATAACAATAGAAAAGATCT GAGTCTATTTGGAGAATGTCATGTCAGACATGGACTACAAAAGGAGAGAACGGCT GGGTTGGACCTTTGGGAGGATGTGGGAATTTGCTTACTATACAGGTGACCAGTAAT GGCACATACCAAATCATAGAGGGAGGAGGAAAGAAAGGAAGGAAAAGAGCAGGT TATAAAGAAGGAGGAAGAAACAACATGGGAAAAAAAAACAGGGTCAGAGAAGAGGC AAGAATAAGAACAAGAGAGAAGGAAGGAGGGAGAGGAAAAGGAAAAGGAAGAA AGAAAAGAAAAAAAAAACAGAAGAAGGCTGGGGTGGGGGGGTTATGTTGTCCT

	GTAACAAGTAGCACACTATAGCTGACAGGATTAGGGTGAAGTCCACTAAGAGGCT TGGGTGAGACAGACATAGGAAACAGGTAGACAGAAAAACCCAGAAGGAACATTG TCATCTTGCTCTCCTGTGTGAAAAACGGAAGCTTTGCCTCTGTGAATCCAAGAAAGA GACGTACCTCTGTTCTTATCTACACAAAAGAGAAGGTGGCAGAAACCTCATCTTAC TGTCAGTGAGAGGACTAAATGGACTTTTGAATCAAAAGCACTTAGCACAGTACCTA CCACACAGCAGAAATCAAGGGCTTTTACCTGTCTCCTCTTCCAAACCTCACACCC TGAAAATCCATCACAAACCCTGTGGAACCATAAAAAAGATATCCACCCCT
Mouse CPS1 RR36_v1 SEQ ID NO:83	CCTCTATCTCCACTCTCATTAATATGGGTGTCCTATTGCTCTTATTTTCTTATTA GAAAAGGGGGACACAGACACACACATAAATATATACAAACACATGCACACACACA TACATATATACACACATGTACATACACTCCAAGATGTTTTGATGAAAAAGGCAGTT ATAAATTAGAATCTGGATGAGAAATCAAGCCAGGCAGGTTTTATTTCTTGCTATCTG TTGGTTTGGTTTTACTTGGGTTTGGAGACTAGGGCTGTGTTTTGAGATGGGAGACA ATGAACAAATATCTGGATATTTACCTGGAAAGTGGAGTTGTAAATTTTATGATAG AAAGGGTATAACCAAGGAGTAAAGACTCAAAGAGTGGCCAAAGGGGGGATATGA AGAAGATGGAAAGTAAGTCATTTCTGATCTGCCAGACATACTTCCACTAGTATAAC TGGAAGGCAGAAGGACTAGACAACCTTTCTTCTGCAAGTTGATAAATTCAGTAG TGTAAGAGTAGAGCACAGCCATCTCATGACTTCCATTTTTCAGTTGATGTGGGGTG CAGTTTTTCACTGAAGGTTGCAAGGATGCAAACCCTTTAAAGGATTTGACCTGTGA TAGGCTGCCATGACCCAGTAGATGCCCTGTACCTATGCTCATACTGGCAGCACTA AGTAAACTCAGTGAGTTTAAAAAACAAACGAAATATAAAGCTTTGGGAGGGAGG GGATGGTGGTGGGCAGGAAGGAGGAGTTGGAGAGGGGAGAATGGAAGGAGACTA GATCAAAACATGTTATGTGCTGAATGAATTCTCAAACAGTAACAAAAAGAAAACCTC CTTAGGAGTAAACTAGATCAAAACATGTTATGTGCATTCATGAATTTCCCAACAGT AACAAAAGAAAAGTCTCAGGAACTAGGGCCATGTTCTCCTTACAGTAAGATCCTC AGTAGTATCAGATTTTACCCGCGATAGCAATGGTGAATTCATATGACATCAGAAT GTACATGAATATGGCTTTTCTCCAGCTATTTTCAAAAACAAGTGTGCAGCCTAGCAG GTGGCATATTACTACCGAGAGTTCAAGCATTACCTAGCAATATAGGAAGAAATGG GGTGTGAAATATGAGACTCTAGAAAAGAAATAACTACAATAGTAGACCCTAAATTCT AAGACAAATGAAAAGATTGCTCAAAAGTGAGGAGATGTCTCAGTCAGTGGTGGCA CATACTTTAATCCCAGCACCTAGAGGCAGGGGAATCTCTGAGTTTCAGGACAGA CAAGTAAGTCTCCAGAGCAAGTTCTGGGACAGCCAAGGCTACACAGAGAATCCCT GACACATGCATGTGCACATATGTACCTACGTGTACACACCACACACACACACAC ACACACACACACACACAAAAATCACAGCTCTAAAAACTACTGAGGCAGATTCT GAAAGATCCATACAGTAAATATATGAATTCAAAAAATAGGAAAAAGATGAGAAA ACTAAGACATTTGGATTTTAAAGGTGGCTCTGTTTCTGATAAAGATCATCTGGGAG TTGGGGGGGGCATAATTAAGCTGTTACGCTGACAATCTTTTTTCATTTACACAATT CTACCTCTCTGTGGTCAACCAACACAGTCCAAATACTATGAATCCTGTTTATAAGG CATAACCACCATCAATATGAGAAAAATCATAATAAACAAAGCAAATTTCTTTCCTTT CTTTAGGCAAAATTGAACATCACAGAAATATTAGTATAAATAAAGTTCTAAGAGTA ATCTTTGTTGAGATTTTCTTTTTTCATTTTACAGGGTTAATAGCACTCATGTGGCCTT GAACCTCTCTATGCCAGTACAATTGATCAATCAGCATTTCACCGATTGCTTCACTCC TCCTTCTCCCCATAAGAGGAGAGAAACCTTGCAAAACGTGTTTGTCTGTTTGTTA TTCTGGATAAAGCCGATAACGAGTTGCAGCTGCTGAACAGGGGTGACTGCTTGGCG AGGCCACGGCTGTAACCTATAGATAGAACAGAGCAGCCAAAGATGTGCCTCGGGC TGGAGCCAGCTCTGCAAAATAGGCCACACTCTGGGCTATGATACATGCATTTCTTA GCTGACAATTTACTCCTGGAGAAGCTTGATTGGCGACAGACTCAAAAAGAGAGAA TTTGAAATATCACTCCTCAGCTCAAAGTGTTTTCTCTGTTTCTGACCTGAAGGATT GGCTTATGTCAGTCTCAATCAAGATGCCTTATAGTAGTACTTGAGGCTGACTTGGAA CAATATGGGTCCCTCTGGACAGAGTGTACACCTGATGATTCTGTCTTGGGGCAAT GCCTGAGGCCGCACAGTCCCTAGTGCTGAAACTGAGCTCACGCCCACTCAACTGA GTTTTGTGCTCTTCCCTGTGTACTTAAGGGCTGTGGGCCAAAAAGACATGCAGCC AACAACTGCCCCTGAACCATTAACAGCTCTCTAAACCGAGCTGATGGGGAACAG AGTATCATTGTCCATTATTTATAATGTGATCTTCTACTTTATCCTCAATTATTAAGA CACAAGGAAAAACAAGAACAGTCAACATTATAAGGATTGGGTCAAAATGAATACAT GCTTTGAGCATAAACCAAGATCAAGATAACTCTTGTGCTTGTGAAAAAGTTTT

	CAAGCCTTCATCCTTTAGCAAGTTGCTCTGACTCCTCAGACCTCTGTTTGTTCACAG GTAGAATGGGAATGATCCTCAGAGCTGTGGAGGGTTATCCAGAGACTTCTGATAAA GTAAGTTATATGAAATGTCTACCATAGCAAGGAATACTCTAAAGTTGTCTAGCAG AAATGACGAGCAGGTTTCAGCCAGTCAAGGTTCTGTACCAAGCCTGAAGACTAA CTTCATCCCCGGGATCCACATAATGGAAGGAGAGTGAGAACCCACAGTTGTCTC TACATACACACACGCACATACACCACAAAATAAGATGTAATAAAATATGTTCTAAT GCAATTTTTCATTATATAGTGGAATATCAATTGTGTATATCCTATAGTAATTGTA TTTCAATATGTAACCTTAAAGAGATACAAAAATGTGTGCAAAAATTATATATGTTTT TACAATAAGAATATATATATATACACACTGTGCCATTAATGAATCAAGCCAAATAA CATTTTAATGTATTAGTGTTCTTTTCTGTTTGAAGTCACTTTACTGGCCTTGCCCCG CTTATATGTTTGAACCTTTTGGATTATTGTAAGTGGAAAACAATGTGAGGTCTGG GATCCAGATAAAAAGACTCCCTGAGGCAGATTACTCCACACACCTAAGTATCACAT GGCTGAACCAAGTATCCAGTACCACACTCAGTGAACAGACTGAGCAGCAAAACAAGG CGCTGAGGGCCAATACAGGGCCCCCAACAATTCATCCCTCTGCAGAAATCATGGAT GGTCCAGAGCACACCCTGTGTCCTTACCACCTTTCCCTCTCTACCACCCAATCAAT CACATGAGCTAAACAACCTGTCTTGAATTGGAATGGCGAGCCAGTTCCCTAAATGGA GGGCTTGGACCGCAGAGCTGCACCTAAGAAGAGAATTTAGCTCGTTAAATGAAAG ATGTGTTTCCAGTCAATGAAATAGATCAGGTTAATTATTTAAAAATCTCCAGCTTCA TTGCACATGTGAGTCGACTGCAGGGAATTCGAAACCTTGCTGCAAAAGTAATCAATA GAGATATTTCTAGGCAAAAAAAAAAAAAAGTATGTTGGTGAGCATGGTGGCACACG CCTTTAATCCCAGCAGTCAGGAGGCAAGTGAGGCCATGAGTGCGAGGCCAGCCTG ATCTACAGAGTGAGTTCTGGGACAGCCAGGACTACACAGAGACACCATCTCAAAA AATAATAATAAACAACAATAATAAAAAAGTATTTGGACCACAGGCTGCACGT CTCTCTCACAAGATCAGAGTGACCTGGCACAGTGTCCTGCTGATAACAGCTCTGGTC TGAGGGTTTCAAAGACATTAAGTGGTATCATGCATAATGCAAGATAGATGCTGTTG TTCTTTCCATTACACATATAAGGGAAGTGAAGCAGAGACTCCCTTAAAGTTGTCTTCT CAAGGTTTCCCTATTTATTTATGATGGGGCTTAAATTGAAAAAGTCTAAGGCACA CAGATGTGTCTTTTTTTAAGCAATTATACAGAGCAATGCATCTCTTCAAACGTTAG TAATGCAGACACATGCCGCGATTTTCATAGTTTCATTAGCAAAATGACTAGGACAAAA TCTAAAGAAATATTGTAAAGTTCATCATGATGCTTCCCTCTGCACCTAAAAATATTA TCACCTCATAGGGAGGTTTGTGTTTAAAGTTTATCTCTGATAATTTAATTATCTCAAT TGGAATAATGGCAATGTACTGCTCATTTGACTAAAAATTGGATAAAAAATAAAGC TAAGAAGGATGGTATGGTAATATTAGCAATAGTTTGTACTTTATTTGAAATACGTTT GTATTATAGAAATAAAAGTAAACATGGGGAAAGTATGTTAGATGCTGTTGAAAAAC AGTGCCACATTGTTTCCCTAACATTTCCAGTGATTGTCAAAGAGCTGCTTTCTAATT ATAGAATAGTATTTAAATAGGGACCAATGACATTCTAAGAACACTAATAGAAAG TAGTTATTATTCTCCTGTATTTCTTTAATAATAATAGCTACTTTCTATTAGTGTTCT TAGAATAGAACCCTTGGTTGAGTGTTACTCTGGTCAGTCTACCTTGATTTTCTGTC TTGGATGAGTTTGC GTTGTGTGTCTACAAAAAATCTCACAAACAGCAGCATATGA GGAATCACATTAACCTTCTTTGAAAAAAGAAAGTATTTATTATAAGCAACATAAT TTCCATTGAAAAAGTAAAAAGTGAAGTCAATTTCTAAAATTAATACATAAGG ATAACTCACTTCAATAAATTGAGTAAGTTTGTCAATTATAGAATTATATTTTCTTAA ATTCTCATGAAGAAGTAAACATCTGTAATTCCAGAACTTGGGAAGCTAAACCAAGA AAATCATGAGTTTGGAGCTAACCTGAACCTCATAGTCACCCTGACTCAAAACAAAA GTTCTGATTCTGATAAAGAGCAATTTGATACTATTCTATATGGGTTCTATTATGC AATCTTTAATATACAAAAACAGAATACTTTAAATGACATTATTATTGTGAATTGAT GGAAAAATAGACAAAGCTTTATTATAAAATTAATAAAGTTTGTATGAAATTCA TAATGTCTTTTAAATGTGAATGACATATTAGAAAAAAGTCACTTATCAACTGT GAATCTAATTTTATATATAGTTACATTATCTTTATAACTGTTTAAAGTCTGTGAGA AAAAATGTATAATTAATGAAAGATGATGACTGACAGCACCATCTCTCAGATCAG GAAAACCAGCTCAGATGAAATGAGAAAAAGATAATGTTCACTACCAAAAAATC TATATCAGGTAGTTTATTTATTTAGATTTTTAACAATTGTTCTGCTATATATCAAG GTGATGCAGATAGATAGATAGATAGATAGATA
Mouse CPS1 RR37_v1	TTTAAATAATTAACCTGATCTATTTTCATTGACTGGAAACACATCTTTCATTTAACGA GCTAAATCTCTTCTTAGGTGCAGCTCTGCGGTCCAAGCCCTCCATTTAGGGAAGTG

SEQ ID NO:84	GCTCGCCATTCCAATTCAAGACAGTTGTTTAGCTCATGTGATTGATTGGGTGGTAG AGAGGGGAAAGGTGGTAGGGACCAGTGGTGTGCTCTGGACCATCCATGATTTCTGC AGAGGGATGAATTGTTGGGGGCCCTGTATTGGCCCTCAGCGCCTTGTTTGCTGCTC AGTCTGTTCACTGAGTGTGGTACTGGATACTGGTTCAGCCATGTGATACTTAGGTGT GTGGAGTAATCTGCCTCAGGGAGTCTTTTTATCTGGATCCCAGACCTCACATTGTTT TCCAGTTACAATAATCCAAAAGGAGTTCAAACATATAAGCGGGCAAGGCCAGTAA GATGACTTTCAAAACAGAAAAGAACTAATACATTAAAAATGTTATTTGGCTTGAT TCATTAATGGCACAGTGTGTATATATATATATTCTTATTGTAAAAACATATATAATT TTTGACACATTTTTGTATCTCTTTAAGTTACATATTGAAAAGTACAATTACTATAG GATATACACAATTGATATTCCACTATATAATGAAAAATTGCATTAGAACATATTTT ATTACATCTTATTTTGTGGTGTATGTGCGTGTGTGTATGTAGAGGACAACGTGGGG TTCTCACTCTCCTTCCATTATGTGGATCCCGGGGATGAAGTTAGTCTTCAGGCTTGG TGACAGGAACCTTGACTGGCTGAACCTGCTCGTCATTTCTGCTAGACAACCTTTAGA GTATTCCTTGCTAATGGTAGACATTTTCATATAACTTACTTTATCAGAAGTCTCTGGA TAACCCCTCCACAGCTGTGAGGATCATTCCCATTTCTACCTGTGAACAAACAGAGGTG TGAGGAGTCAGAGCAACTTGCTAAAGGATGAAGGCTTGAAAACTTTTTTCAAGCAA GCACAAGAGTTATCTTGATTCTGGTTTATGCTCAAAGCATGTATTCATTTTGACCCA ATCCTTATAATGTTGACTGTTCTGTGTTTCCTTGCTCTTAATAATTGAGGATAAAA GTAGAAGATCACATTATAAATAATGGACAATGATACTCTGTTCCCCATCAGCTCGG TTAGAGAGCTGTTTAAATGGTTCAGGGCAGATTGTTGGCTGCATGTCTTTTGGCCCC ACAGCCCTTAAGTACACAGGGAAGAGGCACAAAACACTCAGTTGAGTTGGGCGTGAG CTCAGTTTCAGCACTAGGGACTGTGCGGCCTCAGGCATTGCCCCAAGACACGAATC ATCAGGTGTACACTCTGTCCAGAGGGACCCATATTGTTCCAAGTCAGCCTCAAGTA CTACTAAAGGCATCTTGATTGAGACTGACATAAGCCAATCCTTCAGGTCAGAAACA GAGAAAAACACTTTGAGCTGAGGAGTGATATTTCAAATTCCTCTTTTTGAGTCTGT CGCCAAATCAAGCTTCTCCAGGAGTAAATTGTCAGCTAATGAAATGCATGTATCATA GCCCAGAGTGTGGCCTATTTGCAGAGCTGGCTCCAGCCCGAGGCACATCTTTGGCT GCTCTGTTCTATCTATAAGTTACAGCCGTGGCCTCGGCAAGCAGTACACCCTGTTCA GCAGCTGCAACTCGTTATCGGCTTTATCCAGAATAACAAACAGAACAAACACGTTT TGCAAGGGTTTCTCTCCTCTTATGGGGAGAAGGAGGAGTGAAGCAATCGGTGAAAT GCTGATTGATCAATTGTACTGGCATAGAGAGGTTCAAGGCCACATGAGTGTATTA ACCTGTAAAAATGAAAAAAGAAAATCTCAACAAAGATTACTCTTAGAACTTTATTT ATACTAATATTTCTGTGATGTTCAATTTTGCCTAAAGAAAGGAAAGAAATTTGCTTT GTTTATTATGATTTTCTCATATTGATGGTGGTTATGCCTTATAACAGGATTCATAG TATTTGGACTGT
Mouse CPS1 RR38_v1 SEQ ID NO:85	AGAAAGTTCAGTGTTATTCAGCGGCAGATTTCCTCACAGGGCAAAGCATTGCATTA ATTTATGTTGGCTGAGTGAGTCACAGTCTGCTCTATTTATTTTCCCCTGTCAACTTC ATTTTGTACAGAGAAAACTTTAGTAAACACAAGGCGGATGGTTTTTGCACAGGGA GTGTCAAGCCACTGTAAAGAAATCAGTTATGTATTTTAGCTGTATTATTTTACAATCA TGTTGGTCCCCCTCCCCCCCCGGGATTTTTTTTTTTCTTCTTTGCCCCCACTCTA TCATGTCTTAGTAATTTTTCTGGTGAAATTTGTATTGCTAGAGGAGAAAAGTATC ATGTGGGATGTGAGTACTAGAACAGGCTGGAGTCCAGCCAGCCGTCCTAGTGAA GAATTCACAGAACTGGATCTTCTCTCCCTAGTCTCTGCCAGAAATCTCTGTTTACA GTAATGCTCAAAAGCCATTTTGGCCTATCACCGTCCCTGTCACACCTAGAATATGA TCTCAAAATTCTACTTTCAAACCTTAAAGGGCGGAAAAAGGACCATGTAAATGAAGC AATGATGCTAAATTAATATATTTTCTACTTTTGTCTTATAGAAGCATTTACTTCAAT GTAAATCTTATTTAAGAAAGTGCTTCCCTCGTTAAACATAGACTTTTCATGGTACTTC TCCTGATGTGACGCTGAAGTGAAGTAGCTACAAAGGCAGTTTGTATGTGCAGACAA CTCAGAACTTAGTTTTGAGATATTAACCTTCTTATTACCATAGTTGCATTCTCTACT CCTCAGGTCACTATAACATTTTAATTTTCTATAATCAAGACAAGTTGGACTATATCT TCACAATAAGTACATTTATTTCTTACCTTGTCTACCAAAAAAGAAAATTAATAATG GAAGTTTTTCTTTTTTCGCCATCCTAATGGACAACAAATCTTTTGTGCTGTGTTCA AAGAACAACCAAGGTGTTTT
Mouse CPS1 RR39_v1	GAGCAGTTTGTCTGTTCAGCACATTATAAGAGGGGGAGGGTTTTGGCAATAATAA TCACTGTGCAAAAGAGGGCTGCTGATGAATTTGCTGTTTTCAAAAAACATTTTCGT

SEQ ID NO:86	AGAAATAATTTACTAGTTAGAATGAGCACATATCTAATGATTTAGTCATCACACTC TATGAAATTTACACTGTAAGCATGTTTTGGTCAAGTTTTAAGAACTTCTTTGACCA GGATTAGCTAAACTGACACAGTTAGCATCTTTCTAATTGTTTTAATATTCATCAAGT TATTTTTTTAAAGGTATCAATTATGTGGAACCTCAGGTCTAGATTGACCCTTTTTCC TTTTTAAAGAAAAGCTAAACTAAAACTTTTACTAAAGGCTATTTAGTACTGAATA ACTCATAAATAACGAGATGACTCTATATTTATCCAGATGCCAGATTTTTATATATAC AAAACAAAAGAACCAGAAAACCTATTTTAAAGGTTATTTTTTAAATCTATCTAAAAAC TATCTATATAATTTATACTATTTGCCTTCTAAAAATGTAGGTAAGGCACCTTAGATGT TGTGAATTTTCTTGAAATCATTTTTAGTTAAAGCCAATACTGTTTCTGATATATAT TGATTGATATCCTAGCATTTTCTTAGTAAGCATTTTCTGAATTCCTTTAGTTACTCTAC ATCTTATTTCCAAACAAATATAAGAATTCAGTGAGACTAAAGTACTCAGATCCTGT GGCTTTGGAATGAAAAATTATAAAACAATAAGGTATAAGATAGAAAACAGTGAGAA CATGATTTGCTATTGTAGTTAAGTCTGGTCAAGTCTCAATCCAATTTACCTGATCTG AATTACAAAAACAAGATAGCCAGTATAATCCCTGCTATTTGAATATTGTTGTTATT TTAAATTTAAATGTAATACCAAAAAGTAAAGTCAGAATTACTTTTCAACCTCATT TTGACATTTACTTAAAGTTGTATCATCTTAACTTTACGTGATGGCATAAACCCCTCTG AGCTCTGAAATCTGTTCTTTGCACCTCCACTCTCGGGTGTGCTTTCTGTCTTGCTGG ATCTTGCCCGAGCCACTCTCTCCACCTCATTCTACACCGTCACACCCGCTTTTCCAA GTATGACCAATACACAGGAAGAGGATGGACATTGGCTAAGAGCTGAATTCTGATT CTGGCCTCGACTCTTTCAGTGTGGTGCTAGACAAGCTAGTTACAAAGCTAAGACAC ACTATCAGCTATACAAACAGGAACAGCAATCGATAACCAGGAGTTGTTTCTAAACTT AATGGAGAAGGCAAGCAGGTGCCTAACGATGAGAATAAATGGCAAATTACTTAAC ATTATTCATGACTAGAACAATTAACAAGTTTATTTAAATATGTATTTATGCACAC ATAGACATACCTTTTATTATAAATATGCAATGTGCTAAAAATTGTAATCATACACTA GTGCTTAGCTTCTTATGTAAGATTTTAAATTTATTATTGAATAATTTCCATTTTTT ATCATTAAGATTAAAGTTTGATTAAATTAACCTACATGACATGTTTTTAAATTTTAA TTGTACCAAAGTAGTACTTTTTACATCTTTTATTCAATATTTAACTTTACAAGTAAT TTTCAGTTTATTTTCTAATTTCTATTCTAGATTCTGTTATCTAAATATACTTTATGC AAGCATAGTCAGCTATGACTAACTTAGGACCTCTTGCTATTCAATATTAGCACTAC ATATGCCTGTCTTCCAAAAACAATCTATCCACCACAGTTTTCTTTTTTGGCAGACA TTTTCTCCATCTTTTGGACTGACTTACATCTGACCTTCCCACTTGGATTGCTCT GCTCTGTTTCTGTTAACTGTGCTTCAATTTTCCAAGGTCACTTGAATTCTGAATC AACTTTCGAAGGAGTTGTCTATTTTCTTTTCACTTGCCTCAACATACTTGGC T
Mouse CPS1 RR40_v1 SEQ ID NO:87	TCCCTTTAGCAGGATATTTGATATAATAAATCTGACACCTTCTGGGCCCTCCTGTTT CCAAGGGAATTTGATCTAGGAAGATGTGTTTCAGATTCTCGGAACTGGAATAATG CTTTCACAACTTTAAGTTTCATTATCCTAAAAATGTTATCGCAGCTCGCCAGGAAAG GAACGCACAATTATTTCTCCCTCCAATGTCGAAGGTTGAGAATGGCATTATTATAA GGCATGAGTATTGTTGTTGTTGCTGCTGCTGCTGCTGCTGCTGCTGCTGCTGCTGTT CTTGTTCTTGTTGACGTGGTTATGGTAGTGAGATGGAGTTGGTGGTGGTGGTGGTTTA TAAAGACTTTTTATTTTAGAAAATCAATGCTATGAAAGGAAAATGAGAATAAGCTA GAAAGGAAGGACAATAAAAGGAGAAAAGAAAAGAGAAGGCGGCAGACTGATCTCTG AACTCTACTAACTGCTAACAATTAGTCAAAGAACCTCCTTGGATATCAAAATTTCTG ATATAGCTTTGAGTATTGGAGAATTGGTTGGTTTCTTTTTTCTGGTATTGTTCACTTG ATGTCATTATCCTTAACCTGCTCTTGCTTCACTAAGATCATTCACAGCTCAGAAG AATTAATATATATTCCCATCAATTGATTCTGGGTTGGAAAAATAAAAGTGTCTT AAAAACTTCAGGAAATTCAAAAGCAAAGCAAGGATCATTTTTTTAAAAAGTTAAAG ACTGTGAAAAGATTTCAAATGTTGATTTAAAGTTACCTGACTAACTGGGCATT TGGCGGGTGGGCTGTAAAACTCAACACTTGAGAGATGGGAAGGCCTGAAGTTC AAGGCCAGTCTTTAGCTGCTACATAGTAAGTTTAAAGACTAACTGTGCTATGTTAG ACCTTGCTCAAAAAATGAAAAGCAAATGTTATTGTGGTGAGAAGCTGAGGCTGAA GTAGTGTCTAGGAGTCTGACAAAAGAATGATTACACATGTTTAAAGAGCAGGG GAAATGACATAATCAAAGTACTGTGTTAGTATAAATCGTACATTAACGTGTGCTT GGAAAAGGGCTTTTCAAATGTGAATAATAATTATGTTAACAATGGTAAATGCATT TTAAATTATTAATATTCTGACTCAGTCACTTGGCCATGTCTGGTTTCTACAATTG

[illegible]

	CCAAATACTCATGAAACAACAAATCTTTAGCTCTTATCCACCTAACAAATATACC ACAATATAATTACTACTTGACAGAGAGAAAAAGTAAAGGTTTCATACCAGATTATGTT AAAGTTATAGGGATTTGTAATCAATTTTCTCAAGATCTCCTCATCAGAATCCAATG AGTCACTCAGCTCACCAGTGTCTCTTTTCCAAATCTTGACTGTGAGCAGCTAAG AAAAGATGAGCCACATCAGAATCAAGGCAAGCAAAGTTTGTGACTGTTCAAGCTTA GACTCAGGATGGCTGGAACAAGACTTCCATGTCCAAGCCCCAAGTCAGGACAGTC CTTTTTTAAAGCAGATTAATCTTTTCTTCAGACTTGAAAACCTCTGTGCTATGTCTA GGAAAGTAACTACTCCGCTACCTTGATACTGAACTCTGTGTTTCTCCCAGACCTAA GATAAGACACCTTTCTTTATCTCCTCTGGGGAAAGAAAATGGCTTCAAAGTCCAGT CCAGGAGACAAGCCATACGGCAATGCCAATAGTATCAGAGGCCTTGTTGGATCAC CTGACTTAGAATTACTATAGGAGGCAATGTAACAAACACTTCAATTTTTAAAAATC CAAAATTAGCATATTTCTTAGTAAAAATGGTCACGAATGTCTTACAGAATGTCAC TATTAAGTGACAACCTATTGGTTTGCACATTAACCTAATGCTTCTGGATGATTTAACCA ACAGAAATGTGCTACAACCTTACAACCTTTAATCTC
Mouse CPS1 RR41_v1 SEQ ID NO:88	TTGGTCATACTTGGAAGCGGGTGTGACGGTGTAGAATGAGGTGGAGAGAGTGG GCTGGGCAAGATCCAGCAAGACAGAAAGCACACCCGAGAGTGGAGGTGCAAAGA ACAGATTTTCAGAGCTCAGAAGGGTTTATGCCATCACGTAAAGTTAAGATGATACAA CTTAAGTAAATGTCAAAAAATGAGGGATGAAAGTAATTCTGACTTTACTTTTGGTA TTACATTTAAATTTAAAAATAACAACAATATTCAAATAGCAGGGAATTATACTGGC TATCTTGTTTTGTAAATTCAGATCAGGTAAATTGGATTGAGACTTGACCAGACTTAA CTACAATAGCAAAATCATGTTCTCACTGTTTCTATCTTATACCTTATTGTTTATAATT TTTCATTCCAAAGCCACAGGATCTGAGTACTTTAGTCTCACTGAATCTTATATTG TTTGGAAATAAGATGTAGAGTAACATAAAAGAATTTCAGGAAATGCTTACTAAGAAA TGCTAGGATATCAATCAATATATATCAGGAAACAGTATTGGCTTTAACTAAAAATG ATTTCAGAAATTCACAACATCTAAGTGCCTTACCTACATTTTTAGAAGGCAAAT AGTATAAATTATATAGATAGTTTTAGATAGATTAAAAAATAAACCTTTAAAAATAGT TTTCTGGTTCTTTGTTTTGTATATATAAAAAATCTGGCATCTGGATAAATATAGAGT CATCTCGTTATTTATGAGTTATTCAGTACTAAATAGCCTTTAGTAAAGTTTTAGT TTAGCTTTTCTTTAAAAAGGAAAAAAGGGTCAATCTAGACCTGAGTTCCACATAAT T
Human CPS1 RR89_v1 SEQ ID NO: 89	TTCTTATCAAATACCTTGTCATTGCAACAACCTGTAGTCCATAAAAAACATAAGGA CTCTTTGATCTAACCCTCTACTAAGTCCTTCTACTAAAATGTATAGAATGGAATTTT TTTTTAAATATCCAGTTTTTGCTTTAAAATGTTTCAGTTAATGGTTTAAATTTAAAA CTTTAAAGATTTTTGAGAATTGTTTCATGTGTGACAATCACATAATTTGTCAAGTAAA CAGTCATCATTTGCATATACAGATGACAAAACTTAGGTTTCAGAGAATATGTGAC TTGTCCAAGAACAGGGCATTAGGAAATGCATAACAGGGGTTAGATTCCAGATCTTT TTGTGCCAATCCAGAGTATATCCCCTATTACACTGTTACAGCCTGCTGAATGTAA TAATGAGTGCTGAACATTTTCAGTACTAATGGAAAAAGATTATGGTATCTAAAACT TTTTAGTATTTAGTATTTATGGTTGTTGATCATTTATACCTTGATATCAACTTTCT TTAAAAATATAGAGCACCTTGAAATTCCTTCTCTTCTGTAAGTAAAAATACAACCTG TGCCGATTGGCAAAGCACTCTATAAAATATTAGCCGCTGACAAATACCCAGGGAAG GGCCACATAAAATTATAAGTGCCTCATTGCTGTCGTCAAACCCACCGTCTCTGTCA TCAAAGAGAGAGGAAAAAGCAAACCTCTAAATATGTCGAAAAAGCAACCCAATTTA CAGGGCAATGATTATAGATGTGACTACAGGGTGTCTTTCCCAATCCATTTACCATCT ATAACTGGACATAATGCTACTAACCCTTTAAAGTGACTGTTCTCAGTGCCCTTCACTG ACCATATGTAACTACATCCTAATGATTTTAACTATCTTTAAAAATATGATGTCCATC TAAAAATAGTAAATTTGGATATATTTTTCTAAGACAGTTGAGTTTTTAAAGTGAAG GCAGGAAGAAAAGTAGATAGAGGACTATTTCAACAATACTGAATAATAACACAAG TCCCTTGGGCTGTTCTATGGAATTTAATTCATATTGTGAAGTTCAAGAACTTCT ATTTTTGTGCTTGGCATTCTCCAAACTCTGGCCAGTAATGATTGAGTGTGAGTA ATGGCTTTTACACCATGAAATGATGGCTTAGTGCTCCTACAAATTTGTCAATCTTAG CTGTGCACTGTGACAGACCCTTGAAACAGATCTGTCACCATGAGCTAGAAGTCTT TCACAGTAATCCATCCACATAATTAGACCATTTTGTGCGTGGTTGTGATTGTGGTGGT GGTTGTATGGAGCACTTATTGTGATCTTGGAGAATTGGATTCTAATTTCAATCATAT CTGTGCCATTTAAGTAAGTACTCAATTCGCGGTTTCTGGGGTCTGATGAAGATGC

	ACCTATCCTTACCTACATACCTACCTTCTCACAGAGTGAGAAGAAGATATTCCAAG TCACCCAACTTTGAAGTATTAGATGGCACATATAATCATAGGGGATAACTTTTCATT ACTATTGATTTTCTCTGAACTGATACATGAGTACCTTGAGGTATTACTAACAATAAA TTCTCATAGTTTACATCTAGTTACAATGTCTTTGATGTTAGTTTAGAATATTCTCCTT TCCCATTCTTTTGCTATAATTAAGCTAAATTCAAGAAAATATATATACTAGACATA ATGCCACTAACCTTTAGTGACTGCTCCAGTGCCCTTTATGGCCATTATGTAACTAC ATCCTAATGATTTTAACTATCTTTAAACATGATGTCCATTTA
Human CPS1 RR90_v1 SEQ ID NO: 90	TTATGGTATTGCTGTTGAATCATTATCTACGTAACTATTTGCACTTCAGAAAAAG TAGAGGCCCCACATGTTTTTTTTCCATTTTCACCAAGGCCTAAGGCTATATAACATA CGTGCTTTCTGGCTTACCTGATGTTTCTAAGCTATTAGTTTCGCCTCAGTACTCATCCT CTAAAAAATAAACTCTGAACTAAGCACTGAAAAGTAGAAAAGCCTAAAGCCAGAAT TTATTTTCAGGTAATTATTGTGTAGATAATATGGTAAAAAGTTAAAAATCAAGTAAAT GAAATCTTATTCTTTTATTCTTGAATTACACTATTAAGATATGGATTTTGAATTT TAGAATTTTCAGCACAATTTGTCTTTGAAATATTTTCATGAGACTTCTCTGCAGTTACA AGGCCTAACACTTCAAAATTTCTGAAGCACTGTAAACAGCAGTAATCAATTAGGCCTT ACCACATTCTCAGTTAATAATCTTACAACATTCCAAGTTAATATTAAGTCATCGGTC TTTGGTTAAACATAAAGCCAATGTTAAGGGGACAAAATCAAAAGGTTAATTTACTTA AGTACTTTTATGTTTGAACATTTATAAACAAAAGATTAAAGATTTATGAATCATTTTT ATTCTAATAAGGTTTCTCATTGTAAATAAAATACAGCATTATAAAAAATTTTCATTAC AAAGTATGTTCAATAAAGTGTAGGTTTATTAATATGCCTTACTGAGCATCTGCTATGT GGCAAGTTGTTCAGAATCCTGGAGGAACCTACATATCATAAGCTAATTTTTACTGT ATGGTGGTGATAAATTAAAAATGGTCTTATATTTCAGTCTGCATTATAGAAGAACT TAGTAAAAATCTTTCATAATGTAGCAACCCTATTGATTCATTTATGAGAACTTCAAA TTAGTCAGTTACCTCCCTATGAAATTTAAAAAGATCAATGTATAGCATTTAACAAGTT GAAAAAATAAAAAAGCAAACAGAGTAGCCTTGAAAATATTTTTATAAGTTCAACT CATTTAGATCACATGAAGAAAATCAAAATGGAAGCTAAAGATCCCTAGGGCTAAGG AGCCTAACACAAACTTTGACCTTGGCCCGCGCAGCTTTTTTCGGGCCTCCGTCATTG CAAAATGCCCCAGGAAATACAAATCCCATCAAGGGCAGTCAGCGTAGCATACCAAA CTCCTCCTGAAGGCTTGAAGTGAATTCTAGCATGCCCATTCGCTAAGAGATACTGA AACTTTCTACAGCACCCCTCAATTTTTTGGAACAGGTTGGAAATATGAAGAAAGTC TAATACAGATGTAAAGGCAGAGGAATAGTCTCCATTTCCATAGCAATAAGACCTAA TGTCACCTCTAGATCGTCAGAAAGTCTGGCTAGACATGAGCAAATTTGGAATGAGGG AGAGGAAAGCACAGGTCAAGATTAGTACTAGTCCCTTGGGCAGTTCTACAGCCAG AATGCTTAGCTTCTGACCCAAAGCTGGGACTAGGGTACTGAGTGATGTGCTTAGGG CCTAACTCTCAAAGAGATACACCATGACACTAACAGTGACAGCCTCCTTAAATTTT GCATCTCAGGTACCTCACTCACTTAACCTAGTCTAGGACATTTAAACTATAGTTTTT TCAAGAGTTTTATGTCAAGAAGCTCATAATGTCAAGGCGTTGTTGGTGACTAATAA ATGAATCTATATTTTAGAAAAATGGGGATATAAAAAATGGAAAAAATTAATGTT CAAAAGAAAGGCCATCTCCCAATTAGAGAAATTGTCATGCCAAAAGTATGTAAA GTTGTCCATCAGGCAAACTAATTCTGCAACAGCTCATTGCGGACTGAACACAATTA ATATTTCAAAAATGTAGTTTGCCATAGATGAAATCCGTCCTAAAAATGTGTCTATAT GTAGTAAAAGTCCCAATAAAATAGTTATTCTTAAAAGTGTGTGATAACCCCATCCCC ACTCTTACATCTAACGTGTACAGAGGCTCCAATATGATAATGAGTTATATTTCTGT GACTATCTTTAAAGCTACTACAATGTAAGTAAATTATTCTAATTGTAGGAGTTTTTA TAGTTGCCAATTTCTAATCAAATGACAATAGCTCCTCAAGACGGAAGTAAATAGAT ACTTCTATGTGAAAATCAGAATATAAAATCTTAAAAATGAATGCCTTTCAAAAGAA ATAATGACTACCAAGTGCTCATTTCGTAGCTGAAGTATCAGAGAGGACACTTGGATTG TTAGGTTCTAGCTTAATTATAACACAGGTCACCATTTGTTAAAAAATGAGTGGATT AATGTTAGAAGGAGTACTTATTGAACACTTTTCTATTTCATAGGGAAGTAAAGCTTTA CAATTAATACTTTTGATTTCCAAATTCAT

[0102] The present disclosure describes ASOs that increase the amount or stability of the target regRNA, thereby to increase expression of the target gene. This is different from the

ASOs previously described that were designed to inhibit eRNAs (see, *e.g.*, PCT Application Publication No. WO2013/177248 and PCT Application Publication No. WO2017/075406). Without wishing to be bound by theory, it is hypothesized that the ASOs' ability to upregulate regRNAs is attributable to the selection of a target sequence in the regRNA and/or the chemical modifications of the ASOs.

Sequences of ASOs

[0103] As disclosed herein, ASOs that bind a sequence closer to the 5' or 3' end of the target CPS1 regRNA are more likely to upregulate the regRNA. Without wishing to be bound by theory, it is hypothesized that such ASO hybridizes to a terminal portion of the target CPS1 regRNA and prevents or slows 5'→3' and/or 3'→5' RNA degradation without blocking the functional region of the regRNA. In certain embodiments, the ASO disclosed herein is complementary to a sequence in the target regRNA that is no more than 300, 250, 200, 150, 100, 50, 40, 30, 20, or 10 nucleotides from the 5' or 3' end of the target regRNA. In certain embodiments, the ASO disclosed herein is complementary to a sequence in the target regRNA that is no more than 300, 250, 200, 150, 100, 50, 40, 30, 20, or 10 nucleotides from the 5' end of the target regRNA (*i.e.*, the 5' most nucleotide of the regRNA sequence forming a duplex with the ASO is no more than 300, 250, 200, 150, 100, 50, 40, 30, 20, or 10 nucleotides from the 5' end of the target regRNA). In certain embodiments, the ASO disclosed herein is complementary to a sequence in the target regRNA that is no more than 300, 250, 200, 150, 100, 50, 40, 30, 20, or 10 nucleotides from the 3' end of the target regRNA (*i.e.*, the 3' most nucleotide of the regRNA sequence forming a duplex with the ASO is no more than 300, 250, 200, 150, 100, 50, 40, 30, 20, or 10 nucleotides from the 3' end of the target regRNA).

[0104] In certain embodiments, the ASO is no more than 25, 30, 40, 50, 60, 70, 80, 90, or 100 nucleotides in length. In certain embodiments, the ASO is no more than 8, 10, 15, 20, 25, 30, 35, 40, 45, 50, 55, 60, 65, 70, 75, 80, 85, 90, 95, or 100 nucleotides in length. In certain embodiments, the ASO is at least 8, 10, 15, 20, 25, 30, 35, 40, 45, 50, 55, 60, 65, 70, 75, 80, 85, 90, 95, or 100 nucleotides in length. In certain embodiments, the ASO is at least 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 in length.

[0105] In certain embodiments, the ASO is designed to lack a stable secondary structure formed within itself or between other identical ASO molecules, thereby increasing the amount of the ASO in a single-stranded form available to hybridize with the target regRNA. Methods to

predict secondary structures are known in the art (see, *e.g.*, Seetin and Mathews, *Methods Mol. Biol.* (2012) 905:99-122; Zhao *et al.*, *PLoS Comput. Biol.* (2021) 17(8):e1009291) and web-based programs (*e.g.*, RNAfold) are available to public users.

[0106] For example, ASOs have been designed to target a human CPS1 eRNA. The nucleotide sequences of these ASOs are provided in **Table 2** below.

Table 2. Exemplary ASO sequences targeting regRNAs

Name	Sequence	SEQ ID NO
hCPS1-ASO-1	TGCAGGCACACACATCAGGC	1
hCPS1-ASO-2	ATGCAGGCACACACATCAGGCT	2
hCPS1-ASO-3	AATGCAGGCACACACATCAGGCTG	3
hCPS1-ASO-4	GCACACACATCAGGCTGGGG	4
hCPS1-ASO-5	AATGCAGGCACACACATCAG	5
hCPS1-ASO-6	TGAATGCAGGCACACACATC	6
hCPS1-ASO-7	GGGACCCTGTGTACTTGGA	7
hCPS1-ASO-8	GCAGAGTGACAGGCATGAAT	8
hCPS1-ASO-9	TGCCATTGACTTGCATAATG	9
hCPS1-ASO-10	GTCAATGCTCAGAACATAGT	10
hCPS1-ASO-11	TAGATAATAACCCACCACAC	11
hCPS1-ASO-12	GTCAAGTACTAGGTTGTATT	12
hCPS1-ASO-13	TTAGCCTGTGAAATCCCTCA	13
hCPS1-ASO-14	CTTATGAGTCACTCTCTGAT	14
hCPS1-ASO-15	TCTTTGTGAGCCAGGTCATC	15
hCPS1-ASO-16	CGCAGCTGAGCAGAGTGACA	91
hCPS1-ASO-17	CAGTCCTCCTTCATATAAGC	92
hCPS1-ASO-18	TGACCACATGTACACAGTCC	93
hCPS1-ASO-19	GTTACACTTTTAGGACAGAT	94
hCPS1-ASO-20	GGTAGGGAATGTTAAAGTCA	95
hCPS1-ASO-21	TATAAGAGTTGGTTGGTAGG	96
hCPS1-ASO-22	CAAAGGAGTTGAGGCTATAA	97
hCPS1-ASO-23	GGGAGTTTACATTAGGATAG	98
hCPS1-ASO-24	GGCTAGACTGAAATCTATAA	99
hCPS1-ASO-25	GCTAGTTTCATACTTGAGTG	100
hCPS1-ASO-26	CACAATGGAGGTTGGAACAG	101
hCPS1-ASO-27	TCCATCAATTATAATTCCAC	102
hCPS1-ASO-28	ATTAGAGACTTGGAATCC	103
hCPS1-ASO-29	GGTCCATGTCTTAGTCATC	104
hCPS1-ASO-30	AGACTTGCAAACACGGTGT	105
hCPS1-ASO-31	TTTTATCAGTAAAGGGTCCC	106
hCPS1-ASO-32	AGTCTAGAGAGAAATGTGGG	107
hCPS1-ASO-33	GGATAGAATTCTCCTACTCT	108
hCPS1-ASO-34	CAACAATCAACAATTCTAGG	109
hCPS1-ASO-35	TTCCATAGAAATGTCAACAA	110
hCPS1-ASO-36	GACTACAAAGCATGATGAAT	111
hCPS1-ASO-37	CATTTATAGCAGTTGACTAC	112
hCPS1-ASO-38	GCTTGACCAAGGAAAAGACT	113
hCPS1-ASO-39	GTGGAAGTACTGAGGAGTCC	114
hCPS1-ASO-40	TAATCAAATATGACAGTGGA	115
hCPS1-ASO-41	CCTCCCTTCATCACTTATGT	116
hCPS1-ASO-42	ACTATAATATATTCTCTCCC	117

hCPS1-ASO-43	CCCTAAGGTACCCATGCAAT	118
hCPS1-ASO-44	GTCATAGTCCCATTACCCTA	119
hCPS1-ASO-45	GGAAACTTTTATAGGATGCAA	120
hCPS1-ASO-46	CCTCATTATGGAAACTTTTC	121
hCPS1-ASO-47	CGATATAAACTCAATCCTCA	122
hCPS1-ASO-48	GTAGTGAGGGTTGTCTTCC	123
hCPS1-ASO-49	CTCTTGCTTTTTATGTGTG	124
hCPS1-ASO-50	CGCCTTGATCTCACCTCTTG	125
hCPS1-ASO-51	GTCCAATACTAGTTACGCC	126
hCPS1-ASO-52	AGTACTTACTGGCTTAGTCC	127
hCPS1-ASO-53	CTAGAGAACTGAGGACTGAG	128
hCPS1-ASO-54	GGAAAACTCCCAACCTAGAG	129
hCPS1-ASO-55	AAATGAATTGGAGGAGAATG	130
hCPS1-ASO-56	GGCGAAATTTGTGTTGAAGA	131
hCPS1-ASO-57	TTGAACAAGAAATAAAGGCG	132
hCPS1-ASO-58	GTATTCATAATAGTCATGGA	133
hCPS1-ASO-59	TCAGCCTTCATCCATAAATA	134
hCPS1-ASO-60	TATGCCTTAAAAATGTTGAGC	135
hCPS1-ASO-61	CATGGGAGACTTAGTATGCC	136
hCPS1-ASO-62	TGAAAAGGTACCATATCATG	137
hCPS1-ASO-63	GTATAGAATGGGAAAATGAA	138
hCPS1-ASO-64	AGCCTAGATGCAGGGTATAG	139
hCPS1-ASO-65	ATGAAGTCATGTGGTATATT	140
hCPS1-ASO-66	GCCGTGGCATGAGCAATAGC	141
hCPS1-ASO-67	TGCAAATTCACCAAGTAGAT	142
hCPS1-ASO-68	TGTGTTATACTGAAGGATGC	143
hCPS1-ASO-69	GCATAGAATTATGTTGAGCT	144
hCPS1-ASO-70	AGATCAAGTTCCTGTGCAT	145
hCPS1-ASO-71	CTGGTGCCATGAAAGTTGCC	146
hCPS1-ASO-72	GGCTCATACTAGTTTATACA	147
hCPS1-ASO-73	AAGCTAAACAAAATAGGCTC	148
hCPS1-ASO-74	CATGGCTCCTGGTGATAGAA	149
hCPS1-ASO-75	GATTTCAAAGTGCTTCATGG	150
hCPS1-ASO-76	AGTCCTCACGCTTACTTAAT	151
hCPS1-ASO-77	CAGGCACACACATCAGGCTG	152
hCPS1-ASO-78	GCAGGCACACACATCAGGCT	153
hCPS1-ASO-79	ATGCAGGCACACACATCAGG	154
hCPS1-ASO-80	GAATGCAGGCACACACATCA	155
hCPS1-ASO-81	TGCAGGCACACACATCAGGC	156
hCPS1-ASO-82	TGCAGGCACACACATCAGGCTG	157
hCPS1-ASO-83	CAGGCACACACATCAGGCTG	158
hCPS1-ASO-84	GCAGGCACACACATCAGGCT	159
hCPS1-ASO-85	ATGCAGGCACACACATCAGG	160
hCPS1-ASO-86	TGCAGGCACACACATCAGGC	161
hCPS1-ASO-87	TGCAGGCACACACATCAGG	162
hCPS1-ASO-88	TGCAGGCACACACATCAG	163
hCPS1-ASO-89	TGCAGGCACACACAT	164
hCPS1-ASO-91	TGCAGGCACACACATCAGGC	166
hCPS1-ASO-92	CAGGCATGAATGCAGGCACA	167
hCPS1-ASO-93	ACAGGCATGAATGCAGGCAC	168
hCPS1-ASO-94	GTGACAGGCATGAATGCAGG	169
hCPS1-ASO-95	AGTGACAGGCATGAATGCAG	170
hCPS1-ASO-96	GAGTGACAGGCATGAATGCA	171

hCPS1-ASO-97	AATGCAGGCACACACA	172
hCPS1-ASO-98	TGAATGCAGGCACACA	173
hCPS1-ASO-99	CATGAATGCAGGCACA	174
hCPS1-ASO-100	TGCAGGCACACACATC	175
hCPS1-ASO-101	CAGGCACACACATCAG	176
hCPS1-ASO-102	GGCACACACATCAGGC	177
hCPS1-ASO-103	CACACACATCAGGCTG	178
hCPS1-ASO-104	CACACATCAGGCTGGG	179
hCPS1-ASO-105	TGCAGGCACACACATCAGGCTTTTTTTTTT	180
hCPS1-ASO-106	TTTTTTTTTTTGCAGGCACACACATCAGGC	181
hCPS1-ASO-107	ACATTACTTTAAATGATTAC	182
hCPS1-ASO-108	GATGTTATTACAAAGTTCTT	183
hCPS1-ASO-109	GGAGGCAATATTATGTTAAA	184
hCPS1-ASO-110	GCATAATGCTTTTTGGAGGC	185
hCPS1-ASO-111	CTTGCATAATGCTTTTTGGA	186
hCPS1-ASO-112	ACTTGCATAATGCTTTTTGG	187
hCPS1-ASO-113	GACTTGCATAATGCTTTTTG	188
hCPS1-ASO-114	CCATTGACTTGCATAATGCT	189
hCPS1-ASO-115	GCCATTGACTTGCATAATGC	190
hCPS1-ASO-116	TCTAGCATTATGTCAATGC	191
hCPS1-ASO-117	CTCTGTAAACACTAAAAGTAT	192
hCPS1-ASO-118	TCTCTGTAAACACTAAAAGTA	193
hCPS1-ASO-119	ATCTCTGTAAACACTAAAAGT	194
hCPS1-ASO-120	GATAATAACCCACCACACAA	195
hCPS1-ASO-121	GAAATGTGGAATAACAGAAT	196
hCPS1-ASO-122	ATGTCAAGTACTAGGTTGTA	197
hCPS1-ASO-123	CCTTATTGACATATCTGGTA	198
hCPS1-ASO-124	TCAGGGCACTTTATTTTATG	199
hCPS1-ASO-125	GAAATCCCTCAGGGCACTTT	200
hCPS1-ASO-126	TGAAATCCCTCAGGGCACTT	201
hCPS1-ASO-127	GTGAAATCCCTCAGGGCACT	202
hCPS1-ASO-128	TGTGAAATCCCTCAGGGCAC	203
hCPS1-ASO-129	CTGTGAAATCCCTCAGGGCA	204
hCPS1-ASO-130	GCATTTAGCCTGTGAAATCC	205
hCPS1-ASO-131	TAGAAGCATTTAGCCTGTGA	206
hCPS1-ASO-132	GTCTTCTTTTCTATTAATAC	207
hCPS1-ASO-133	AGTCACTCTCTGATAAAATG	208
hCPS1-ASO-134	GTGAGCCAGGTCATCAAAGG	209
hCPS1-ASO-135	TTTGTGAGCCAGGTCATCAA	210
hCPS1-ASO-136	CATTCTTTGTGAGCCAGGTC	211
hCPS1-ASO-137	GGAAGTACATTCTTTGTGAG	212
hCPS1-ASO-138	ACTTGGAAGTACATTCTTTG	213
hCPS1-ASO-139	GTGTACTTGGAAAGTACATTC	214
hCPS1-ASO-140	GACCCTGTGTACTTGGAAAGT	215
hCPS1-ASO-141	TGGGGACCCTGTGTACTTGG	216
hCPS1-ASO-142	ATCAGGCTGGGGACCCTGTG	217
hCPS1-ASO-143	ACACATCAGGCTGGGGACCC	218
hCPS1-ASO-144	GGCACACACATCAGGCTGGG	219
hCPS1-ASO-145	ATGAATGCAGGCACACACAT	220
hCPS1-ASO-146	AGGCATGAATGCAGGCACAC	221
hCPS1-ASO-147	TGACAGGCATGAATGCAGGC	222
hCPS1-ASO-148	AGAGTGACAGGCATGAATGC	223
hCPS1-ASO-149	GAGCAGAGTGACAGGCATGA	224

hCPS1-ASO-150	CAGCTGAGCAGAGTGACAGG	225
hCPS1-ASO-151	TGCACGCAGCTGAGCAGAGT	226
hCPS1-ASO-152	TGTCTGCACGCAGCTGAGCA	227
hCPS1-ASO-153	AAGCTGTCTGCACGCAGCTG	228
hCPS1-ASO-154	ATATAAGCTGTCTGCACGCA	229
hCPS1-ASO-155	CCTTCATATAAGCTGTCTGC	230
hCPS1-ASO-156	GTCCTCCTTCATATAAGCTG	231
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hCPS1-ASO-182	CTTGAGTGTTCAGGCTAGAC	257
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hCPS1-ASO-196	CCACAATGGAGGTTGGAACA	271
hCPS1-ASO-197	TCCACAATGGAGGTTGGAAC	272
hCPS1-ASO-198	TTCCACAATGGAGGTTGGA	273
hCPS1-ASO-199	ATTCCACAATGGAGGTTGGA	274
hCPS1-ASO-200	AATTCCACAATGGAGGTTGG	275
hCPS1-ASO-201	TAATTCCACAATGGAGGTTG	276
hCPS1-ASO-202	ATCCATCAATTATAATTCCA	277

hCPS1-ASO-203	AATCCATCAATTATAATTCC	278
hCPS1-ASO-204	AAATCCATCAATTATAATTC	279
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hCPS1-ASO-212	GACTTGGAAAAATCCATCAAT	287
hCPS1-ASO-213	AGACTTGGAAAAATCCATCAA	288
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hCPS1-ASO-222	TATTCTGAATTAGAGACTTG	297
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hCPS1-ASO-225	ACGGTGTGTGTGTGTATATA	300
hCPS1-ASO-226	AACTACGGTGTGTGTGTATA	301
hCPS1-ASO-227	TGCAAACACTACGGTGTGTGTG	302
hCPS1-ASO-228	GACTTGCAAACACTACGGTGTG	303
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hCPS1-ASO-230	CCAGATGCAGACTTGCAAAC	305
hCPS1-ASO-231	GGTCCCAGATGCAGACTTGC	306
hCPS1-ASO-232	AAAGGGTCCCAGATGCAGAC	307
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hCPS1-ASO-251	GTACCCATGCAATGAATACT	326
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hCPS1-ASO-319	GTTAGATCAAAGAGTCCTTA	489
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hCPS1-ASO-323	GATGACTGATTTACTTGACA	493
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hCPS1-ASO-413	GACAAATTGTGCTGAAATTC	583
hCPS1-ASO-414	CCTTGTAAGTGCAGAGAAGT	584

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hCPS1-ASO-460	TAATCTTGACCTGTGCTTTC	630
hCPS1-ASO-461	GGACTAGTACTAATCTTGAC	631
hCPS1-ASO-462	ACTGCCCAAGGGACTAGTAC	632
hCPS1-ASO-463	AGCATTCTGGCTGTAGAACT	633
hCPS1-ASO-464	TTGGGTCAGAAGCTAAGCAT	634
hCPS1-ASO-465	CAGTACCCTAGTCCCAGCTT	635
hCPS1-ASO-466	GCACATCACTCAGTACCCTA	636
hCPS1-ASO-467	CTTTGAGAGTTAGGCCCTAA	637

hCPS1-ASO-468	TAGTGTCATGGTGTATCTCT	638
hCPS1-ASO-469	AGGAGGCTGTCACTGTTAGT	639
hCPS1-ASO-470	GAGTGAGGTACCTGAGATGC	640
hCPS1-ASO-471	CTAGGTTAAGTGAGTGAGGT	641
hCPS1-ASO-472	GTTTAAATGTCCTAGACTAG	642
hCPS1-ASO-473	GAGCTTCTTGACATAAAACT	643
hCPS1-ASO-474	CAACGCCTTGACATTATGAG	644
hCPS1-ASO-475	TAGTCACCAACAACGCCTTG	645
hCPS1-ASO-476	AGATGGCCTTTCTTTTGAAC	646
hCPS1-ASO-477	TCTAATTGGGAGATGGCCTT	647
hCPS1-ASO-478	GCAATACTTCTCTAATTGGG	648
hCPS1-ASO-479	TACTTTTGGCATGCAATACT	649
hCPS1-ASO-480	GATGGACAACCTTTACATACT	650
hCPS1-ASO-481	AATTAGTTTGCCTGATGGAC	651
hCPS1-ASO-482	GAGCTGTTGCAGAAATTAGTT	652
hCPS1-ASO-483	AGTCCCAAATGAGCTGTTGC	653
hCPS1-ASO-484	TTAATTGTGTTCAAGTCCCAA	654
hCPS1-ASO-485	CATCTATGGCAAACCTACATT	655
hCPS1-ASO-486	GGACGGATTTTCATCTATGGC	656
hCPS1-ASO-487	TATAGACACATTTTAGGACG	657
hCPS1-ASO-488	GGTTATCACACACTTTTAAG	658
hCPS1-ASO-489	GTACACGTTAGATGTAAGAG	659
hCPS1-ASO-490	TATTGGAGCCTCTGTACACG	660
hCPS1-ASO-491	CTCATTATCATATTGGAGCC	661
hCPS1-ASO-492	GTCACAGGAAATATAACTCA	662

Table 3 provides additional chemical modifications of selected hCPS1-ASOs.

Table 3: Additional Chemical Modifications of selected hCPS1-ASOs		
Key: MOE (M); DNA (d); LNA (L); PS (=); PO(-); 5-MethylCytosine (5C); GalNAc (ag); Teg-GalNAc (TEG); BioTeg (BioTEG); cET (c); AlaGal-GalNAc (AlGal); cholesterol (CholITEG)		
SE Q ID NO	Name	Sequence
16	hCPS1-ASO-1a	MT=.MG=.M5C=.MA=.MG=.dG=.dC=.dA=.dC=.dA=.dC=.dA=.dC=.dA=.dT=.M5C=.MA=.MG=.MG=.M5C
17	hCPS1-ASO-1b	MT=.MG=.M5C=.MA=.MG=.MG=.M5C=.MA=.M5C=.MA=.M5C=.MA=.M5C=.MA=.MT=.M5C=.MA=.MG=.MG=.M5C
18	hCPS1-ASO-1c	MT=.MG=.M5C=.MA=.MG=.dG=.dC=.dA=.M5C=.dA=.dC=.MA=.dC=.dA=.dT=.M5C=.MA=.MG=.MG=.M5C
19	hCPS1-ASO-1d	MT=.MG=.M5C=.MA=.MG=.LG=.dC=.dA=.L5C=.dA=.dC=.LA=.dC=.dA=.LT=.M5C=.MA=.MG=.MG=.M5C
20	hCPS1-ASO-1e	MT=.MG=.M5C=.LA=.MG=.dG=.dC=.LA=.dC=.dA=.dC=.LA=.dC=.dA=.dT=.L5C=.MA=.MG=.MG=.M5C
21	hCPS1-ASO-1f	MT=.MG=.M5C=.MA=.LG=.dG=.dC=.dA=.L5C=.dA=.dC=.dA=.L5C=.dA=.dT=.M5C=.LA=.MG=.MG=.M5C

22	hCPS1- ASO- 1g	MT=.MG=.M5C-.MA-.MG=.dG=.dC=.dA=.dC=.dA=.dC=.dA=.dC=.dA=.dT=.M5C-.MA-.MG=.MG=.M5C
23	hCPS1- ASO-2	MA=.MT=.MG=.M5C=.MA=.MG=.dG=.dC=.dA=.dC=.dA=.dC=.dA=.dC=.dA=.dT=.M5C=.MA=.MG=.MG=.M5C=.MT
24	hCPS1- ASO-3	MA=.MA=.MT=.MG=.M5C=.MA=.MG=.dG=.dC=.dA=.dC=.dA=.dC=.dA=.dC=.dA=.dT=.M5C=.MA=.MG=.MG=.M5C=.MT=.MG
392	hCPS1- ASO- 81a	MT=.MG=.M5C=.MA=.MG=.LG=.M5C=.MA=.L5C=.MA=.M5C=.LA=.M5C=.MA=.LT=.M5C=.MA=.MG=.MG=.M5C
393	hCPS1- ASO- 81b	MT=.MG=.M5C=.LA=.MG=.LG=.M5C=.LA=.M5C=.LA=.M5C=.LA=.M5C=.LA=.MT=.L5C=.MA=.LG=.MG=.M5C
394	hCPS1- ASO- 81c	MT=.MG=.L5C=.MA=.LG=.MG=.L5C=.MA=.L5C=.MA=.L5C=.MA=.L5C=.MA=.LT=.M5C=.LA=.MG=.MG=.M5C
395	hCPS1- ASO- 81d	MT=.MG=.L5C=.MA=.MG=.LG=.M5C=.MA=.L5C=.MA=.M5C=.LA=.M5C=.MA=.LT=.M5C=.MA=.LG=.MG=.M5C
396	hCPS1- ASO- 81e	MT=.MG=.M5C=.MA=.LG=.MG=.M5C=.MA=.L5C=.MA=.M5C=.MA=.L5C=.MA=.MT=.M5C=.LA=.MG=.MG=.M5C
397	hCPS1- ASO- 81f	MT=.MG=.M5C=.LA=.MG=.MG=.M5C=.LA=.M5C=.MA=.M5C=.LA=.M5C=.MA=.MT=.L5C=.MA=.MG=.MG=.M5C
398	hCPS1- ASO- 81g	MT=.MG=.M5C=.MA=.MG=.LG=.M5C=.MA=.M5C=.MA=.L5C=.MA=.M5C=.MA=.MT=.L5C=.MA=.MG=.MG=.M5C
399	hCPS1- ASO- 81h	MT=.MG=.M5C=.MA=.LG=.MG=.M5C=.MA=.M5C=.LA=.M5C=.MA=.M5C=.MA=.LT=.M5C=.MA=.MG=.MG=.M5C
400	hCPS1- ASO- 81i	LT=.MG=.L5C=.MA=.LG=.dG=.dC=.dA=.dC=.dA=.dC=.dA=.dC=.dA=.dT=.L5C=.MA=.LG=.MG=.L5C
401	hCPS1- ASO- 81j	LT=.MG=.L5C=.MA=.LG=.MG=.M5C=.MA=.M5C=.MA=.M5C=.MA=.M5C=.MA=.MT=.L5C=.MA=.LG=.MG=.L5C
402	hCPS1- ASO- 81k	MT=.MG=.M5C=.MA=.MG=.MG=.dC=.dA=.M5C=.dA=.dC=.MA=.dC=.dA=.MT=.M5C=.MA=.MG=.MG=.M5C
403	hCPS1- ASO- 81l	MT=.MG=.M5C=.MA-.MG=.dG=.d5C=.dA=.d5C=.dA=.d5C=.dA=.d5C=.dA=.dT=.M5C-.MA=.MG=.MG=.M5C
404	hCPS1- ASO- 81m	MT=.MG=.M5C-.MA-.MG=.dG=.d5C=.dA=.d5C=.dA=.d5C=.dA=.d5C=.dA=.dT=.M5C-.MA-.MG=.MG=.M5C
405	hCPS1- ASO- 81n	MT=.MG-.M5C-.MA-.MG=.dG=.d5C=.dA=.d5C=.dA=.d5C=.dA=.d5C=.dA=.dT=.M5C-.MA-.MG-.MG=.M5C
406	hCPS1- ASO- 81o	MT-.MG-.M5C-.MA-.MG=.dG=.d5C=.dA=.d5C=.dA=.d5C=.dA=.d5C=.dA=.dT=.M5C-.MA-.MG-.MG-.M5C
407	hCPS1- ASO- 82a	MT=.MG=.M5C=.MA=.MG=.MG=.dC=.dA=.dC=.dA=.dC=.dA=.dC=.dA=.dT=.dC=.MA=.MG=.MG=.M5C=.MT=.MG

408	hCPS1- ASO- 86a	MT=.MG=.L5C=.MA=.LG=.dG=.dC=.dA=.dC=.dA=.dC=.dA=.dC=.dA=.dT=.L5C=.MA=.LG =.MG=.M5C
409	hCPS1- ASO- 86b	MT=.MG=.M5C-.MA-.MG=.dG=.d5C=.dA=.d5C=.dA=.d5C=.dA=.d5C=.dA=.dT=.M5C- .MA-.MG=.MG=.M5C-.[TEG]
410	hCPS1- ASO- 87a	MT=.MG=.M5C-.MA-.MG=.dG=.dC=.dA=.dC=.dA=.dC=.dA=.dC=.dA=.dT=.M5C-.MA- .MG=.MG
411	hCPS1- ASO- 88a	MT=.MG=.M5C-.MA-.MG=.dG=.dC=.dA=.dC=.dA=.dC=.dA=.dC=.dA=.dT=.M5C-.MA-.MG
412	hCPS1- ASO- 89a	MT=.MG=.M5C-.MA-.MG=.dG=.dC=.dA=.dC=.dA=.dC=.dA=.dC=.dA=.dT
414	hCPS1- ASO- 91a	MT=.MG=.M5C-.MA-.MG=.dG=.d5C=.dA=.d5C=.dA=.d5C=.dA=.d5C=.dA=.dT=.M5C- .MA-.MG=.MG=.M5C-.[AlGal]
415	hCPS1- ASO- 91b	MT=.MG=.M5C-.MA-.MG=.dG=.d5C=.dA=.d5C=.dA=.d5C=.dA=.d5C=.dA=.dT=.M5C-.MA- .MG=.MG=.M5C-.[TEG]
416	hCPS1- ASO- 91c	dT=.dG=.d5C=.dA=.dG=.dG=.d5C=.dA=.d5C=.dA=.d5C=.dA=.d5C=.dA=.dT=.d5C=.dA=.dG =.dG=.d5C-.[TEG]
417	hCPS1- ASO- 91d	CholTEG- .MT=.MG=.M5C=.MA=.MG=.dG=.d5C=.dA=.d5C=.dA=.d5C=.dA=.d5C=.dA=.dT=.M5C=.M A=.MG=.MG=.M5C
418	hCPS1- ASO- 91e	CholTEG-.MT=.MG=.M5C=.MA- .MG=.dG=.d5C=.dA=.d5C=.dA=.d5C=.dA=.d5C=.dA=.dT=.M5C=.MA=.MG=.MG=.M5C
419	hCPS1- ASO- 91f	CholTEG-.MT=.MG=.M5C=.MA- .MG=.dG=.d5C=.dA=.d5C=.dA=.d5C=.dA=.d5C=.dA=.dT=.M5C=.MA=.MG=.MG=.M5C
420	hCPS1- ASO- 91g	CholTEG-.MT-.MG-.M5C-.MA- .MG=.dG=.d5C=.dA=.d5C=.dA=.d5C=.dA=.d5C=.dA=.dT=.M5C-.MA-.MG-.MG-.M5C
421	hCPS1- ASO- 91h	CholTEG=.MT=.MG=.M5C=.MA=.MG=.dG=.d5C=.dA=.d5C=.dA=.d5C=.dA=.d5C=.dA=.dT =.M5C=.MA=.MG=.MG=.M5C
422	hCPS1- ASO- 91i	CholTEG=.MT=.MG=.M5C=.MA- .MG=.dG=.d5C=.dA=.d5C=.dA=.d5C=.dA=.d5C=.dA=.dT=.M5C=.MA=.MG=.MG=.M5C
423	hCPS1- ASO- 91j	CholTEG=.MT=.MG=.M5C=.MA- .MG=.dG=.d5C=.dA=.d5C=.dA=.d5C=.dA=.d5C=.dA=.dT=.M5C=.MA=.MG=.MG=.M5C
424	hCPS1- ASO- 91k	CholTEG=.MT-.MG-.M5C-.MA- .MG=.dG=.d5C=.dA=.d5C=.dA=.d5C=.dA=.d5C=.dA=.dT=.M5C-.MA-.MG-.MG-.M5C
425	hCPS1- ASO- 97a	cA=.cA=.cT=.dG=.d5C=.dA=.dG=.dG=.d5C=.dA=.d5C=.dA=.d5C=.cA=.c5C=.cA
426	hCPS1- ASO- 98a	cT=.cG=.cA=.dA=.dT=.dG=.d5C=.dA=.dG=.dG=.d5C=.dA=.d5C=.cA=.c5C=.cA

427	hCPS1-ASO-99a	c5C=.cA=.cT=.dG=.dA=.dA=.dT=.dG=.d5C=.dA=.dG=.dG=.d5C=.cA=.c5C=.cA
428	hCPS1-ASO-100a	cT=.cG=.c5C=.dA=.dG=.dG=.d5C=.dA=.d5C=.dA=.d5C=.dA=.d5C=.cA=.cT=.c5C
429	hCPS1-ASO-101a	c5C=.cA=.cG=.dG=.d5C=.dA=.d5C=.dA=.d5C=.dA=.d5C=.dA=.dT=.c5C=.cA=.cG
430	hCPS1-ASO-102a	cG=.cG=.c5C=.dA=.d5C=.dA=.d5C=.dA=.d5C=.dA=.dT=.d5C=.dA=.cG=.cG=.c5C
431	hCPS1-ASO-103a	c5C=.cA=.c5C=.dA=.d5C=.dA=.d5C=.dA=.dT=.d5C=.dA=.dG=.dG=.c5C=.cT=.cG
432	hCPS1-ASO-104a	c5C=.cA=.c5C=.dA=.d5C=.dA=.dT=.d5C=.dA=.dG=.dG=.d5C=.dT=.cG=.cG=.cG
433	hCPS1-ASO-105a	MT-.MG-.M5C-.MA-.MG-.dG-.d5C-.dA-.d5C-.dA-.d5C-.dA-.d5C-.dA-.dT-.M5C-.MA-.MG-.MG-.M5C-.dT-.dT-.dT-.dT-.dT-.dT-.dT-.dT-.dT-.dT-.[BioTEG]
434	hCPS1-ASO-106a	[BioTEG]P.dT-.dT-.dT-.dT-.dT-.dT-.dT-.dT-.dT-.dT-.MT-.MG-.M5C-.MA-.MG-.dG-.d5C-.dA-.d5C-.dA-.d5C-.dA-.d5C-.dA-.dT-.M5C-.MA-.MG-.MG-.M5C
435	hCPS1-ASO-279a	cG=.cG=.c5C=.dA=.dT=.dG=.dA=.dA=.dT=.dG=.d5C=.dA=.dG=.cG=.c5C=.cA
436	hCPS1-ASO-280a	c5C=.cA=.cG=.dG=.d5C=.dA=.dT=.dG=.dA=.dA=.dT=.dG=.d5C=.cA=.cG=.cG
437	hCPS1-ASO-281a	cG=.cA=.c5C=.dA=.dG=.dG=.d5C=.dA=.dT=.dG=.dA=.dA=.dT=.cG=.c5C=.cA
438	hCPS1-ASO-282a	cG=.cT=.cG=.dA=.d5C=.dA=.dG=.dG=.d5C=.dA=.dT=.dG=.dA=.cA=.cT=.cG
439	hCPS1-ASO-283a	c5C=.cA=.c5C=.dA=.dT=.d5C=.dA=.dG=.dG=.d5C=.dT=.dG=.dG=.cG=.cG=.cA
440	hCPS1-ASO-284a	c5C=.cA=.cT=.d5C=.dA=.dG=.dG=.d5C=.dT=.dG=.dG=.dG=.cA=.c5C=.c5C
441	hCPS1-ASO-285a	cT=.c5C=.cA=.dG=.dG=.d5C=.dT=.dG=.dG=.dG=.dG=.dA=.d5C=.c5C=.c5C=.cT
442	hCPS1-ASO-286a	cA=.cG=.cG=.d5C=.dT=.dG=.dG=.dG=.dG=.dA=.d5C=.d5C=.d5C=.cT=.cG=.cT
443	hCPS1-ASO-287a	L5C=.LA=.LT=.dG=.dA=.dA=.dT=.dG=.d5C=.dA=.dG=.dG=.d5C=.LA=.L5C=.LA
444	hCPS1-ASO-288a	LT=.LG=.LA=.dA=.dT=.dG=.d5C=.dA=.dG=.dG=.d5C=.dA=.d5C=.LA=.L5C=.LA

445	hCPS1- ASO- 289a	LA=.LA=.LT=.dG=.d5C=.dA=.dG=.dG=.d5C=.dA=.d5C=.dA=.d5C=.LA=.L5C=.LA
446	hCPS1- ASO- 290a	LT=.LG=.L5C=.dA=.dG=.dG=.d5C=.dA=.d5C=.dA=.d5C=.dA=.d5C=.LA=.LT=.L5C
447	hCPS1- ASO- 291a	L5C=.LA=.LG=.dG=.d5C=.dA=.d5C=.dA=.d5C=.dA=.d5C=.dA=.dT=.L5C=.LA=.LG
448	hCPS1- ASO- 292a	LG=.LG=.L5C=.dA=.d5C=.dA=.d5C=.dA=.d5C=.dA=.dT=.d5C=.dA=.LG=.LG=.L5C
449	hCPS1- ASO- 293a	L5C=.LA=.L5C=.dA=.d5C=.dA=.d5C=.dA=.dT=.d5C=.dA=.dG=.dG=.L5C=.LT=.LG
450	hCPS1- ASO- 294a	L5C=.LA=.L5C=.dA=.d5C=.dA=.dT=.d5C=.dA=.dG=.dG=.d5C=.dT=.LG=.LG=.LG
451	hCPS1- ASO- 295a	LG=.LG=.L5C=.dA=.dT=.dG=.dA=.dA=.dT=.dG=.d5C=.dA=.dG=.LG=.L5C=.LA
452	hCPS1- ASO- 296a	L5C=.LA=.LG=.dG=.d5C=.dA=.dT=.dG=.dA=.dA=.dT=.dG=.d5C=.LA=.LG=.LG
453	hCPS1- ASO- 297a	LG=.LA=.L5C=.dA=.dG=.dG=.d5C=.dA=.dT=.dG=.dA=.dA=.dT=.LG=.L5C=.LA
454	hCPS1- ASO- 298a	LG=.LT=.LG=.dA=.d5C=.dA=.dG=.dG=.d5C=.dA=.dT=.dG=.dA=.LA=.LT=.LG
455	hCPS1- ASO- 299a	L5C=.LA=.L5C=.dA=.dT=.d5C=.dA=.dG=.dG=.d5C=.dT=.dG=.dG=.LG=.LG=.LA
456	hCPS1- ASO- 300a	L5C=.LA=.LT=.d5C=.dA=.dG=.dG=.d5C=.dT=.dG=.dG=.dG=.dG=.LA=.L5C=.L5C
457	hCPS1- ASO- 301a	LT=.L5C=.LA=.dG=.dG=.d5C=.dT=.dG=.dG=.dG=.dG=.dA=.d5C=.L5C=.L5C=.LT
458	hCPS1- ASO- 302a	LA=.LG=.LG=.d5C=.dT=.dG=.dG=.dG=.dG=.dA=.d5C=.d5C=.d5C=.LT=.LG=.LT
459	hCPS1- ASO- 303a	MG=.M5C=.MA=.MT=.dG=.dA=.dA=.dT=.dG=.d5C=.dA=.dG=.dG=.d5C=.MA=.M5C=.MA =.M5C
460	hCPS1- ASO- 303b	LG=.M5C=.LA=.MT=.dG=.dA=.dA=.dT=.dG=.d5C=.dA=.dG=.dG=.d5C=.MA=.L5C=.MA=. L5C
461	hCPS1- ASO- 304a	MG=.M5C=.MA=.M5C=.dA=.d5C=.dA=.d5C=.dA=.dT=.d5C=.dA=.dG=.dG=.M5C=.MT=.M G=.MG
462	hCPS1- ASO- 304b	LG=.M5C=.LA=.M5C=.dA=.d5C=.dA=.d5C=.dA=.dT=.d5C=.dA=.dG=.dG=.M5C=.LT=.MG =.LG

463	hCPS1- ASO- 305a	MA=.M5C=.MA=.M5C=.dA=.d5C=.dA=.dT=.d5C=.dA=.dG=.dG=.d5C=.dT=.MG=.MG=.MG =.MG
464	hCPS1- ASO- 305b	LA=.M5C=.LA=.M5C=.dA=.d5C=.dA=.dT=.d5C=.dA=.dG=.dG=.d5C=.dT=.MG=.LG=.MG=. LG
465	hCPS1- ASO- 306a	L5C=.MA=.M5C=.MA=.d5C=.dA=.d5C=.dA=.dT=.d5C=.dA=.dG=.dG=.d5C=.MT=.MG=.M G=.LG
466	hCPS1- ASO- 306b	L5C=.MA=.L5C=.MA=.d5C=.dA=.d5C=.dA=.dT=.d5C=.dA=.dG=.dG=.d5C=.MT=.LG=.MG =.LG
467	hCPS1- ASO- 307a	MG=.MG=.M5C=.MA=.MT=.dG=.dA=.dA=.dT=.dG=.d5C=.dA=.dG=.dG=.d5C=.MA=.M5C =.MA=.M5C=.MA
468	hCPS1- ASO- 307b	LG=.MG=.L5C=.MA=.MT=.dG=.dA=.dA=.dT=.dG=.d5C=.dA=.dG=.dG=.d5C=.MA=.M5C=. LA=.M5C=.LA
469	hCPS1- ASO- 308a	LG=.MG=.L5C=.MA=.MT=.dG=.dA=.dA=.LT=.dG=.d5C=.LA=.dG=.dG=.d5C=.MA=.M5C= .LA=.M5C=.LA
470	hCPS1- ASO- 308b	MG=.MG=.M5C=.MA=.MT=.dG=.dA=.dA=.dT=.dG=.d5C=.dA=.dG=.dG=.d5C=.MA=.M5C- .MA=.M5C=.MA
471	hCPS1- ASO- 309a	LG=.MG=.L5C=.MA=.M5C=.dA=.d5C=.dA=.d5C=.dA=.dT=.d5C=.dA=.dG=.dG=.M5C=.MT =.LG=.MG=.LG
472	hCPS1- ASO- 309b	LG=.MG=.L5C=.MA=.M5C=.dA=.d5C=.dA=.L5C=.dA=.dT=.L5C=.dA=.dG=.dG=.M5C=.M T=.LG=.MG=.LG
473	hCPS1- ASO- 309c	MG=.MG=.M5C=.MA=.M5C=.dA=.d5C=.dA=.d5C=.dA=.dT=.d5C=.dA=.dG=.dG=.M5C- .MT=.MG=.MG=.MG
474	hCPS1- ASO- 310a	M5C=.MA=.M5C=.MA=.M5C=.dA=.d5C=.dA=.dT=.d5C=.dA=.dG=.dG=.d5C=.dT=.MG=.M G=.MG=.MG=.MA
475	hCPS1- ASO- 310b	L5C=.MA=.L5C=.MA=.M5C=.dA=.d5C=.dA=.dT=.d5C=.dA=.dG=.dG=.d5C=.dT=.MG=.MG =.LG=.MG=.LA
476	hCPS1- ASO- 310c	L5C=.MA=.L5C=.MA=.M5C=.dA=.d5C=.dA=.LT=.d5C=.dA=.LG=.dG=.d5C=.dT=.MG=.M G=.LG=.MG=.LA
477	hCPS1- ASO- 310d	M5C=.MA=.M5C=.MA=.M5C=.dA=.d5C=.dA=.dT=.d5C=.dA=.dG=.dG=.d5C=.dT=.MG- .MG=.MG=.MG=.MA
478	hCPS1- ASO- 311a	MG=.M5C=.MA=.M5C=.MA=.d5C=.dA=.d5C=.dA=.dT=.d5C=.dA=.dG=.dG=.d5C=.MT=.M G=.MG=.MG=.MG
479	hCPS1- ASO- 311b	LG=.M5C=.LA=.M5C=.MA=.d5C=.dA=.d5C=.dA=.dT=.d5C=.dA=.dG=.dG=.d5C=.MT=.MG =.LG=.MG=.LG
480	hCPS1- ASO- 311c	MG=.M5C=.MA=.M5C=.MA=.d5C=.dA=.d5C=.dA=.dT=.d5C=.dA=.dG=.dG=.d5C=.MT- .MG=.MG=.MG=.MG

481	hCPS1- ASO- 312a	dT=.dG=.d5C=.dA=.dG=.dG=.d5C=.dA=.d5C=.dA=.d5C=.dA=.dT=.d5C=.dA=.dG=.dG=.d5C
482	hCPS1- ASO- 313a	MA=.MT=.M5C=.MA=.MG=.dG=.d5C=.dT=.dG=.dG=.dG=.dG=.dA=.d5C=.d5C=.M5C=.MT=.MG=.MT=.MG-.[TEG]
483	hCPS1- ASO- 314a	MG=.MG=.M5C=.MA=.M5C=.dA=.d5C=.dA=.d5C=.dA=.dT=.d5C=.dA=.dG=.dG=.M5C=.MT=.MG=.MG=.MG-.[TEG]
484	hCPS1- ASO- 315a	MA=.MT=.MG=.MA=.MA=.dT=.dG=.d5C=.dA=.dG=.dG=.d5C=.dA=.d5C=.dA=.M5C=.MA=.M5C=.MA=.MT-.[TEG]
485	hCPS1- ASO- 316a	MT=.MG=.M5C=.MA=.MG=.dG=.d5C=.dA=.d5C=.dA=.d5C=.dA=.d5C=.dA=.dT=.M5C=.MA=.MG=.MG=.M5C-.[TEG]
486	hCPS1- ASO- 316b	MT=.MG=.M5C=.MA=.MG=.dG=.mC=.dA=.d5C=.dA=.d5C=.dA=.d5C=.dA=.dT=.M5C=.MA=.MG=.MG=.M5C-.[TEG]

[0107] In some embodiments, hCPS1-ASO-317-492 (SEQ ID NOs: 487-662) comprise pS bonds, 5-MethylCytosines and fully MOE nucleotides.

Hybridization and ΔG

[0108] The term “hybridizing” or “hybridizes” as used herein is to be understood as two nucleic acid strands (*e.g.*, an oligonucleotide and a target nucleic acid) forming hydrogen bonds between base pairs on opposite strands thereby forming a duplex. The affinity of the binding between two nucleic acid strands is the strength of the hybridization. It is often described in terms of the melting temperature (T_m) defined as the temperature at which half of the oligonucleotides are duplexed with the target nucleic acid. At physiological conditions T_m is not strictly proportional to the affinity (Mergny and Lacroix, 2003, *Oligonucleotides* 13:515-537). The standard state Gibbs free energy ΔG° is a more accurate representation of binding affinity and is related to the dissociation constant (K_d) of the reaction by $\Delta G^\circ = -RT \ln(K_d)$, where R is the gas constant and T is the absolute temperature. Therefore, a very low ΔG° of the reaction between an oligonucleotide and the target nucleic acid reflects a strong hybridization between the oligonucleotide and target nucleic acid. ΔG° is the free energy associated with a reaction where aqueous concentrations are 1M, the pH is 7, and the temperature is 37° C. The hybridization of oligonucleotides to a target nucleic acid is a spontaneous reaction and for spontaneous reactions ΔG° is less than zero. ΔG° can be measured experimentally, for example, by use of the isothermal titration calorimetry (ITC) method as described in Hansen *et al.*, 1965, *Chem. Comm.* 36-38 and Holdgate *et al.*, 2005, *Drug Discov Today*. The skilled person will

know that commercial equipment is available for ΔG° measurements. ΔG° can also be estimated numerically by using the nearest neighbor model as described by SantaLucia, 1998, *Proc Natl Acad Sci USA*. 95: 1460-1465 using appropriately derived thermodynamic parameters described by Sugimoto *et al.*, 1995, *Biochemistry* 34:11211-11216 and McTigue *et al.*, 2004, *Biochemistry* 43:5388-5405. In order to have the possibility of modulating its intended nucleic acid target by hybridization, oligonucleotides of the present disclosure hybridize to a target nucleic acid with estimated ΔG° values below -10 kcal/mol for oligonucleotides that are 10-30 nucleotides in length. In some embodiments the degree or strength of hybridization is measured by the standard state Gibbs free energy ΔG° . The oligonucleotides may hybridize to a target nucleic acid with estimated ΔG° values below the range of -10 kcal/mol, such as below -15 kcal/mol, such as below -20 kcal/mol and such as below -25 kcal/mol for oligonucleotides that are 8-30 nucleotides in length. In some embodiments the oligonucleotides hybridize to a target nucleic acid with an estimated ΔG° value of -10 to -60 kcal/mol, such as -12 to -40 kcal/mol, -15 to -30 kcal/mol, -16 to -27 kcal/mol, or -18 to -25 kcal/mol.

Duplex Region

[0109] The phrase “duplex region” refers to the region in two complementary or substantially complementary polynucleotides that form base pairs with one another, either by Watson-Crick base pairing or any other manner that allows for a stabilized duplex between polynucleotide strands that are complementary or substantially complementary. For example, a polynucleotide strand having 21 nucleotide units can base pair with another polynucleotide of 21 nucleotide units, yet only 19 bases on each strand are complementary or substantially complementary, such that the “duplex region” has 19 base pairs. The remaining bases may, for example, exist as 5' and 3' overhangs. Further, within the duplex region, 100% complementarity is not required; substantial complementarity is allowable within a duplex region. Substantial complementarity refers to 70% or greater complementarity. For example, a mismatch in a duplex region consisting of 19 base pairs results in 94.7% complementarity, rendering the duplex region substantially complementary. Duplex regions can be formed by two separate oligonucleotide strands, as well as by single oligonucleotide strands that can form hairpin structures comprising a duplex region.

[0110] A dsRNA includes two RNA strands that are complementary and hybridize to form a duplex structure under conditions in which the dsRNA will be used. One strand of a dsRNA (the

antisense strand) includes a region of complementarity that is substantially complementary, and generally fully complementary, to a target sequence. The target sequence can be derived from the sequence of a CPS1 regRNA, such as an eRNA or paRNA. The other strand (the sense strand) includes a region that is complementary to the antisense strand, such that the two strands hybridize and form a duplex structure when combined under suitable conditions. As described elsewhere herein and as known in the art, the complementary sequences of a dsRNA can also be contained as self-complementary regions of a single nucleic acid molecule, as opposed to being on separate oligonucleotides. Generally, the duplex structure is between 15 and 50 base pairs in length, *e.g.*, between, 15-50, 15-49, 15-48, 15-47, 15-46, 15-45, 15-44, 15-43, 15-42, 15-41, 15-40, 15-39, 15-38, 15-37, 15-36, 15-35, 15-34, 15-33, 15-32, 15-31, 15-30, 15-29, 15-28, 15-27, 15-26, 15-25, 15-24, 15-23, 15-22, 15-21, 15-20, 15-19, 15-18, 15-17, 18-50, 18-49, 18-48, 18-47, 18-46, 18-45, 18-44, 18-43, 18-42, 18-41, 18-40, 18-39, 18-38, 18-37, 18-36, 18-35, 18-34, 18-33, 18-32, 18-31, 18-30, 18-30, 18-29, 18-28, 18-27, 18-26, 18-25, 18-24, 18-23, 18-22, 18-21, 18-20, 19-50, 19-49, 19-48, 19-47, 19-46, 19-45, 19-44, 19-43, 19-42, 19-41, 19-40, 19-39, 19-38, 19-37, 19-36, 19-35, 19-34, 19-33, 19-32, 19-31, 19-30, 19-30, 19-29, 19-28, 19-27, 19-26, 19-25, 19-24, 19-23, 19-22, 19-21, 19-20, 20-50, 20-49, 20-48, 20-47, 20-46, 20-45, 20-44, 20-43, 20-42, 20-41, 20-40, 20-39, 20-38, 20-37, 20-36, 20-35, 20-34, 20-33, 20-32, 20-31, 20-30, 20-30, 20-29, 20-28, 20-27, 20-26, 20-25, 20-24, 20-23, 20-22, 20-21, 21-50, 21-49, 21-48, 21-47, 21-46, 21-45, 21-44, 21-43, 21-42, 21-41, 21-40, 21-39, 21-38, 21-37, 21-36, 21-35, 21-34, 21-33, 21-32, 21-31, 21-30, 21-29, 21-28, 21-27, 21-26, 21-25, 21-24, 21-23, 21-22, 22-50, 22-49, 22-48, 22-47, 22-46, 22-45, 22-44, 22-43, 22-42, 22-41, 22-40, 22-39, 22-38, 22-37, 22-36, 22-35, 22-34, 22-33, 22-32, 22-31, 22-30, 22-29, 22-28, 22-27, 22-26, 22-25, 22-24, 22-23, 23-50, 23-49, 23-48, 23-47, 23-46, 23-45, 23-44, 23-43, 23-42, 23-41, 23-40, 23-39, 23-38, 23-37, 23-36, 23-35, 23-34, 23-33, 23-32, 23-31, 23-30, 23-29, 23-28, 23-27, 23-26, 23-25, or 23-24 base pairs in length. Ranges and lengths intermediate to the above recited ranges and lengths are also contemplated to be part of the disclosure.

[0111] Similarly, the region of complementarity to the target sequence can be between 15 and 50 nucleotides in length, *e.g.*, between 15-50, 15-49, 15-48, 15-47, 15-46, 15-45, 15-44, 15-43, 15-42, 15-41, 15-40, 15-39, 15-38, 15-37, 15-36, 15-35, 15-34, 15-33, 15-32, 15-31, 15-30, 15-29, 15-28, 15-27, 15-26, 15-25, 15-24, 15-23, 15-22, 15-21, 15-20, 15-19, 15-18, 15-17, 18-50, 18-49, 18-48, 18-47, 18-46, 18-45, 18-44, 18-43, 18-42, 18-41, 18-40, 18-39, 18-38, 18-37,

18-36, 18-35, 18-34, 18-33, 18-32, 18-31, 18-30, 18-30, 18-29, 18-28, 18-27, 18-26, 18-25, 18-24, 18-23, 18-22, 18-21, 18-20, 19-50, 19-49, 19-48, 19-47, 19-46, 19-45, 19-44, 19-43, 19-42, 19-41, 19-40, 19-39, 19-38, 19-37, 19-36, 19-35, 19-34, 19-33, 19-32, 19-31, 19-30, 19-30, 19-29, 19-28, 19-27, 19-26, 19-25, 19-24, 19-23, 19-22, 19-21, 19-20, 20-50, 20-49, 20-48, 20-47, 20-46, 20-45, 20-44, 20-43, 20-42, 20-41, 20-40, 20-39, 20-38, 20-37, 20-36, 20-35, 20-34, 20-33, 20-32, 20-31, 20-30, 20-30, 20-29, 20-28, 20-27, 20-26, 20-25, 20-24, 20-23, 20-22, 20-21, 21-50, 21-49, 21-48, 21-47, 21-46, 21-45, 21-44, 21-43, 21-42, 21-41, 21-40, 21-39, 21-38, 21-37, 21-36, 21-35, 21-34, 21-33, 21-32, 21-31, 21-30, 21-29, 21-28, 21-27, 21-26, 21-25, 21-24, 21-23, 21-22, 22-50, 22-49, 22-48, 22-47, 22-46, 22-45, 22-44, 22-43, 22-42, 22-41, 22-40, 22-39, 22-38, 22-37, 22-36, 22-35, 22-34, 22-33, 22-32, 22-31, 22-30, 22-29, 22-28, 22-27, 22-26, 22-25, 22-24, 22-23, 23-50, 23-49, 23-48, 23-47, 23-46, 23-45, 23-44, 23-43, 23-42, 23-41, 23-40, 23-39, 23-38, 23-37, 23-36, 23-35, 23-34, 23-33, 23-32, 23-31, 23-30, 23-29, 23-28, 23-27, 23-26, 23-25, or 23-24 nucleotides in length. Ranges and lengths intermediate to the above recited ranges and lengths are also contemplated to be part of the disclosure.

Chemical Modifications of ASOs

[0112] In certain embodiments, the ASO does not consist of only DNA. In certain embodiments, the ASO comprises at least one chemical modification relative to a natural nucleotide (*e.g.*, ribonucleotide). Various chemical modifications can be included in the ASOs of the present disclosure. The modifications can include one or more modifications in a ribose group, one or more modifications in a phosphate group, one or more modifications in a nucleobase, one or more terminal modifications, or a combination thereof. In some embodiments, an exemplary ASO sequence targeting a regRNA as shown in **Table 2** is chemically modified. For example, hCPS1-ASO-1 may be chemically modified to comprise the modifications of any one of hCPS1-ASO1-1a to hCPS1-ASO1-1g as shown in **FIG. 5A**. Such modifications can be, but are not limited to, 2'-O-(2-methoxyethyl) (2'-MOE, MOE), locked nucleic acid (LNA), 5-methyl on the cytidine, cET, phosphorothioate (PS) linkage, and/or a phosphodiester (PO) linkage, or any combination thereof. Chemical modifications of RNA are known in the art and described in, for example, PCT Application Publication No. WO2013/177248. In certain embodiments, each cytidine in the ASO is modified by 5-methyl. Exemplary ASOs comprising chemical modifications are shown in **FIGs. 5A and 14**.

[0113] Various chemical modifications for use with ASOs of the present disclosure include, but are not limited to: 3'-terminal deoxy-thymine (dT) nucleotides, 2'-O-methyl modified nucleotides, 2'-fluoro modified nucleotides, 2'-deoxy-modified nucleotides, locked nucleotides, unlocked nucleotides, conformationally restricted nucleotides, constrained ethyl nucleotides, abasic nucleotides, 2'-amino-modified nucleotides, 2'-O-allyl-modified nucleotides, 2'-C-alkyl-modified nucleotides, 2'-hydroxyl-modified nucleotides, 2'-methoxyethyl modified nucleotides, 2'-O-alkyl-modified nucleotides, morpholino nucleotides, phosphoramidates, non-natural base comprising nucleotides, tetrahydropyran modified nucleotides, 1,5-anhydrohexitol modified nucleotides, cyclohexenyl modified nucleotides, nucleotides comprising a phosphorothioate group, nucleotides comprising a methylphosphonate group, nucleotides comprising a 5'-phosphate, and nucleotides comprising a 5'-phosphate mimic.

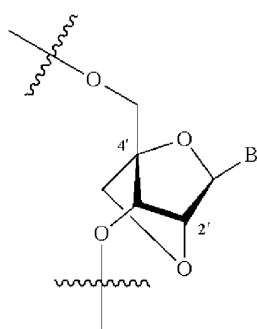
[0114] In certain embodiments, the ASO comprises an RNA polynucleotide chemically modified to be resistant to one or more nuclear RNases (*e.g.*, the exosome complex). In some embodiments, all nucleotide bases are modified in the ASO. In certain embodiments, the chemical modifications comprises β -D-ribonucleosides, 2'-modified nucleosides (*e.g.*, 2'-O-(2-methoxyethyl) (2'-MOE), 2'-O-CH₃, or 2'-fluoro-arabino (FANA)), bicyclic sugar modified nucleosides (*e.g.*, having a constrained ethyl or locked nucleic acid (LNA)), and/or one or more modified internucleotide bonds (*e.g.*, phosphorothioate internucleotide linkage). In certain embodiments, the chemical modification comprises 2'-MOE and a phosphorothioate internucleotide bond. In certain embodiments, at least 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, or more consecutive nucleotides of the ASO are modified by 2'-MOE. In certain embodiments, each nucleotide of the ASO is modified by 2'-MOE. In certain embodiments, at least 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, or more consecutive internucleotide bonds of the ASO are phosphorothioate internucleotide bonds. In certain embodiments, each internucleotide bond of the ASO is a phosphorothioate internucleotide bond.

[0115] Internucleotide linkage modifications that can be used with the ASOs of the present disclosure include, but are not limited to, phosphorothioate "PS" (P(S)), phosphoramidate (P(NR₁R₂) such as dimethylaminophosphoramidate (P(N(CH₃)₂)), phosphonocarboxylate (P(CH₂)_nCOOR) such as phosphonoacetate "PACE" (P(CH₂COO-)), thiophosphonocarboxylate ((S)P(CH₂)_nCOOR) such as thiophosphonoacetate "thioPACE"

((S)P(CH₂COO⁻)), alkylphosphonate (P(C1-3alkyl)) such as methylphosphonate —P(CH₃), boranophosphonate (P(BH₃)), and phosphorodithioate (P(S)₂).

[0116] The chemical structures can also be described in writing. In such cases, ‘M’ indicates MOE; ‘d’ indicates DNA, ‘L’ indicates LNA, ‘=’ indicates a phosphorothioate (PS) linkage, ‘-’ indicates a phosphodiester (PO) linkage; ‘5C’ indicates 5-MethylCytosine, ‘ag’ indicates GalNAc, ‘tg’ or “TEG” indicates Teg-GalNAc, ‘ag’ or ‘AlGal’ indicates GalNAc, ‘BioTEG’ indicates biotin, ‘CholTEG’ indicates cholesterol, ‘c’ indicates cET, and ‘^’ indicates FANA.

[0117] To avoid ambiguity, this LNA has the formula:



wherein B is the particular designated base.

[0118] Exemplary written descriptions of selected ASOs are provided in **Table 3**, with corresponding **FIGs. 5A** and **14** providing visual representation of the modifications.

[0119] In some embodiments, the ASO comprises a sequence selected from the group consisting of SEQ ID NOs: 1-15, 91-391, or 487-662. In some embodiments, the ASO comprises a sequence and chemical modification selected from the group consisting of SEQ ID NOs: 16-48, 392-480, or 482-486. In some embodiments, the ASO comprises a sequence and/or chemical modification selected from the group consisting of SEQ ID NOs: 1-48 or 91-662.

[0120] In some embodiments, the regulatory RNA comprises a sequence selected from the group consisting of SEQ ID NOs: 80-88. In some embodiments, the ASO comprises a sequence selected from the group consisting of SEQ ID NOs: 51-68.

[0121] In some embodiments, the ASO comprises a sequence set forth in **Table 2**. In some embodiments, the ASO comprises a sequence and/or the chemical modification set forth in **Table 3**, and **FIGs. 4A, 5A, 5B**, and **14**.

[0122] In certain embodiments, the ASO comprises one or more chemical modifications at the 5' end, the 3' end, or both. Without wishing to be bound by theory, chemical modifications

at one or both termini of a polynucleotide (*e.g.*, polyribonucleotide) may stabilize the polynucleotide. In certain embodiments, the ASO comprises one or more chemical modifications in at least 1, 2, 3, 4, or 5 nucleotides at the 5' end of the ASO. In certain embodiments, the ASO comprises one or more chemical modifications in at least 1, 2, 3, 4, or 5 nucleotides at the 3' end of the ASO. In certain embodiments, the ASO comprises one or more chemical modifications in at least 1, 2, 3, 4, or 5 nucleotides at the 5' end of the ASO and one or more chemical modifications in at least 1, 2, 3, 4, or 5 nucleotides at the 3' end of the ASO.

High Affinity Modified Nucleosides

[0123] A high affinity modified nucleoside is a modified nucleoside which, when incorporated into the oligonucleotide enhances the affinity of the oligonucleotide for its complementary target, for example as measured by the melting temperature (T_m). A high affinity modified nucleoside of the present disclosure preferably result in an increase in melting temperature between +0.5 to +12° C, such as between +1.5 to +10° C or +3 to +8° C per modified nucleoside. Numerous high affinity modified nucleosides are known in the art and include for example, many 2' substituted nucleosides as well as locked nucleic acids (LNA) (see *e.g.* Freier & Altmann, Nucl. Acid Res., 1997, 25, 4429-4443 and Uhlmann, Curr. Opinion in Drug Development, 2000, 3(2), 293-213), each of which is hereby incorporated by reference.

Sugar Modifications

[0124] The ASOs described herein may comprise one or more nucleosides which have a modified sugar moiety, *i.e.* a modification of the sugar moiety when compared to the ribose sugar moiety found in DNA and RNA. Numerous nucleosides with modification of the ribose sugar moiety have been made, primarily with the aim of improving certain properties of oligonucleotides, such as affinity and/or nuclease resistance. Such modifications include those where the ribose ring structure is modified, *e.g.* by replacement with a hexose ring (HNA), or a bicyclic ring, which typically have a biradical bridge between the C2 and C4 carbons on the ribose ring (LNA), or an unlinked ribose ring which typically lacks a bond between the C2 and C3 carbons (*e.g.* UNA). Other sugar modified nucleosides include, for example, bicyclohexose nucleic acids (see *e.g.*, PCT Application Publication No. WO2011/017521) or tricyclic nucleic acids (see *e.g.*, PCT Application Publication No. WO2013/154798), both of which are hereby incorporated by reference. Modified nucleosides also include nucleosides where the sugar moiety

is replaced with a non-sugar moiety, for example in the case of peptide nucleic acids (PNA), or morpholino nucleic acids.

[0125] Sugar modifications also include modifications made via altering the substituent groups on the ribose ring to groups other than hydrogen, or the 2'-OH group naturally found in DNA and RNA nucleosides. Substituents may, for example be introduced at the 2', 3', 4' or 5' positions.

[0126] In some embodiments, oligonucleotides comprise modified sugar moieties, such as any one of a 2'-*O*-methyl (2'OMe) moiety, a 2'-*O*-methoxyethyl moiety, a bicyclic sugar moiety, PNA (*e.g.*, an oligonucleotide comprising one or more *N*-(2-aminoethyl)-glycine units linked by amide bonds or carbonyl methylene linkage as repeating units in place of a sugar-phosphate backbone), locked nucleoside (LNA) (*e.g.*, an oligonucleotide comprising one or more locked ribose, and can be a mixture of 2'-deoxy nucleotides or 2'OMe nucleotides), c-ET (*e.g.*, an oligonucleotide comprising one or more cET sugar), cMOE (*e.g.*, an oligonucleotide comprising one or more cMOE sugar), morpholino oligomer (*e.g.*, an oligonucleotide comprising a backbone comprising one or more phosphorodiamidate morpholino oligomers), 2'-deoxy-2'-fluoro nucleoside (*e.g.*, an oligonucleotide comprising one or more 2'-fluoro- β -D-arabinonucleoside), tcDNA (*e.g.*, an oligonucleotide comprising one or more tcDNA modified sugar), constrained ethyl 2'-4'-bridged nucleic acid (cEt), *S*-cEt, ethylene bridged nucleic acid (ENA) (*e.g.*, an oligonucleotide comprising one or more ENA modified sugar), hexitol nucleic acids (HNA) (*e.g.*, an oligonucleotide comprising one or more HNA modified sugar), or tricyclic analog (tcDNA) (*e.g.*, an oligonucleotide comprising one or more tcDNA modified sugar).

[0127] In some embodiments, oligonucleotides comprise nucleobase modifications selected from the group consisting of 2-thiouracil ("2-thioU"), 2-thiocytosine ("2-thioC"), 4-thiouracil ("4-thioU"), 6-thioguanine ("6-thioG"), 2-aminoadenine ("2-aminoA"), 2-aminopurine, pseudouracil, hypoxanthine, 7-deazaguanine, 7-deaza-8-azaguanine, 7-deazaadenine, 7-deaza-8-azaadenine, 5-methylcytosine ("5-methylC"), 5-methyluracil ("5-methylU"), 5-hydroxymethylcytosine, 5-hydroxymethyluracil, 5,6-dehydrouracil, 5-propynylcytosine, 5-propynyluracil, 5-ethynylcytosine, 5-ethynyluracil, 5-allyluracil ("5-allylU"), 5-allylcytosine ("5-allylC"), 5-aminoallyluracil ("5-aminoallylU"), 5-aminoallyl-cytosine ("5-aminoallylC"), an abasic nucleotide, Z base, P base, Unstructured Nucleic Acid ("UNA"), isoguanine ("isoG"), and isocytosine ("isoC"), glycerol nucleic acid (GNA), thiomorpholino (C₄H₉NS) or

thiophosphoramidate morpholinos (TMOs). Synthesis of glycerol nucleic acid (GNA) (also known as glycol nucleic acids) is described in Zhang et al, *Current Protocols in Nucleic Acid Chemistry* 4.40.1-4.40.18, September 2010, hereby incorporated by reference. Synthesis of thiophosphoramidate morpholino oligonucleotides is described in Langer et al, *J. Am. Chem. Soc.* 2020, 142, 38, 16240–16253

2' Sugar Modified Nucleosides

[0128] A 2' sugar modified nucleoside is a nucleoside which has a substituent other than H or -OH at the 2' position (2' substituted nucleoside) or comprises a 2' linked biradical capable of forming a bridge between the 2' carbon and a second carbon in the ribose ring, such as LNA (2'-4' biradical bridged) nucleosides.

[0129] Without wishing to be bound by theory, the 2' modified sugar may provide enhanced binding affinity and/or increased nuclease resistance to the oligonucleotide. Examples of 2' substituted modified nucleosides are 2'-O-alkyl-RNA, 2'-O-methyl-RNA, 2'-alkoxy-RNA, 2'-O-methoxyethyl-RNA (MOE), 2'-amino-DNA, 2'-Fluoro-RNA, and 2'-F-ANA nucleoside. For further examples, please see e.g. Freier & Altmann; *Nucl. Acid Res.*, 1997, 25, 4429-4443 and Uhlmann; *Curr. Opinion in Drug Development*, 2000, 3(2), 293-213, and Deleavey and Damha, *Chemistry and Biology* 2012, 19, 937, each of which are hereby incorporated by reference.

Locked Nucleic Acid Nucleosides (LNA Nucleoside)

[0130] A "LNA nucleoside" is a 2'-sugar modified nucleoside which comprises a biradical linking the C2' and C4' of the ribose sugar ring of said nucleoside (also referred to as a "2'-4' bridge"), which restricts or locks the conformation of the ribose ring. In other words, a locked nucleoside is a nucleoside comprising a bicyclic sugar moiety comprising a 4'-CH₂-O-2' bridge. This structure effectively "locks" the ribose in the 3'-endo structural conformation. The addition of locked nucleosides to oligonucleotides has been shown to increase oligonucleotide stability in serum, and to reduce off-target effects (Grunweller, A. *et al.*, (2003) *Nucleic Acids Research* 31(12):3185-3193). These nucleosides are also sometimes termed bridged nucleic acid or bicyclic nucleic acid (BNA). The locking of the conformation of the ribose is associated with an enhanced affinity of hybridization (duplex stabilization) when the LNA is incorporated into an oligonucleotide for a complementary RNA or DNA molecule. This can be routinely determined by measuring the melting temperature of the oligonucleotide/complement duplex. Exemplary

LNA nucleosides include beta-D-oxy-LNA, 6'-methyl-beta-D-oxy LNA such as (S)-6'-methyl-beta-D-oxy-LNA (ScET) and ENA.

[0131] Examples of bicyclic nucleosides for use in the polynucleotides of the invention include without limitation nucleosides comprising a bridge between the 4' and the 2' ribosyl ring atoms. In certain embodiments, the polynucleotide agents of the invention include one or more bicyclic nucleosides comprising a 4' to 2' bridge. Examples of such 4' to 2' bridged bicyclic nucleosides, include but are not limited to 4'-(CH₂)-O-2' (LNA); 4'-(CH₂)-S-2'; 4'-(CH₂)₂-O-2' (ENA); 4'-CH(CH₃)-O-2' (also referred to as "constrained ethyl" or "cEt") and 4'-CH(CH₂OCH₃)-O-2' (and analogs thereof; see, *e.g.*, U.S. Pat. No. 7,399,845); 4'-C(CH₃)(CH₃)-O-2' (and analogs thereof; see *e.g.*, U.S. Pat. No. 8,278,283); 4'-CH₂-N(OCH₃)-2' (and analogs thereof; see *e.g.*, U.S. Pat. No. 8,278,425); 4'-CH₂-O-N(CH₃)₂-2' (see, *e.g.*, U.S. Patent Publication No. 2004/0171570); 4'-CH₂-N(R)-O-2', wherein R is H, C₁-C₁₂ alkyl, or a protecting group (see, *e.g.*, U.S. Pat. No. 7,427,672); 4'-CH₂-C(H)(CH₃)-2' (see, *e.g.*, Chattopadhyaya et al., J. Org. Chem., 2009, 74, 118-134); and 4'-CH₂-C(=CH₂)-2' (and analogs thereof; see, *e.g.*, U.S. Pat. No. 8,278,426). The entire contents of each of the foregoing are hereby incorporated herein by reference.

[0132] Additional representative U.S. Patents and US Patent Publications that teach the preparation of locked nucleic acid nucleotides include, but are not limited to, the following: U.S. Pat. Nos. 6,268,490; 6,525,191; 6,670,461; 6,770,748; 6,794,499; 6,998,484; 7,053,207; 7,034,133; 7,084,125; 7,399,845; 7,427,672; 7,569,686; 7,741,457; 8,022,193; 8,030,467; 8,278,425; 8,278,426; 8,278,283; US 2008/0039618; and US 2009/0012281, the entire contents of each of which are hereby incorporated herein by reference.

[0133] Any of the foregoing bicyclic nucleosides can be prepared having one or more stereochemical sugar configurations including for example α -L-ribofuranose and β -D-ribofuranose (*see* PCT Publication No. WO 99/14226, contents of which are incorporated by reference herein).

[0134] An oligonucleotide of the invention can also be modified to include one or more constrained ethyl nucleosides. As used herein, a "constrained ethyl nucleoside" or "cEt" is a locked nucleoside comprising a bicyclic sugar moiety comprising a 4'-CH(CH₃)-O-2' bridge. In some embodiments, a constrained ethyl nucleoside is in the *S* conformation referred to herein as "S-cEt."

[0135] An oligonucleotide of the invention may also include one or more "conformationally restricted nucleosides" ("CRN"). CRN are nucleoside analogs with a linker connecting the C2' and C4' carbons of ribose or the -C3 and -C5' carbons of ribose. CRN lock the ribose ring into a stable conformation and increase the hybridization affinity to mRNA. The linker is of sufficient length to place the oxygen in an optimal position for stability and affinity resulting in less ribose ring puckering.

[0136] Representative publications that teach the preparation of certain of the above noted CRN include, but are not limited to, US Patent Publication No. 2013/0190383; and PCT Publication No. WO 2013/036868, the entire contents of each of which are hereby incorporated herein by reference.

[0137] In some embodiments, an oligonucleotide of the invention comprises one or more monomers that are UNA (unlocked nucleoside) nucleosides. UNA is unlocked acyclic nucleoside, wherein any of the bonds of the sugar has been removed, forming an unlocked "sugar" residue. In one example, UNA also encompasses monomer with bonds between C1'-C4' have been removed (i.e., the covalent carbon-oxygen-carbon bond between the C1' and C4' carbons). In another example, the C2'-C3' bond (i.e., the covalent carbon-carbon bond between the C2' and C3' carbons) of the sugar has been removed (see Nuc. Acids Symp. Series, 52, 133-134 (2008) and Fluiters *et al.*, Mol. Biosyst., 2009, 10, 1039 hereby incorporated by reference).

[0138] Representative U.S. publications that teach the preparation of UNA include, but are not limited to, U.S. Pat. No. 8,314,227; and US Patent Publication Nos. 2013/0096289; 2013/0011922; and 2011/0313020, the entire contents of each of which are hereby incorporated herein by reference.

[0139] The ribose molecule may also be modified with a cyclopropane ring to produce a tricyclodeoxynucleic acid (tricyclo DNA). The ribose moiety may be substituted for another sugar such as 1,5,-anhydrohexitol, threose to produce a threose nucleoside (TNA), or arabinose to produce an arabino nucleoside. The ribose molecule can also be replaced with non-sugars such as cyclohexene to produce cyclohexene nucleoside or glycol to produce glycol nucleosides.

[0140] Potentially stabilizing modifications to the ends of nucleoside molecules can include N-(acetylaminocaproyl)-4-hydroxyprolinol (Hyp-C6-NHAc), N-(caproyl-4-hydroxyprolinol (Hyp-C6), N-(acetyl-4-hydroxyprolinol (Hyp-NHAc), thymidine-2'-O-deoxythymidine (ether), N-(aminocaproyl)-4-hydroxyprolinol (Hyp-C6-amino), 2-docosanoyl-uridine-3"-phosphate,

inverted base dT(idT) and others. Disclosure of this modification can be found in PCT Publication No. WO 2011/005861.

[0141] Other alternative chemistries of an oligonucleotide of the invention include a 5' phosphate or 5' phosphate mimic, *e.g.*, a 5'-terminal phosphate or phosphate mimic of an oligonucleotide. Suitable phosphate mimics are disclosed in, for example US Patent Publication No. 2012/0157511, the entire contents of which are incorporated herein by reference.

[0142] Additional non-limiting, exemplary LNA nucleosides are disclosed in PCT Publication Nos. WO 99/014226, WO 00/66604, WO 98/039352, WO 2004/046160, WO 00/047599, WO 2007/134181, WO 2010/077578, WO 2010/036698, WO 2007/090071, WO 2009/006478, WO 2011/156202, WO 2008/154401, WO 2009/067647, WO 2008/150729, Morita et al., Bioorganic & Med. Chem. Lett. 12, 73-76, Seth et al. J. Org. Chem. 2010, Vol 75(5) pp. 1569-81, Mitsuoka et al., Nucleic Acids Research 2009, 37(4), 1225-1238, and Wan and Seth, J. Medical Chemistry 2016, 59, 9645-9667, each of which are hereby incorporated by reference.

[0143] In some embodiments, the length of the ASO is $5 \times n + 5$ nucleotides (n is an integer of 3 or greater), wherein the nucleotides at positions $5 \times m$ are ribonucleotides modified by LNA (m is an integer from 1 to n) and the nucleotides at the remaining positions are ribonucleotides modified by 2'-O-methoxyethyl.

[0144] In some embodiments, the nucleotide sugar modification is 2'-O—C1-4alkyl such as 2'-O-methyl (2'-OMe), 2'-deoxy (2'-H), 2'-O—C1-3alkyl-O—C1-3alkyl such as 2'-methoxyethyl ("2'-MOE"), 2'-fluoro ("2'-F"), 2'-amino ("2'-NH₂"), 2'-arabinosyl ("2'-arabino") nucleotide, 2'-F-arabinosyl ("2'-F-arabino") nucleotide, 2'-locked nucleic acid ("LNA") nucleotide, 2'-amido bridge nucleic acid (AmNA), 2'-unlocked nucleic acid ("ULNA") nucleotide, a sugar in L form ("L-sugar"), or 4'-thioribosyl nucleotide.

Mixmers and Gapmers

[0145] The ASO can have a mixmer and/or gapmer structure, for example, in a pattern disclosed by the ASOs in **FIG. 5A**, **FIG. 5B**, or **FIG. 14**.

[0146] In certain embodiments, the ASO is a mixmer. As used herein, the term "mixmer" refers to an oligonucleotide comprising an alternating composition of DNA monomers and nucleoside analogue monomers across at least a portion of the oligonucleotide sequence. In certain embodiments, the ASO is a mixmer based on the gapmer structure, comprising a mixture

of DNA nucleotides and 2'-MOE nucleotides in the gap, flanked by RNA sequences in the wings. Mixmers may be designed to comprise a mixture of affinity enhancing nucleotide analogues, such as in non-limiting example 2'-O-alkyl-RNA monomers, 2'-amino-DNA monomers, 2'-fluoro-DNA monomers, LNA monomers, arabino nucleic acid (ANA) monomers, 2'-fluoro-ANA monomers, HNA monomers, INA monomers, 2'-MOE-RNA (2'-O-methoxyethyl-RNA), 2'Fluoro-DNA, and LNA. In some embodiments, the mixmer is incapable of recruiting RNase H. In some embodiments, the mixmer comprises one type of affinity enhancing nucleotide analogue together with DNA and/or RNA.

[0147] Multiple different modifications can be interspaced in a mixmer. For example, the ASO can comprise LNA modification in a plurality of nucleotides and a different modification in some or all of the rest of the nucleotides. In some embodiments, any two adjacent LNA-modified nucleotides are separated by at least 1, 2, 3, 4, or 5 nucleotides. Throughout the ASO, the distance between adjacent LNA-modified nucleotides can either be constant (*e.g.*, any two adjacent LNA-modified nucleotides are separated by 1, 2, 3, 4, or 5 nucleotides) or variable. In some embodiments, the length of the ASO is $3 \times n$, $3 \times n - 1$, or $3 \times n - 2$ nucleotides (n is an integer of 6 or greater), wherein (a) (i) the nucleotides at positions $3 \times m - 2$ (m is an integer from 1 to n) are ribonucleotides comprising a first modification (*e.g.*, LNA), (ii) the nucleotides at positions $3 \times m - 1$ (m is an integer from 1 to n) are ribonucleotides comprising a first modification (*e.g.*, LNA), or (iii) the nucleotides at positions $3 \times m$ (m is an integer from 1 to n) are ribonucleotides comprising a first modification (*e.g.*, LNA); and (b) the nucleotides at the remaining positions comprise a second, different modification (*e.g.*, 2'-O-methoxyethyl). The ASO called hCPS1-ASO-1d herein has such a structure. In some embodiments, the length of the ASO is $2 \times n$ or $2 \times n - 1$ nucleotides (n is an integer of 9 or greater), wherein (a) (i) the nucleotides at positions $2 \times m - 1$ (m is an integer from 1 to n) are ribonucleotides comprising a first modification (*e.g.*, LNA), or (ii) the nucleotides at positions $2 \times m$ (m is an integer from 1 to n) are ribonucleotides comprising a first modification (*e.g.*, LNA); and (b) the nucleotides at the remaining positions comprise a second, different modification (*e.g.*, 2'-O-methoxyethyl). The ASO called hCPS1-ASO-1e herein has such a structure. Similar modification patterns, for example, where the first modification is repeated every 4, 5, or more nucleotides, are also contemplated herein.

[0148] In some embodiments, the ASO further comprises a GalNAc or Teg-GalNAc moiety at the 5' or 3' end of the ASO. In some embodiments, the ASO further comprises a cholesterol or biotin moiety at the 5' or 3' end of the ASO.

[0149] In certain embodiments, the ASO comprises a DNA sequence (*e.g.*, having at least 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, or 15 contiguous nucleotides of unmodified DNA) flanked by RNA sequences. Such structure is known as “gapmer,” in which the internal DNA region is referred to as the “gap” and the external RNA regions is referred to as the “wings” (see, *e.g.*, PCT Application Publication No. WO2013/177248). Gapmers were known to facilitate degradation of the target RNA by recruiting nuclear RNAses (*e.g.*, RNase H). Surprisingly, in the present disclosure, it has been discovered that a gapmer binding a regRNA (*e.g.*, hCPS1-ASO-1a), like regRNAs having the same sequence but having different chemical modifications (*e.g.*, hCPS1-ASO-1g), can also increase target gene expression.

[0150] In certain embodiments, the gapmer is about 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 26, 27, 28, 29, 30, or more nucleotides in length. In certain embodiments, the gap is about 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, or more nucleotides in length. In certain embodiments, one or both wings are about 2, 3, 4, 5, 6, 7, 8, 9, 10, or more nucleotides in length. In certain embodiments, one or both wings comprises RNA modifications, for example, β -D-ribonucleosides, 2'-modified nucleosides (*e.g.*, 2'-O-(2-methoxyethyl) (2'-MOE), 2'-O-CH₃, or 2'-fluoro-arabino (FANA)), and bicyclic sugar modified nucleosides (*e.g.*, having a constrained ethyl or locked nucleic acid (LNA)). In certain embodiments, each ribonucleotide in the gapmer is modified by 2'-MOE. In certain embodiments, the gapmer comprises one or more modified internucleotide bonds, *e.g.*, phosphorothioate (PS) internucleotide linkage. In certain embodiments, each two adjacent nucleotides in the gapmer are linked by a phosphorothioate internucleotide bond.

[0151] In certain embodiments, the ASO does not comprise 7 or more, 8 or more, 9 or more, 10 or more, 10 or more, 11 or more, 12 or more, 13 or more, 14 or more, or 15 or more contiguous nucleotides of unmodified DNA. In some embodiments, such a DNA sequence is disrupted by modified (*e.g.*, 2'-MOE modified) ribonucleotides every 2, 3, 4, 5, or more nucleotides. In some embodiments, the ASO comprises only ribonucleotides and no deoxyribonucleotides.

[0152] The structural features of mixmer and gapmer can be combined. In certain embodiments, the ASO has a structure similar to that of a mixmer disclosed herein (*e.g.*, one

having interspaced modifications), except that the second modification in the gap is changed to a third modification (*e.g.*, deoxyribonucleotide). In certain embodiments, the ASO has a structure similar to that of a gapmer disclosed herein, except that in the gap the nucleotides are modified in a mixmer pattern.

[0153] In certain embodiments, the ASO further comprises a ligand moiety, *e.g.*, a ligand moiety that specifically targets a tissue or organ in a subject. For example, N-acetylgalactosamine (GalNAc) specifically targets liver. In certain embodiments, the ligand moiety comprises GalNAc. In certain embodiments, the ligand moiety comprises a three-cluster GalNAc moiety, commonly denoted GAINAc3. Other types of GalNAc moieties are one-cluster, two cluster or four cluster GAINAc, denoted as GAINAc1, GAINAc2, or GAINAc4. In certain embodiments, the ligand moiety comprises GalNAc1, GALNAc2, GAINAc3, or GalNAc4.

III. PHARMACEUTICAL COMPOSITIONS

[0154] In certain embodiments, the ASOs disclosed herein can be present in pharmaceutical compositions. The pharmaceutical composition can be formulated for use in a variety of drug delivery systems. One or more pharmaceutically acceptable excipients or carriers can also be included in the composition for proper formulation. Suitable formulations for use in the present disclosure are found in Remington's Pharmaceutical Sciences, Mack Publishing Company, Philadelphia, Pa., 17th ed., 1985. For a brief review of methods for drug delivery, *see, e.g.*, Langer, Science 249:1527-1533, 1990, hereby incorporated by reference in its entirety.

[0155] Exemplary carriers and pharmaceutical formulations suitable for delivering nucleic acids are described in Durymanov and Reineke (2018) Front. Pharmacol. 9:971; Barba *et al.* (2019) Pharmaceutics 11(8): 360; Ni *et al.* (2019) Life (Basel) 9(3): 59. It is understood that the presence of a ligand moiety conjugated to the ASO may circumvent the need for a carrier for delivery to a tissue or organ targeted by the ligand moiety.

[0156] The delivery of an oligonucleotide of the disclosure to a cell *e.g.*, a cell within a subject, such as a human subject *e.g.*, a subject in need thereof, such as a subject having a CPS1 related disorder or other urea cycle disorders can be achieved in a number of different ways. For example, delivery may be performed by contacting a cell with an oligonucleotide of the disclosure either *in vitro* or *in vivo*. *In vivo* delivery may also be performed directly by

administering a composition comprising an oligonucleotide to a subject. These alternatives are discussed further below.

[0157] In general, any method of delivering a nucleic acid molecule (*in vitro* or *in vivo*) can be adapted for use with an oligonucleotide of the disclosure (see *e.g.*, Akhtar S. and Julian R L., (1992) Trends Cell. Biol. 2(5):139-144 and PCT Publication No. WO 94/02595, which are incorporated herein by reference in their entireties). *For in vivo* delivery, factors to consider in order to deliver an oligonucleotide molecule include, for example, biological stability of the delivered molecule, prevention of non-specific effects, and accumulation of the delivered molecule in the target tissue. The non-specific effects of an oligonucleotide can be minimized by local administration, for example, by direct injection or implantation into a tissue or topically administering the preparation. Local administration to a treatment site maximizes local concentration of the agent, limits the exposure of the agent to systemic tissues that can otherwise be harmed by the agent or that can degrade the agent, and permits a lower total dose of the oligonucleotide molecule to be administered.

[0158] For administering an oligonucleotide systemically for the treatment of a disease, the oligonucleotide can include alternative nucleobases, alternative sugar moieties, and/or alternative internucleoside linkages, or alternatively delivered using a drug delivery system; both methods act to prevent the rapid degradation of the oligonucleotide by endo- and exo-nucleases *in vivo*. Modification of the oligonucleotide or the pharmaceutical carrier can also permit targeting of the oligonucleotide composition to the target tissue and avoid undesirable off-target effects. Oligonucleotide molecules can be modified by chemical conjugation to lipophilic groups such as cholesterol to enhance cellular uptake and prevent degradation. In an alternative embodiment, the oligonucleotide can be delivered using drug delivery systems such as a nanoparticle, a lipid nanoparticle, a polyplex nanoparticle, a lipoplex nanoparticle, a dendrimer, a polymer, liposomes, or a cationic delivery system. Positively charged cationic delivery systems facilitate binding of an oligonucleotide molecule (negatively charged) and also enhance interactions at the negatively charged cell membrane to permit efficient uptake of an oligonucleotide by the cell. Cationic lipids, dendrimers, or polymers can either be bound to an oligonucleotide, or induced to form a vesicle or micelle that encases an oligonucleotide. The formation of vesicles or micelles further prevents degradation of the oligonucleotide when administered systemically. In general, any methods of delivery of nucleic acids known in the art may be adaptable to the delivery of the

oligonucleotides of the disclosure. Methods for making and administering cationic oligonucleotide complexes are well within the abilities of one skilled in the art (see *e.g.*, Sorensen, D R., *et al.* (2003) J. Mol. Biol 327:761-766; Verma, U N. *et al.*, (2003) Clin. Cancer Res. 9:1291-1300; Arnold, A S *et al.*, (2007) J. Hypertens. 25:197-205, which are incorporated herein by reference in their entirety). Some non-limiting examples of drug delivery systems useful for systemic delivery of oligonucleotides include DOTAP (Sorensen, D R., *et al.* (2003), *supra*; Verma, U N. *et al.*, (2003), *supra*), OligofectamineTM, "solid nucleic acid lipid particles" (Zimmermann, T S. *et al.*, (2006) Nature 441:111-114), cardiolipin (Chien, P Y. *et al.*, (2005) Cancer Gene Ther. 12:321-328; Pal, A. *et al.*, (2005) Int J. Oncol. 26:1087-1091), polyethyleneimine (Bonnet M E. *et al.*, (2008) Pharm. Res. Aug 16 Epub ahead of print; Aigner, A. (2006) J. Biomed. Biotechnol. 71659), Arg-Gly-Asp (RGD) peptides (Liu, S. (2006) Mol. Pharm. 3:472-487), and polyamidoamines (Tomalia, D A. *et al.*, (2007) Biochem. Soc. Trans. 35:61-67; Yoo, H. *et al.*, (1999) Pharm. Res. 16:1799-1804). In some embodiments, an oligonucleotide forms a complex with cyclodextrin for systemic administration. Methods for administration and pharmaceutical compositions of oligonucleotides and cyclodextrins can be found in U.S. Pat. No. 7,427,605, which is herein incorporated by reference in its entirety. In some embodiments the oligonucleotides of the disclosure are delivered by polyplex or lipoplex nanoparticles. Methods for administration and pharmaceutical compositions of oligonucleotides and polyplex nanoparticles and lipoplex nanoparticles can be found in U.S. Patent Publication Nos. 2017/0121454; 2016/0369269; 2016/0279256; 2016/0251478; 2016/0230189; 2015/0335764; 2015/0307554; 2015/0174549; 2014/0342003; 2014/0135376; and 2013/0317086, which are herein incorporated by reference in their entirety.

[0159] In some embodiments, the compounds described herein may be administered in combination with additional therapeutics. Examples of additional therapeutics include standard of care urea cycle disorder treatments such as low protein diet or nitrogen scavengers including, but not limited to, glycerol phenylbutyrate, sodium benzoate, phenylbutyrate, or phenylacetate.

Membranous Molecular Assembly Delivery Methods

[0160] Oligonucleotides of the disclosure can also be delivered using a variety of membranous molecular assembly delivery methods including liquid nanoparticles (LNPs), polymeric, biodegradable microparticles, or microcapsule delivery devices known in the art. For example, a colloidal dispersion system may be used for targeted delivery of an oligonucleotide

agent described herein. Colloidal dispersion systems include macromolecule complexes, nanocapsules, microspheres, beads, and lipid-based systems including oil-in-water emulsions, micelles, mixed micelles, and liposomes. Liposomes are artificial membrane vesicles that are useful as delivery vehicles *in vitro* and *in vivo*. It has been shown that large unilamellar vesicles (LUVs), which range in diameter from 0.2-4.0 μm can encapsulate a substantial percentage of an aqueous buffer containing large macromolecules. Liposomes are useful for the transfer and delivery of active ingredients to the site of action. Because the liposomal membrane is structurally similar to biological membranes, when liposomes are applied to a tissue, the liposomal bilayer fuses with bilayer of the cellular membranes. As the merging of the liposome and cell progresses, the internal aqueous contents that include the oligonucleotide are delivered into the cell where the oligonucleotide can specifically bind to a target RNA. In some cases, the liposomes are also specifically targeted, *e.g.*, to direct the oligonucleotide to particular cell types. The composition of the liposome is usually a combination of phospholipids, usually in combination with steroids, especially cholesterol. Other phospholipids or other lipids may also be used. The physical characteristics of liposomes depend on pH, ionic strength, and the presence of divalent cations.

[0161] A liposome containing an oligonucleotide can be prepared by a variety of methods. In one example, the lipid component of a liposome is dissolved in a detergent so that micelles are formed with the lipid component. For example, the lipid component can be an amphipathic cationic lipid or lipid conjugate. The detergent can have a high critical micelle concentration and may be nonionic. Exemplary detergents include cholate, CHAPS, octylglucoside, deoxycholate, and lauroyl sarcosine. The oligonucleotide preparation is then added to the micelles that include the lipid component. The cationic groups on the lipid interact with the oligonucleotide and condense around the oligonucleotide to form a liposome. After condensation, the detergent is removed, *e.g.*, by dialysis, to yield a liposomal preparation of oligonucleotide.

[0162] If necessary, a carrier compound that assists in condensation can be added during the condensation reaction, *e.g.*, by controlled addition. For example, the carrier compound can be a polymer other than a nucleic acid (*e.g.*, spermine or spermidine). The pH can also be adjusted to favor condensation.

[0163] Methods for producing stable polynucleotide delivery vehicles, which incorporate a polynucleotide/cationic lipid complex as a structural component of the delivery vehicle, are

further described in, *e.g.*, WO 96/37194, the entire contents of which are incorporated herein by reference. Liposome formation can also include one or more aspects of exemplary methods described in Feigner, P. L. *et al.*, (1987) *Proc. Natl. Acad. Sci. USA* 8:7413-7417; U.S. Pat. No. 4,897,355; U.S. Pat. No. 5,171,678; Bangham *et al.*, (1965) *M. Mol. Biol.* 23:238; Olson *et al.*, (1979) *Biochim. Biophys. Acta* 557:9; Szoka *et al.*, (1978) *Proc. Natl. Acad. Sci.* 75: 4194; Mayhew *et al.*, (1984) *Biochim. Biophys. Acta* 775:169; Kim *et al.*, (1983) *Biochim. Biophys. Acta* 728:339; and Fukunaga *et al.*, (1984) *Endocrinol.* 115:757. Commonly used techniques for preparing lipid aggregates of appropriate size for use as delivery vehicles include sonication and freeze-thaw plus extrusion (see, *e.g.*, Mayer *et al.*, (1986) *Biochim. Biophys. Acta* 858:161. Microfluidization can be used when consistently small (50 to 200 nm) and relatively uniform aggregates are desired (Mayhew *et al.*, (1984) *Biochim. Biophys. Acta* 775:169). These methods are readily adapted to packaging oligonucleotide preparations into liposomes.

[0164] Liposomes fall into two broad classes. Cationic liposomes are positively charged liposomes which interact with the negatively charged nucleic acid molecules to form a stable complex. The positively charged nucleic acid/liposome complex binds to the negatively charged cell surface and is internalized in an endosome. Due to the acidic pH within the endosome, the liposomes are ruptured, releasing their contents into the cell cytoplasm (Wang *et al.* (1987) *Biochem. Biophys. Res. Commun.*, 147:980-985).

[0165] Liposomes, which are pH-sensitive or negatively charged, entrap nucleic acids rather than complex with them. Since both the nucleic acid and the lipid are similarly charged, repulsion rather than complex formation occurs. Nevertheless, some nucleic acid is entrapped within the aqueous interior of these liposomes. pH sensitive liposomes have been used to deliver nucleic acids encoding the thymidine kinase gene to cell monolayers in culture. Expression of the exogenous gene was detected in the target cells (Zhou *et al.* (1992) *Journal of Controlled Release*, 19:269-274).

[0166] One major type of liposomal composition includes phospholipids other than naturally derived phosphatidylcholine. Neutral liposome compositions, for example, can be formed from dimyristoyl phosphatidylcholine (DMPC) or dipalmitoyl phosphatidylcholine (DPPC). Anionic liposome compositions generally are formed from dimyristoyl phosphatidylglycerol, while anionic fusogenic liposomes are formed primarily from dioleoyl phosphatidylethanolamine (DOPE). Another type of liposomal composition is formed from phosphatidylcholine (PC) such

as, for example, soybean PC, and egg PC. Another type is formed from mixtures of phospholipid and/or phosphatidylcholine and/or cholesterol.

[0167] Examples of other methods to introduce liposomes into cells *in vitro* and *in vivo* include U.S. Pat. No. 5,283,185; U.S. Pat. No. 5,171,678; WO 94/00569; WO 93/24640; WO 91/16024; Feigner, (1994) J. Biol. Chem. 269:2550; Nabel, (1993) Proc. Natl. Acad. Sci. 90:11307; Nabel, (1992) Human Gene Ther. 3:649; Gershon, (1993) Biochem. 32:7143; and Strauss, (1992) EMBO J. 11:417.

[0168] Non-ionic liposomal systems have also been examined to determine their utility in the delivery of drugs to the skin, in particular systems comprising non-ionic surfactant and cholesterol. Non-ionic liposomal formulations comprising NOVASOME™ I (glyceryl dilaurate/cholesterol/polyoxyethylene-10-stearyl ether) and NOVASOME™ II (glyceryl distearate/cholesterol/polyoxyethylene-10-stearyl ether) were used to deliver cyclosporin-A into the dermis of mouse skin. Results indicated that such non-ionic liposomal systems were effective in facilitating the deposition of cyclosporine A into different layers of the skin (Hu *et al.*, (1994) S.T.P. Pharma. Sci., 4(6):466).

[0169] Liposomes may also be sterically stabilized liposomes, comprising one or more specialized lipids that result in enhanced circulation lifetimes relative to liposomes lacking such specialized lipids. Examples of sterically stabilized liposomes are those in which part of the vesicle-forming lipid portion of the liposome (A) comprises one or more glycolipids, such as monosialoganglioside GM₁, or (B) is derivatized with one or more hydrophilic polymers, such as a polyethylene glycol (PEG) moiety. While not wishing to be bound by any particular theory, it is thought in the art that, at least for sterically stabilized liposomes containing gangliosides, sphingomyelin, or PEG-derivatized lipids, the enhanced circulation half-life of these sterically stabilized liposomes derives from a reduced uptake into cells of the reticuloendothelial system (RES) (Allen *et al.*, (1987) FEBS Letters, 223:42; Wu *et al.*, (1993) Cancer Research, 53:3765).

[0170] Various liposomes comprising one or more glycolipids are known in the art. Papahadjopoulos *et al.* (Ann. N.Y. Acad. Sci., (1987), 507:64) reported the ability of monosialoganglioside GM₁, galactocerebroside sulfate, and phosphatidylinositol to improve blood half-lives of liposomes. These findings were expounded upon by Gabizon *et al.* (Proc. Natl. Acad. Sci. U.S.A., (1988), 85:6949). U.S. Pat. No. 4,837,028 and WO 88/04924, both to Allen *et al.*, disclose liposomes comprising (1) sphingomyelin and (2) the ganglioside GM₁ or a

galactocerebroside sulfate ester. U.S. Pat. No. 5,543,152 (Webb *et al.*) discloses liposomes comprising sphingomyelin. Liposomes comprising 1,2-sn-dimyristoylphosphatidylcholine are disclosed in WO 97/13499 (Lim *et al.*).

[0171] In one embodiment, cationic liposomes are used. Cationic liposomes possess the advantage of being able to fuse to the cell membrane. Non-cationic liposomes, although not able to fuse as efficiently with the plasma membrane, are taken up by macrophages *in vivo* and can be used to deliver oligonucleotides to macrophages.

[0172] Further advantages of liposomes include: liposomes obtained from natural phospholipids are biocompatible and biodegradable; liposomes can incorporate a wide range of water and lipid soluble drugs; liposomes can protect encapsulated oligonucleotides in their internal compartments from metabolism and degradation (Rosoff, in "Pharmaceutical Dosage Forms," Lieberman, Rieger and Banker (Eds.), 1988, volume 1, p. 245). Important considerations in the preparation of liposome formulations are the lipid surface charge, vesicle size and the aqueous volume of the liposomes.

[0173] A positively charged synthetic cationic lipid, N-[1-(2,3-dioleoyloxy)propyl]-N,N,N-trimethylammonium chloride (DOTMA) can be used to form small liposomes that interact spontaneously with nucleic acid to form lipid-nucleic acid complexes which are capable of fusing with the negatively charged lipids of the cell membranes of tissue culture cells, resulting in delivery of oligonucleotide (see, *e.g.*, Feigner, P. L. *et al.*, (1987) Proc. Natl. Acad. Sci. USA 8:7413-7417, and U.S. Pat. No. 4,897,355 for a description of DOTMA and its use with DNA).

[0174] A DOTMA analogue, 1,2-bis(oleoyloxy)-3-(trimethylammonia)propane (DOTAP) can be used in combination with a phospholipid to form DNA-complexing vesicles.

LIPOFECTIN™ (Bethesda Research Laboratories, Gaithersburg, Md.) is an effective agent for the delivery of highly anionic nucleic acids into living tissue culture cells that comprise positively charged DOTMA liposomes which interact spontaneously with negatively charged polynucleotides to form complexes. When enough positively charged liposomes are used, the net charge on the resulting complexes is also positive. Positively charged complexes prepared in this way spontaneously attach to negatively charged cell surfaces, fuse with the plasma membrane, and efficiently deliver functional nucleic acids into, for example, tissue culture cells. Another commercially available cationic lipid, 1,2-bis(oleoyloxy)-3,3-

(trimethylammonia)propane ("DOTAP") (Boehringer Mannheim, Indianapolis, Ind.) differs from DOTMA in that the oleoyl moieties are linked by ester, rather than ether linkages.

[0175] Other reported cationic lipid compounds include those that have been conjugated to a variety of moieties including, for example, carboxyspermine which has been conjugated to one of two types of lipids and includes compounds such as 5-carboxyspermylglycine dioctaoleoylamide ("DOGS") (TRANSFECTAM™, Promega, Madison, Wis.) and dipalmitoylphosphatidylethanolamine 5-carboxyspermyl-amide ("DPPES") (see, *e.g.*, U.S. Pat. No. 5,171,678).

[0176] Another cationic lipid conjugate includes derivatization of the lipid with cholesterol ("DC-Chol") which has been formulated into liposomes in combination with DOPE (See, Gao, X. and Huang, L., (1991) *Biochim. Biophys. Res. Commun.* 179:280). Lipopolylysine, made by conjugating polylysine to DOPE, has been reported to be effective for transfection in the presence of serum (Zhou, X. *et al.*, (1991) *Biochim. Biophys. Acta* 1065:8). For certain cell lines, these liposomes containing conjugated cationic lipids, are said to exhibit lower toxicity and provide more efficient transfection than the DOTMA-containing compositions. Other commercially available cationic lipid products include DMRIE and DMRIE-HP (Vical, La Jolla, Calif.) and Lipofectamine (DOSPA) (Life Technology, Inc., Gaithersburg, Md.). Other cationic lipids suitable for the delivery of oligonucleotides are described in WO 98/39359 and WO 96/37194.

[0177] Liposomal formulations are particularly suited for topical administration, liposomes present several advantages over other formulations. Such advantages include reduced side effects related to high systemic absorption of the administered drug, increased accumulation of the administered drug at the desired target, and the ability to administer oligonucleotide into the skin. In some implementations, liposomes are used for delivering oligonucleotide to epidermal cells and also to enhance the penetration of oligonucleotide into dermal tissues, *e.g.*, into skin. For example, the liposomes can be applied topically. Topical delivery of drugs formulated as liposomes to the skin has been documented (see, *e.g.*, Weiner *et al.*, (1992) *Journal of Drug Targeting*, vol. 2, 405-410 and du Plessis *et al.*, (1992) *Antiviral Research*, 18:259-265; Mannino, R. J. and Fould-Fogerite, S., (1998) *Biotechniques* 6:682-690; Itani, T. *et al.*, (1987) *Gene* 56:267-276; Nicolau, C. *et al.* (1987) *Meth. Enzymol.* 149:157-176; Straubinger, R. M. and

Papahadjopoulos, D. (1983) *Meth. Enzymol.* 101:512-527; Wang, C. Y. and Huang, L., (1987) *Proc. Natl. Acad. Sci. USA* 84:7851-7855).

[0178] Non-ionic liposomal systems have also been examined to determine their utility in the delivery of drugs to the skin, in particular systems comprising non-ionic surfactant and cholesterol. Non-ionic liposomal formulations comprising NOVASOME I (glyceryl dilaurate/cholesterol/polyoxyethylene-10-stearyl ether) and NOVASOME II (glyceryl distearate/cholesterol/polyoxyethylene-10-stearyl ether) were used to deliver a drug into the dermis of mouse skin. Such formulations with oligonucleotides are useful for treating a dermatological disorder.

[0179] The targeting of liposomes is also possible based on, for example, organ-specificity, cell-specificity, and organelle-specificity and is known in the art. In the case of a liposomal targeted delivery system, lipid groups can be incorporated into the lipid bilayer of the liposome in order to maintain the targeting ligand in stable association with the liposomal bilayer. Various linking groups can be used for joining the lipid chains to the targeting ligand. Additional methods are known in the art and are described, for example in U.S. Patent Application Publication No. 20060058255, the linking groups of which are herein incorporated by reference.

[0180] Liposomes that include oligonucleotides can be made highly deformable. Such deformability can enable the liposomes to penetrate through pore that are smaller than the average radius of the liposome. For example, transfersomes are yet another type of liposomes, and are highly deformable lipid aggregates which are attractive candidates for drug delivery vehicles. Transfersomes can be described as lipid droplets which are so highly deformable that they are easily able to penetrate through pores which are smaller than the droplet. Transfersomes can be made by adding surface edge activators, usually surfactants, to a standard liposomal composition. Transfersomes that include oligonucleotides can be delivered, for example, subcutaneously by infection in order to deliver oligonucleotides to keratinocytes in the skin. In order to cross intact mammalian skin, lipid vesicles must pass through a series of fine pores, each with a diameter less than 50 nm, under the influence of a suitable transdermal gradient. In addition, due to the lipid properties, these transfersomes can be self-optimizing (adaptive to the shape of pores, *e.g.*, in the skin), self-repairing, and can frequently reach their targets without fragmenting, and often self-loading. Transfersomes have been used to deliver serum albumin to

the skin. The transfersome-mediated delivery of serum albumin has been shown to be as effective as subcutaneous injection of a solution containing serum albumin.

[0181] Other formulations amenable to the present disclosure are described in PCT Publication Nos. WO 2009/088891, WO 2009/132131, and WO 2008/042973, which are hereby incorporated by reference in their entirety.

[0182] Surfactants find wide application in formulations such as emulsions (including microemulsions) and liposomes. The most common way of classifying and ranking the properties of the many different types of surfactants, both natural and synthetic, is by the use of the hydrophile/lipophile balance (HLB). The nature of the hydrophilic group (also known as the "head") provides the most useful means for categorizing the different surfactants used in formulations (Rieger, in *Pharmaceutical Dosage Forms*, Marcel Dekker, Inc., New York, N.Y., 1988, p. 285).

[0183] If the surfactant molecule is not ionized, it is classified as a nonionic surfactant. Nonionic surfactants find wide application in pharmaceutical and cosmetic products and are usable over a wide range of pH values. In general, their HLB values range from 2 to about 18 depending on their structure. Nonionic surfactants include nonionic esters such as ethylene glycol esters, propylene glycol esters, glyceryl esters, polyglyceryl esters, sorbitan esters, sucrose esters, and ethoxylated esters. Nonionic alkanolamides and ethers such as fatty alcohol ethoxylates, propoxylated alcohols, and ethoxylated/propoxylated block polymers are also included in this class. The polyoxyethylene surfactants are the most popular members of the nonionic surfactant class.

[0184] If the surfactant molecule carries a negative charge when it is dissolved or dispersed in water, the surfactant is classified as anionic. Anionic surfactants include carboxylates such as soaps, acyl lactylates, acyl amides of amino acids, esters of sulfuric acid such as alkyl sulfates and ethoxylated alkyl sulfates, sulfonates such as alkyl benzene sulfonates, acyl isethionates, acyl taurates and sulfosuccinates, and phosphates. The most important members of the anionic surfactant class are the alkyl sulfates and the soaps.

[0185] If the surfactant molecule carries a positive charge when it is dissolved or dispersed in water, the surfactant is classified as cationic. Cationic surfactants include quaternary ammonium salts and ethoxylated amines. The quaternary ammonium salts are the most used members of this class.

[0186] If the surfactant molecule has the ability to carry either a positive or negative charge, the surfactant is classified as amphoteric. Amphoteric surfactants include acrylic acid derivatives, substituted alkylamides, N-alkylbetaines, and phosphatides.

[0187] The use of surfactants in drug products, formulations and in emulsions has been reviewed (Rieger, in *Pharmaceutical Dosage Forms*, Marcel Dekker, Inc., New York, N.Y., 1988, p. 285).

[0188] The oligonucleotides for use in the methods of the disclosure can also be provided as micellar formulations. Micelles are a particular type of molecular assembly in which amphipathic molecules are arranged in a spherical structure such that all the hydrophobic portions of the molecules are directed inward, leaving the hydrophilic portions in contact with the surrounding aqueous phase. The converse arrangement exists if the environment is hydrophobic.

Lipid Nanoparticle-Based Delivery Methods

[0189] Oligonucleotides of in the disclosure may be fully encapsulated in a lipid formulation, *e.g.*, a lipid nanoparticle (LNP), or other nucleic acid-lipid particle. LNPs are useful for systemic applications, as they exhibit extended circulation lifetimes following intravenous (*i.v.*) injection and accumulate at distal sites (*e.g.*, sites physically separated from the administration site). LNPs include "pSPLP," which include an encapsulated condensing agent-nucleic acid complex as set forth in PCT Publication No. WO 00/03683. The particles of the present disclosure typically have a mean diameter of about 50 nm to about 150 nm, more typically about 60 nm to about 130 nm, more typically about 70 nm to about 110 nm, most typically about 70 nm to about 90 nm, and are substantially nontoxic. In addition, the nucleic acids when present in the nucleic acid-lipid particles of the present disclosure are resistant in aqueous solution to degradation with a nuclease. Nucleic acid-lipid particles and their method of preparation are disclosed in, *e.g.*, U.S. Pat. Nos. 5,976,567; 5,981,501; 6,534,484; 6,586,410; 6,815,432; U.S. Publication No. 2010/0324120 and PCT Publication No. WO 96/40964.

[0190] Non-limiting examples of cationic lipids include N,N-dioleoyl-N,N-dimethylammonium chloride (DODAC), N,N-distearyl-N,N-dimethylammonium bromide (DDAB), N--(I-(2,3-dioleoyloxy)propyl)-N,N,N-trimethylammonium chloride (DOTAP), N--(I-(2,3-dioleoyloxy)propyl)-N,N,N-trimethylammonium chloride (DOTMA), N,N-dimethyl-2,3-dioleoyloxy)propylamine (DODMA), 1,2-DiLinoleoyloxy-N,N-dimethylaminopropane

(DLinDMA), 1,2-Dilinolenyloxy-N,N-dimethylaminopropane (DLenDMA), 1,2-Dilinoleylcarbamoyloxy-3-dimethylaminopropane (DLin-C-DAP), 1,2-Dilinoleoxy-3-(dimethylamino)acetoxyp propane (DLin-DAC), 1,2-Dilinoleoxy-3-morpholinopropane (DLin-MA), 1,2-Dilinoleoyl-3-dimethylaminopropane (DLinDAP), 1,2-Dilinoleylthio-3-dimethylaminopropane (DLin-S-DMA), 1-Linoleoyl-2-linoleyloxy-3-dimethylaminopropane (DLin-2-DMAP), 1,2-Dilinoleoxy-3-trimethylaminopropane chloride salt (DLin-TMA.Cl), 1,2-Dilinoleoyl-3-trimethylaminopropane chloride salt (DLin-TAP.Cl), 1,2-Dilinoleoxy-3-(N-methylpiperazino)propane (DLin-MPZ), or 3-(N,N-Dilinoleylamino)-1,2-propanediol (DLinAP), 3-(N,N-Dioleylamino)-1,2-propanedio (DOAP), 1,2-Dilinoleyloxo-3-(2-N,N-dimethylamino)ethoxypropane (DLin-EG-DMA), 1,2-Dilinolenyloxy-N,N-dimethylaminopropane (DLinDMA), 2,2-Dilinoleyl-4-dimethylaminomethyl-[1,3]-dioxolane (DLin-K-DMA) or analogs thereof, (3aR,5s,6aS)-N,N-dimethyl-2,2-di((9Z,12Z)-octadeca-9,12-dienyetetrahydro-- 3aH-cyclopenta[d][1,3]dioxol-5-amine (ALN100), (6Z,9Z,28Z,31Z)-heptatriaconta-6,9,28,31-tetraen-19-yl-4-(dimethylamino)butanoate (MC3), 1,1'-(2-(4-(2-((2-bis(2-hydroxydodecyl)amino)ethyl)(2-hydroxydodecyl)amino)ethyl)piperazin-1-yeethylazanediyedidodecan-2-ol (Tech G1), or a mixture thereof. The cationic lipid can comprise, for example, from about 20 mol % to about 50 mol % or about 40 mol % of the total lipid present in the particle.

[0191] The ionizable/non-cationic lipid can be an anionic lipid or a neutral lipid including, but not limited to, distearoylphosphatidylcholine (DSPC), dioleoylphosphatidylcholine (DOPC), dipalmitoylphosphatidylcholine (DPPC), dioleoylphosphatidylglycerol (DOPG), dipalmitoylphosphatidylglycerol (DPPG), dioleoyl-phosphatidylethanolamine (DOPE), palmitoyl-oleoylphosphatidylcholine (POPC), palmitoyl-oleoylphosphatidylethanolamine (POPE), dioleoyl-phosphatidylethanolamine 4-(N-maleimidomethyl)-cyclohexane-1-carboxylate (DOPE-mal), dipalmitoyl phosphatidyl ethanolamine (DPPE), dimyristoylphosphoethanolamine (DMPE), distearoyl-phosphatidyl-ethanolamine (DSPE), 16-O-monomethyl PE, 16-O-dimethyl PE, 18-1-trans PE, 1-stearoyl-2-oleoyl-phosphatidylethanolamine (SOPE), cholesterol, or a mixture thereof. The non-cationic lipid can be, for example, from about 5 mol % to about 90 mol %, about 10 mol %, or about 60 mol % if cholesterol is included, of the total lipid present in the particle.

[0192] The conjugated lipid that inhibits aggregation of particles can be, for example, a polyethyleneglycol (PEG)-lipid including, without limitation, a PEG-diacylglycerol (DAG), a PEG-dialkylloxypropyl (DAA), a PEG-phospholipid, a PEG-ceramide (Cer), or a mixture thereof. The PEG-DAA conjugate can be, for example, a PEG-dilauryloxypropyl (C₁₂), a PEG-dimyristyloxypropyl (C₁₄), a PEG-dipalmitoyloxypropyl (C₁₆), or a PEG-distearoyloxypropyl (C₁₈). The conjugated lipid that prevents aggregation of particles can be, for example, from 0 mol % to about 20 mol % or about 2 mol % of the total lipid present in the particle.

[0193] In some embodiments, the nucleic acid-lipid particle further includes cholesterol at, *e.g.*, about 10 mol % to about 60 mol % or about 50 mol % of the total lipid present in the particle.

[0194] The ASO may also be delivered in a lipidoid. The synthesis of lipidoids has been extensively described and formulations containing these compounds are particularly suited for delivery of modified nucleic acid molecules or ASOs (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).

[0195] Lipid compositions for RNA delivery are disclosed in PCT Publication Nos. WO2012/170930A1, WO2013/149141A1, and WO2014/152211A1, each of which is hereby incorporated by reference.

IV. THERAPEUTIC APPLICATIONS

[0196] The present disclosure provides methods for treating diseases and disorders associated with decreased gene expression (*e.g.*, decreased CPS1 gene expression). The method employs an ASO that hybridizes with a regulatory RNA transcribed from a regulatory element of the target gene (*e.g.*, CPS1) or a pharmaceutical composition comprising the ASO. The oligonucleotide compositions described herein are useful in the methods of the disclosure and, while not bound by theory, are believed to exert their desirable effects through their ability to modulate the level, status, and/or activity of CPS1, *e.g.*, by increasing the level of the CPS1 protein in a cell in a subject (*e.g.*, a mammal, a primate, or a human).

[0197] Also provided herein are methods of treating or preventing hyperammonemia in a subject, including administering an ASO described herein to the subject. The disclosure further provides methods of treating or preventing hyperammonemia in a subject that has or is at risk of developing hyperammonemia, including administering an ASO described herein to the subject. In some embodiments, the subject having or at risk of developing hyperammonemia has one or more of the following: a urea cycle disorder, hepatic encephalopathy, acute liver failure, liver cirrhosis, non-alcoholic fatty liver disease, renal dysfunction and/or failure, propionic acidemia, methylmalonic acidemia, isovaleric acidemia, a urinary tract infection, intestinal bacterial overgrowth, a fatty acid oxidation disorder, and a systemic infection. In some embodiments, the subject has or is at risk of developing hyperammonemia associated with the intake of a drug (e.g., valproic acid, carbamazepine, fluorouracil, sulfadiazine, ribavirin, salicylates, and glycine). In some embodiments, the methods include administering an ASO described herein to the subject. In certain embodiments, treatment with an ASO described herein results in decreased ammonia levels (e.g., blood ammonia levels, plasma ammonia levels, systemic ammonia levels, or cerebrospinal fluid ammonia levels) in a subject as compared to a subject (e.g., the same subject prior to the treatment) that has not been treated with the ASO. In some embodiments, the reduction in ammonia levels (e.g., blood ammonia levels, systemic ammonia levels, or cerebrospinal fluid ammonia levels) is a reduction of at least about 5%, 10%, 15%, 20%, 25%, 30%, 40%, 50%, 60%, 70%, 80%, 90%, or 100%, relative to the ammonia levels (e.g., blood ammonia levels, systemic ammonia levels, or cerebrospinal fluid ammonia levels) in the subject (e.g., as compared to the same subject prior to administration of the ASO).

[0198] Methods of measuring ammonia levels (e.g., in a plasma sample) are known in the art and include enzymatic kinetic assays in which ammonia reacts with α -ketoglutarate and reduced nicotinamide adenine dinucleotide phosphate (NADPH) in the presence of L-glutamate dehydrogenase resulting in glutamate and NADP^+ . The amount of oxidized NADPH is then measured (e.g., photometrically) and is equivalent to the amount of ammonia.

[0199] An aspect of the present disclosure relates to methods of treating disorders (e.g., a urea cycle disorder) in a subject (e.g., a human subject) in need thereof. In some embodiments, provided herein are methods of treating a urea cycle disorder in a subject (e.g., a human subject) in need thereof, including administering an ASO provided herein to the subject. In some embodiments, the urea cycle disorder is carbamoyl-phosphate synthetase 1 (CPS1) deficiency,

ornithine transcarbamylase (OTC) deficiency, citrullinemia type I (argininosuccinate synthetase (ASS) deficiency), argininosuccinate lyase (ASL) deficiency, N-acetyl glutamate synthetase (NAGS) deficiency, arginase deficiency (hyperargininemia, ARG1 deficiency), ornithine translocase deficiency (ORNT1 deficiency, hyperornithinemia-hyperammonemia-homocitrullinuria syndrome (HHH)), or citrin deficiency. In some embodiments, the urea cycle disorder is not N-acetyl glutamate synthetase (NAGS) deficiency. In some embodiments, administration of an ASO provided herein to a subject having a urea cycle disorder reduces the risk, frequency and/or severity of a hyperammonemic crisis in the subject (e.g., as compared to a subject that is not administered the ASO (e.g., the same subject prior to administration of the ASO)).

[0200] In some embodiments, the urea cycle disorder is Carbamoylphosphate synthetase I deficiency (CPS1 deficiency). In some embodiments, the urea cycle disorder is hyperammonemia. In some embodiments, the urea cycle disorder is Ornithine transcarbamylase deficiency (OTC deficiency). In some embodiments, the urea cycle disorder is Citrullinemia type I (ASS1 deficiency). In some embodiments, the urea cycle disorder is Argininosuccinic aciduria (ASL deficiency). In some embodiments, the urea cycle disorder is Arginase deficiency (hyperargininemia, ARG1 deficiency). In some embodiments, the urea cycle disorder is Ornithine translocase deficiency (ORNT1 deficiency, hyperornithinemia-hyperammonemia-homocitrullinuria syndrome). In some embodiments, the urea cycle disorder is Citrin deficiency.

[0201] Another aspect of the disclosure includes methods of increasing the level of CPS1 in a cell of a subject identified as having a CPS1 related disorder (e.g., CPS1 deficiency) or other urea cycle disorder. Still another aspect includes a method of increasing expression of CPS1 in a cell in a subject. The methods may include contacting a cell with an ASO described herein, in an amount effective to increase expression of CPS1 in the cell, thereby increasing expression of CPS1 in the cell. In certain embodiments, the methods include contacting a cell with an ASO described herein, in an amount effective to increase expression of CPS1 in the cell, thereby increasing expression of OTC in the cell. In certain embodiments, the methods include contacting a cell with an ASO described herein, in an amount effective to increase expression of CPS1 in the cell, thereby increasing expression of other urea cycle genes in the cell, such as OTC, ASS1, ASL, ARG1, or ORNT1.

[0202] Based on the above methods, further aspects of the present disclosure include an ASO or oligonucleotide of the disclosure, or a composition comprising such an ASO or oligonucleotide, for use in therapy, or for use as a medicament, or for use in treating a CPS1 related disorder (e.g., CPS1 deficiency) or other urea cycle disorder in a subject in need thereof, or for use in increasing the level of CPS1 in a cell of a subject identified as having a CPS1 related disorder or other urea cycle disorder, or for use in increasing expression of CPS1 in a cell in a subject. The uses include the contacting of a cell with the ASO or oligonucleotide, in an amount effective to increase expression of CPS1 in the cell, thereby increasing expression of CPS1 in the cell. Embodiments described below in relation to the methods of the present disclosure are also applicable to these further aspects.

[0203] Contacting of a cell with an ASO or oligonucleotide may be done *in vitro*, *ex vivo*, or *in vivo*. Contacting a cell *in vivo* with the oligonucleotide includes contacting a cell or group of cells within a subject, e.g., a human subject, with the ASO or oligonucleotide. Combinations of *in vitro* and *in vivo* methods of contacting a cell are also possible. Contacting a cell may be direct or indirect, as discussed above. Furthermore, contacting a cell may be accomplished via a targeting ligand, including any ligand described herein or known in the art. In some embodiments, the targeting ligand is a carbohydrate moiety, e.g., a GalNAc3 ligand, or any other ligand that directs the oligonucleotide to a site of interest. The cell can be a liver cell (e.g., a hepatocyte).

[0204] Administration of the ASO or oligonucleotide or pharmaceutical composition disclosed herein could be intravenous, intraarterial, intraperitoneal, intramuscular, subcutaneous, intrapleural, intrathecal, intracavitary, by perfusion through a catheter or by direct intralesional injection. In certain embodiments, the ASO or oligonucleotide or pharmaceutical composition is administered systemically. In certain embodiments, the ASO or oligonucleotide or pharmaceutical composition is administered by a parenteral route. For example, in certain embodiments, the ASO or oligonucleotide or pharmaceutical composition is administered by intravenously (e.g., by intravenous infusion), for example, with a prefilled bag, a prefilled pen, or a prefilled syringe. In other embodiments, the ASO or oligonucleotide or pharmaceutical composition is administered locally to an organ or tissue in which an increase in the target gene expression is desirable (e.g., liver).

[0205] In some embodiments, the ASO or oligonucleotide is administered to a subject such that the ASO or oligonucleotide is delivered to a specific site within the subject. Such targeted delivery can be achieved by either systemic administration or local administration. The increase of expression of CPS1 may be assessed using measurements of the level or change in the level of CPS1 mRNA or CPS1 protein in a sample derived from a specific site within the subject. In some embodiments, the methods include measuring the levels of ammonia in a sample (e.g., blood, urine, plasma or cerebrospinal fluid) derived from the subject. Methods of measuring ammonia levels are well known in the art and described above. In certain embodiments, the methods include a clinically relevant increase of expression of CPS1, e.g., as demonstrated by a clinically relevant outcome after treatment of a subject with an agent to increase the expression of CPS1.

[0206] In other embodiments, the oligonucleotide is administered in an amount and for a time effective to result in reduction (e.g., by 10%, 20%, 30%, 40%, 50%, 60%, 70%, 80%, 90%, or 100%) of one or more symptoms of a CPS1 related disorder or a urea cycle disorder, such as high ammonia level in the blood.

Increase of CPS1 expression level

[0207] The therapeutic methods disclosed herein, using an ASO that targets CPS1, are designed to increase CPS1 expression level in a subject as compared to an untreated subject (e.g., the same subject prior to administration of the ASO or the pharmaceutical composition). Increasing expression of a CPS1 gene includes any level of increasing of a CPS1 gene, e.g., at least partial increase of the expression of a CPS1 gene. Increase may be assessed by an increase in an absolute or relative level of one or more of these variables compared with a control level. The control level may be any type of control level that is utilized in the art, e.g., a pre-dose baseline level, or a level determined from a similar subject, cell, or sample that is untreated or treated with a control (such as, e.g., buffer only control or inactive agent control). In certain embodiments, the method causes a clinically relevant increase of expression of CPS1, e.g. as demonstrated by a clinically relevant outcome after treatment of a subject with an agent to increase the expression of CPS1.

[0208] In certain embodiments, the methods disclosed herein increases CPS1 gene expression by at least about 1%, at least about 2%, at least about 5%, at least about 10%, at least about 15%, at least about 20%, at least about 25%, at least about 30%, at least about 35%, at

least about 40%, at least about 45%, at least about 50%, at least about 55%, at least about 60%, at least about 65%, at least about 70%, at least about 75%, at least about 80%, at least about 85%, at least about 90%, at least about 91%, at least about 92%, at least about 93%, at least about 94%, at least about 95%, at least about 96%, at least about 97%, at least about 98%, or at least about 99%, relative to the pre-dose baseline level. In certain embodiments, the methods disclosed herein increases CPS1 gene expression by at least 2 fold, at least 3 fold, at least 4 fold, at least 5 fold, at least 6 fold, at least 7 fold, at least 8 fold, at least 9 fold, or at least 10 fold relative to the pre-dose baseline level. In certain embodiments, the subject has a deficiency in CPS1 expression, and the method disclosed herein restores the CPS1 expression level or activity to 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 at least 100% of the average CPS1 expression level or activity in subjects of the species of like age and gender.

[0209] The expression of a CPS1 gene may be assessed based on the level of any variable associated with CPS1 gene expression, *e.g.*, CPS1 mRNA level or CPS1 protein level. It is understood that CPS1 is a chromosome-2 gene in certain mammals (*e.g.*, human and mouse). In certain embodiments, the expression level or activity of CPS1 herein refers to the average expression level or activity in the liver.

[0210] In certain embodiments, surrogate markers can be used to detect an increase of CPS1 expression level. For example, effective treatment of a CPS1 related disorder, as demonstrated by acceptable diagnostic and monitoring criteria with an agent to increase CPS1 expression can be understood to demonstrate a clinically relevant increase in CPS1.

[0211] Increase of the expression of a CPS1 gene may be manifested by an increase of the amount of mRNA expressed by a first cell or group of cells (such cells may be present, for example, in a sample derived from a subject) in which a CPS1 gene is transcribed and which has or have been treated (*e.g.*, by contacting the cell or cells with an oligonucleotide of the disclosure, or by administering an oligonucleotide of the disclosure to a subject in which the cells are or were present) such that the expression of a CPS1 gene is increased, as compared to a second cell or group of cells substantially identical to the first cell or group of cells but which has not or have not been so treated (control cell(s) not treated with an oligonucleotide or not treated with an oligonucleotide targeted to the gene of interest).

[0212] In other embodiments, increase of the expression of a CPS1 gene may be assessed in terms of an increase of a parameter that is functionally linked to CPS1 gene expression, *e.g.*, CPS1 protein expression or CPS1 activity. CPS1 increase may be determined in any cell expressing CPS1, either endogenous or heterologous from an expression construct, and by any assay known in the art.

[0213] An increase of CPS1 expression may be manifested by an increase in the level of the CPS1 protein that is expressed by a cell or group of cells (*e.g.*, the level of protein expressed in a sample derived from a subject), relative to a control cell or a control group of cells. An increase of CPS1 expression may also be manifested by an increase in the level of the CPS1 mRNA level in a treated cell or group of cells, relative to a control cell or a control group of cells.

[0214] A control cell or group of cells that may be used to assess the increase of the expression of a CPS1 gene includes a cell or group of cells that has not yet been contacted with an oligonucleotide of the disclosure. For example, the control cell or group of cells may be derived from an individual subject (*e.g.*, a human or animal subject) prior to treatment of the subject with an oligonucleotide.

[0215] The level of CPS1 mRNA that is expressed by a cell or group of cells may be determined using any method known in the art for assessing mRNA expression. In one embodiment, the level of expression of CPS1 in a sample is determined by detecting a transcribed polynucleotide, or portion thereof, *e.g.*, mRNA of the CPS1 gene. RNA may be extracted from cells using RNA extraction techniques including, for example, using acid phenol/guanidine isothiocyanate extraction (RNAzol B; Biogenesis), RNEASY™ RNA preparation kits (Qiagen) or PAXgene (PreAnalytix, Switzerland). Typical assay formats utilizing ribonucleic acid hybridization include nuclear run-on assays, RT-PCR, RNase protection assays, northern blotting, in situ hybridization, and microarray analysis. Circulating CPS1 mRNA may be detected using methods described in PCT Publication No. WO 2012/177906, the entire contents of which are hereby incorporated herein by reference. In some embodiments, the level of expression of CPS1 is determined using a nucleic acid probe. The term "probe," as used herein, refers to any molecule that is capable of selectively binding to a specific CPS1 sequence, *e.g.* to an mRNA or polypeptide. Probes can be synthesized by one of skill in the art, or derived from appropriate biological preparations. Probes may be specifically

designed to be labeled. Examples of molecules that can be utilized as probes include, but are not limited to, RNA, DNA, proteins, antibodies, and organic molecules.

[0216] Isolated mRNA can be used in hybridization or amplification assays that include, but are not limited to, Southern or northern analyses, polymerase chain reaction (PCR) analyses, and probe arrays. One method for the determination of mRNA levels involves contacting the isolated mRNA with a nucleic acid molecule (probe) that can hybridize to CPS1 mRNA. In one embodiment, the mRNA is immobilized on a solid surface and contacted with a probe, for example by running the isolated mRNA on an agarose gel and transferring the mRNA from the gel to a membrane, such as nitrocellulose. In an alternative embodiment, the probe(s) are immobilized on a solid surface and the mRNA is contacted with the probe(s), for example, in an AFFYMETRIX gene chip array. A skilled artisan can readily adapt known mRNA detection methods for use in determining the level of CPS1 mRNA.

[0217] An alternative method for determining the level of expression of CPS1 in a sample involves the process of nucleic acid amplification and/or reverse transcriptase (to prepare cDNA) of for example mRNA in the sample, e.g., by RT-PCR (the experimental embodiment set forth in Mullis, 1987, U.S. Pat. No. 4,683,202), ligase chain reaction (Barany (1991) Proc. Natl. Acad. Sci. USA 88:189-193), self-sustained sequence replication (Guatelli et al. (1990) Proc. Natl. Acad. Sci. USA 87:1874-1878), transcriptional amplification system (Kwoh et al. (1989) Proc. Natl. Acad. Sci. USA 86:1173-1177), Q-Beta Replicase (Lizardi et al. (1988) Bio/Technology 6:1197), rolling circle replication (Lizardi et al., U.S. Pat. No. 5,854,033) or any other nucleic acid amplification method, followed by the detection of the amplified molecules using techniques well known to those of skill in the art. These detection schemes are especially useful for the detection of nucleic acid molecules if such molecules are present in very low numbers. In particular aspects of the invention, the level of expression of CPS1 is determined by quantitative fluorogenic RT-PCR (i.e., the TAQMANTM System) or the DUAL-GLO® Luciferase assay.

[0218] The expression levels of CPS1 mRNA may be monitored using a membrane blot (such as used in hybridization analysis such as northern, Southern, dot, and the like), or microwells, sample tubes, gels, beads or fibers (or any solid support comprising bound nucleic acids). See U.S. Pat. Nos. 5,770,722; 5,874,219; 5,744,305; 5,677,195; and 5,445,934, which are incorporated herein by reference. The determination of CPS1 expression level may also comprise using nucleic acid probes in solution.

[0219] In some embodiments, the level of mRNA expression is assessed using branched DNA (bDNA) assays or real time RT PCR or qPCR. Such methods can also be used for the detection of CPS1 nucleic acids.

[0220] The level of CPS1 protein expression may be determined using any method known in the art for the measurement of protein levels. Such methods include, for example, electrophoresis, capillary electrophoresis, high performance liquid chromatography (HPLC), thin layer chromatography (TLC), hyperdiffusion chromatography, fluid or gel precipitin reactions, absorption spectroscopy, a colorimetric assays, spectrophotometric assays, flow cytometry, immunodiffusion (single or double), immunoelectrophoresis, western blotting, radioimmunoassay (RIA), enzyme-linked immunosorbent assays (ELISAs), immunofluorescent assays, electrochemiluminescence assays, and the like. Such assays can also be used for the detection of proteins indicative of the presence or replication of CPS1 proteins.

V. ADDITIONAL EMBODIMENTS

[0221] **Embodiment 1** An ASO complementary to at least 8 contiguous nucleotides of a regulatory RNA (regRNA) of Carbamoyl-Phosphate Synthetase 1 (CPS1), wherein the ASO is complementary to a sequence in the regRNA that is no more than 200 nucleotides from a terminus of the regRNA.

Embodiment 2 The ASO of embodiment 1, wherein the ASO is complementary to a sequence in the regRNA that is no more than 200 nucleotides from the 3' end of the regRNA.

Embodiment 3 The ASO of embodiment 1, wherein the ASO is complementary to a sequence in the regRNA that is no more than 200 nucleotides from the 5' end of the regRNA.

Embodiment 4 The ASO of embodiments 1 or 2, wherein the ASO comprises a RNA polynucleotide comprising one or more chemical modifications.

Embodiment 5 The ASO of embodiment 1, wherein at least 3, 4, or 5 nucleotides at the 5' end and at least 3, 4, or 5 nucleotides at the 3' end of the ASO comprise ribonucleotides with one or more chemical modifications.

Embodiment 6 The ASO of embodiments 1 or 2, wherein the one or more chemical modifications comprise 2'-O-methoxyethyl, 5-methyl cytidine, locked nucleic acid (LNA), and phosphorothioate internucleotide bond.

Embodiment 7 The ASO of embodiments 1-3, wherein the ASO does not comprise 8 or more contiguous nucleotides of unmodified DNA.

Embodiment 8 An ASO complementary to at least 8 contiguous nucleotides of a regulatory RNA of a CPS1 gene, wherein the ASO does not comprise 8 or more contiguous nucleotides of unmodified DNA.

Embodiment 9 The ASO of embodiments 1-8, wherein the ASO does not comprise a deoxyribonucleotide.

Embodiment 10 The ASO of embodiments 1-9, wherein the ASO does not comprise an unmodified ribonucleotide.

Embodiment 11 The ASO of embodiments 1-10, wherein the length of the ASO is $3 \times n + 2$ nucleotides (n is an integer of 6 or greater), wherein the nucleotides at positions $3 \times m$ are ribonucleotides modified by LNA (m is an integer from 1 to n) and the nucleotides at the remaining positions are ribonucleotides modified by 2'-O-methoxyethyl.

Embodiment 12 The ASO of embodiments 1-11, wherein each nucleotide of the ASO is a ribonucleotide modified by 2'-O-methoxyethyl.

Embodiment 13 The ASO of embodiments 1-12, wherein each cytidine in the ASO is modified by 5-methyl.

Embodiment 14 The ASO of embodiments 1-13, wherein the ASO is no more than 50, 40, 30, or 25 nucleotides in length.

Embodiment 15 The ASO of embodiments 1-14, wherein the regRNA is an eRNA.

Embodiment 16 A pharmaceutical composition comprising the ASO of any one of embodiments 1-15 and a pharmaceutically acceptable carrier or excipient carrier.

Embodiment 17 A method of increasing the amount and/or stability of a regulatory RNA in a cell, the method comprising contacting the cell with the ASO of any one of embodiments 1-15 that hybridizes with the regulatory RNA.

Embodiment 18 A method of increasing transcription of a target gene in a cell, the method comprising contacting the cell with the ASO of any one of embodiments 1-15 that hybridizes with a regulatory RNA of the target gene.

Embodiment 19 The method of embodiments 17 or 18, wherein the cell is a mammalian cell.

Embodiment 20 The method of embodiment 19, wherein the cell is a human cell.

Embodiment 21 The method of embodiments 17-20, wherein the target gene is CPS1.

EXAMPLES

Example 1: Modulation of CPS1 expression using regRNA-targeting ASOs

[0222] This example was designed to assess modulation of CPS1 expression in human hepatocytes using ASOs targeting eRNAs transcribed from an enhancer of human CPS1.

[0223] Regulatory RNAs (regRNAs) within enhancers of CPS1 were identified bioinformatically using ATAC-seq and H3K27Ac ChIP-SEQ data from human and mouse data. Two regRNAs were identified (RR44_v1 and RR44_v2) as conserved between human and mouse, as shown in **FIG. 2**.

[0224] 330 unique antisense oligonucleotides (ASOs) targeting CPS1 were designed, 94 of which target the CPS1 regRNA described above (RR44).

[0225] Donor-derived hepatocytes were cultured *in vitro*. Cells were plated in growth media and treated 4-6 hours after plating with final concentrations of 1.25 μ M, 2.5 μ M, or 5 μ M, or hCPS1-ASO-1a or control (see **FIG. 5A** for human CPS1 sequences and chemical modifications of selected ASOs). Cells were collected 48 hr post treatment and processed for RNA isolation, cDNA synthesis and QPCR analysis. A Taqman probe at 60X was used for CPS1 expression. CPS1 levels were normalized to B2M expression. **FIG. 3** shows CPS1 mRNA after treatment with hCPS1-ASO-1a, demonstrating the ASO targeting regRNA RR44 increased human CPS1 mRNA in a dose-dependent manner.

[0226] Using hCPS1-ASO-1a as a starting point, additional ASOs were designed by base-walking. These ASOs are shown in **FIG. 4A**. Using the methods described above, these additional ASOs were assessed for effect on CPS1 mRNA, and results are shown in **FIG. 4B**. Additional ASOs are shown in **FIG. 5A**.

[0227] The majority of regRNAs do not have large sequence areas that are conserved between human and mouse genomes. For *in vivo* proof of concept, regRNAs around the mouse CPS1 region were identified and ASOs targeting those mouse regRNA (promoter and enhancer) were designed and screened in both wildtype (B6EiC3SnF1/J, [WT]) primary mouse hepatocytes and CPS1 deficient donor (B6EiC3Sn *a/A-CPS1*^{spf-ash}/J, [CPS1D]) primary mouse hepatocytes.

[0228] Primary hepatocytes were isolated from mice of mouse strains B6EiC3SnF1/J (control WT) and OTC deficient donor (B6EiC3Sn *a/A-OTC*^{spf-ash}/J, catalog: 001811) from JAX lab. The spf^{ash} mouse has a variant c.386G>A, p.Arg129His in the *OTC* gene that impacts

splicing, resulting in decreased OTC mRNA levels (5~12% of wt control) in *spf/ash* livers. Thus, male *spf^{ash}* mice have a mild biochemical phenotype with low OTC activity (5%-10% of wild-type).

[0229] Primary hepatocytes were seeded at 20,000 cells per well on day 0. Cells were treated with ASO on day 2 at concentrations of 1.25 μ M, 2.5 μ M, and 5 μ M. Cells were incubated for 2 days and lysate was collected on Day 2 post treatment for mRNA analysis. A Taqman probe was used for determining mouse CPS1 and OTC expression. *Ppia* and *Hprt* were used as housekeeper genes for gene expression normalization. Statistics were performed using one-way ANOVA in Prism (GraphPad)

[0230] CPS1 mRNA levels in treated wildtype and OTC-deficient hepatocytes *in vitro*, are shown in **FIG. 6A**, heatmaps are shown in **FIG. 6B** and **FIG. 6C**. As shown, a subset of the identified ASOs upregulate CPS1 mRNA by 2-fold in treated hepatocytes. Additionally, it was observed that ASOs that upregulate CPS1 may also increase expression of OTC (OTC mRNA levels shown in **FIG. 7A** and heatmaps are shown in **FIG. 7B** and **FIG. 7C**). Thus, ASO targeting regRNA can be used to increase CPS1 expression in diseased mice liver cells. ASO mediated CPS1 upregulation in OTC deficient mouse cells allow these to be tested in a disease model, and have an *in vivo* phenotypic readout.

In vivo modulation of CPS1

[0231] Male B6EiC3Sn a/A-Otc^{spf-ash/J} Mice (homozygous), 4-5 mice/group, were fasted, then challenged with 0.75M NH₄Cl injected intraperitoneally. Two hours later, a dose of 200mg/kg/wk subcutaneous injection of GalNAc-conjugated ASO was administered. Mice were again dosed with GalNAc-conjugated ASO about 48 hours later. About 24 hours later, mice were challenged with 0.75M NH₄Cl injected intraperitoneally, and about 24 hours subsequently were again dosed with GalNAc-conjugated ASO. After 72 hours, mice were injected with 0.75M NH₄Cl intraperitoneally and dosed with GalNAc-conjugated ASO. 48 hours later, mice were injected with 0.75M NH₄Cl intraperitoneally, and 2 hours later, were sacrificed. The timeline is depicted in **FIG. 8**. Serum was collected 30-60 minutes post- NH₄Cl injection, and terminal plasma samples were analyzed by IDEXX for ammonia levels. Liver, serum, and urine were collected following sacrifice.

[0232] As shown in **FIG. 9A**, ASO treatment increased CPS1 mRNA in the mouse liver by about 1.4-fold. Additionally, plasma ammonia levels were decreased following treatment,

indicated increased ureagenesis (**FIG. 9B**). ASOs targeting CPS1 regRNA additionally increased a number of other urea cycle genes, including ASS1, ASL, and ARG1 in OTC-deficient mice (**FIG. 9C**). Importantly, ASOs targeting CPS1 regRNA did not influence expression levels neighboring genes (**FIG. 9D**).

[0233] In an additional experiment, Male B6EiC3Sn a/A-Otc^{spf-ash/J} Mice (homozygous), 4-5 mice/group, were fasted, then challenged with 0.75M NH₄Cl injected intraperitoneally and subcutaneously injected with GalNAc-conjugated ASO. Terminal plasma samples collected 60 min after NH₄Cl injection was analyzed by IDEXX for ammonia levels, with an upper detection limit of 1020 µg/dL. As shown in **FIG. 10**, CPS1 regRNA targeting mCPS1-ASO-2 decreased ammonia back to wildtype levels in the OTC deficient mice.

[0234] As shown in **FIG. 11A** and **11B**, there was a dose dependent impact on plasma ammonia (**FIG. 11A**) and urea (**FIG. 11B**) *in vivo* in male OTCD mice (*Otc^{spf-ash}*) after the ASO treatment. The ammonia challenge was given after overnight fasting of the mice. Briefly, mice received a 0.75 M solution of ammonium chloride via IP injection. Interim plasma was collected at 30 minutes post each ammonium challenge (±5%). Ammonia levels were measured in fresh plasma samples by Beckman Coulter AU® chemistry analyzers. In addition, the reduction in ammonia correlated with the total ASO administered (**FIG. 11C**). Without wishing to be bound by theory this data suggests dose accumulation of the ASO and thus supports a long duration of action of the ASO. In addition, the data suggests that ASO efficacy can be achieved by splitting the dose over time, allowing for a greater safety margin during dosing. For example, at least a 1 month dosing interval may be used.

[0235] A second *in vivo* experiment was performed to assess the ASO duration of action. Male B6EiC3Sn a/A-Otc^{spf-ash/J} Mice (homozygous) or wild type (C57BL/6) mice, 5 mice/group, were fasted, then challenged with 0.75M NH₄Cl injected intraperitoneally. Two hours later, a dose of 100mg/kg/wk subcutaneous injection of GalNAc-conjugated ASO was administered (day 1). WT and one group of OTC-deficient mice were administered PBS as control groups. Mice were again dosed with GalNAc-conjugated ASO on days 3 and 5. Ammonia was administered intraperitoneally to mice on days 8, 11, 15, 19, 22, and 26. Circulating ammonia was measured post-IP ammonia challenge. Mice were sacrificed on day 26 and livers were collected and processed for mRNA and protein expression. mRNA geomean was quantified by GusB, Gapdh,

Actb, Ppia, and Hprt genes. Statistics were done by two way ANOVA. Two way ANOVA, *: $P < 0.05$, **: $P < 0.01$, ***: $P < 0.001$, ****: $P < 0.0001$

[0236] As shown in **FIG. 12A**, Cps1 ASO treatment increased mouse Otc and Cps1 mRNA expression in the OTC deficient mice (1.26 FC of Cps1 and 1.43 FC of Otc). WT C57 mice mRNA is shown on the left bar, Otc^{spf-ash/J} treated with PBS is shown in middle bar, and Otc^{spf-ash/J} treated with ASO is shown on the right. In addition, ASO treatment increased additional urea cycle genes, such as Nags, Ass1, Asl, and Arg1 (**FIG. 12B**). WT C57 mice mRNA is shown on the left bar, Otc^{spf-ash/J} treated with PBS is shown in middle bar, and Otc^{spf-ash/J} treated with ASO is shown on the right.

[0237] In the PBS control group, mouse Otc deficient livers showed hyperammonia 30 min after ammonia treatment (**FIG. 13**, see black triangle at 1.0). Ammonia levels were consistent through the study. Treatment with mouse Cps1 ASO (upside down triangles) decreased ammonia to WT levels (squares) and maintained the wild type (WT) levels throughout the study (**FIG. 13**). ASO was administered on days 1, 3, and 5 but the duration of action was approximately 4 weeks.

[0238] The *in vivo* assay was repeated with hCPS1-ASO-1x in Yecuris mice (*Fah*^{-/-}; *Rag2*^{-/-}; *Il2rg*^{-/-} (FRG) mice with OTC deficient humanized liver). Male humanized Yecuris mice were repopulated with human ornithine transcarbamylase deficient hepatocytes (OTCD) or with healthy wild-type hepatocytes (WT), 5 mice/group. After fasting overnight, 0.75M ¹⁵NH₄Cl was injected intraperitoneally. Two hours later, multiple doses of GalNAc-conjugated hCPS1-ASO-1x were subcutaneously injected on days 1, 8, and 15. In some groups, a single injection of 5, 20, and 50 mg/kg/week doses were performed. WT and one group of OTCD Yecuris FRG mice were administered with PBS as control groups. Ammonia challenge and ureagenesis assay in humanized Yecuris mice were performed in a fasted state, i.e. food withdrawal overnight, prior to the ammonia challenge. After fasting overnight on days 1, 8, 15, and 22 (terminal harvest) the animals were challenged with ¹⁵NH₄Cl by intraperitoneal injection. After 30 minutes, urines and plasmas were collected..

[0239] As shown in **FIG. 15A** and **15B**, hCPS1-ASO-1x decreased *in vivo* plasma ammonia and increased *in vivo* urea in the OTC^{def} mice with humanized liver. hCPS1-ASO-1g also increased OTC protein levels after treatment at 5 mg/kg and 20 mg/kg (**FIG. 15C**).

In vitro modulation of ureagenesis in primary human hepatocytes

[0240] ASOs were also tested for their ability to agonize ureagenesis in human cells *in vitro*. Healthy donor primary human hepatocytes and OTC^{def} primary human hepatocytes were plated and 1.25 μ M of hCPS1-ASO-1a or hCPS1-ASO-1g were incubated with the cells for two days. On the second day 2 M NH₄Cl was added to the cell mixture. Cells and cell media were collected on Day 3 for mRNA and urea quantification. As shown in **FIG. 16**, both ASOs increased CPS1 mRNA and ureagenesis in both healthy and OTC^{def} primary human hepatocytes.

[0241] **Synthesis and characterization of additional ASOs**

[0242] Additional ASOs were synthesized and characterized. Hepatocytes were treated with 5 μ M ASO as described above and CPS1 mRNA fold change was determined.

[0243] **Table 4** proves the mRNA FC and standard deviation in CPS1 mRNA.

Table 4								
Name	FC	SD	Name	FC	SD	Name	FC	SD
hCPS1-ASO-1a	5.5803	0.9290	hCPS1-ASO-85b	2.4815	0.2779	hCPS1-ASO-204	1.0451	0.2891
hCPS1-ASO-16	1.6607	0.2690	hCPS1-ASO-86	2.5546	0.1486	hCPS1-ASO-205	1.0432	0.1968
hCPS1-ASO-17	1.1878	0.2382	hCPS1-ASO-1ab	1.2337	0.1193	hCPS1-ASO-206	0.9000	0.1529
hCPS1-ASO-18	1.3738	0.1466	hCPS1-ASO-1ac	1.3452	0.4155	hCPS1-ASO-207	1.0064	0.2810
hCPS1-ASO-19	1.3322	0.2929	hCPS1-ASO-1ad	1.7071	0.3347	hCPS1-ASO-208	0.8499	0.1017
hCPS1-ASO-20	1.4049	0.2328	hCPS1-ASO-1ae	1.4598	0.2254	hCPS1-ASO-209	0.8872	0.2187
hCPS1-ASO-21	3.6049	0.0613	hCPS1-ASO-1af	1.1069	0.2738	hCPS1-ASO-210	1.0426	0.2646
hCPS1-ASO-22	1.2367	0.1154	hCPS1-ASO-1ag	1.2439	0.3771	hCPS1-ASO-211	0.8667	0.1797
hCPS1-ASO-23	1.0846	0.1572	hCPS1-ASO-1ah	1.9014	0.3037	hCPS1-ASO-212	1.1604	0.2568
hCPS1-ASO-24	1.0683	0.1120	hCPS1-ASO-1ai	3.0003	0.6407	hCPS1-ASO-213	1.0240	0.2239
hCPS1-ASO-25	0.9967	0.1307	hCPS1-ASO-92	1.4093	0.0630	hCPS1-ASO-214	0.9408	0.2219
hCPS1-ASO-26	1.1141	0.2129	hCPS1-ASO-93	1.3278	0.1805	hCPS1-ASO-215	1.2719	0.3355
hCPS1-ASO-27	1.2348	0.2667	hCPS1-ASO-94	1.1871	0.0806	hCPS1-ASO-216	0.9536	0.2038
hCPS1-ASO-28	3.7994	0.7319	hCPS1-ASO-95	1.0937	0.1027	hCPS1-ASO-217	0.9589	0.2111
hCPS1-ASO-29	1.2569	0.2946	hCPS1-ASO-96	1.0708	0.1544	hCPS1-ASO-218	0.9624	0.1812
hCPS1-ASO-30	0.9996	0.1342	hCPS1-ASO-97	1.8697	0.2390	hCPS1-ASO-219	1.0837	0.3110
hCPS1-ASO-31	1.0879	0.2887	hCPS1-ASO-98	2.2671	0.0950	hCPS1-ASO-220	1.0236	0.1605

hCPS1-ASO-32	1.0803	0.0754	hCPS1-ASO-99	3.2286	0.3834	hCPS1-ASO-221	1.0461	0.2903
hCPS1-ASO-33	1.0982	0.2301	hCPS1-ASO-100	1.6813	0.1274	hCPS1-ASO-222	1.0435	0.2238
hCPS1-ASO-34	0.9376	0.0691	hCPS1-ASO-101	2.8205	0.0827	hCPS1-ASO-223	1.1306	0.4103
hCPS1-ASO-35	4.5563	0.0988	hCPS1-ASO-102	3.1424	0.1637	hCPS1-ASO-224	1.0954	0.1792
hCPS1-ASO-36	1.1589	0.1449	hCPS1-ASO-103	3.7109	0.4564	hCPS1-ASO-225	0.8416	0.2138
hCPS1-ASO-37	1.0707	0.1475	hCPS1-ASO-104	5.0641	0.2305	hCPS1-ASO-226	1.0220	0.2833
hCPS1-ASO-38	1.0941	0.1276	hCPS1-ASO-107	1.4662	0.1834	hCPS1-ASO-227	0.8141	0.1635
hCPS1-ASO-39	1.1150	0.1947	hCPS1-ASO-108	1.3163	0.1848	hCPS1-ASO-228	0.7884	0.1280
hCPS1-ASO-40	1.1812	0.0713	hCPS1-ASO-109	1.1404	0.1269	hCPS1-ASO-229	0.8821	0.1602
hCPS1-ASO-41	1.1376	0.1669	hCPS1-ASO-110	1.4157	0.2399	hCPS1-ASO-230	1.0366	0.2360
hCPS1-ASO-42	3.9849	0.9906	hCPS1-ASO-111	1.3974	0.0526	hCPS1-ASO-231	1.0731	0.3336
hCPS1-ASO-43	1.1340	0.1748	hCPS1-ASO-112	1.3309	0.2948	hCPS1-ASO-232	1.0336	0.2169
hCPS1-ASO-44	0.9795	0.1452	hCPS1-ASO-113	1.1250	0.0133	hCPS1-ASO-233	1.0184	0.2427
hCPS1-ASO-45	1.0825	0.3286	hCPS1-ASO-114	1.4471	0.3902	hCPS1-ASO-234	1.0379	0.2667
hCPS1-ASO-46	1.3008	0.2339	hCPS1-ASO-115	1.3250	0.2205	hCPS1-ASO-235	0.7109	0.1642
hCPS1-ASO-47	1.2834	0.2346	hCPS1-ASO-116	1.4592	0.2191	hCPS1-ASO-236	0.9437	0.2016
hCPS1-ASO-48	1.0953	0.2896	hCPS1-ASO-117	1.5146	0.1541	hCPS1-ASO-237	1.1237	0.2948
hCPS1-ASO-49	1.4947	0.3320	hCPS1-ASO-118	1.4798	0.3053	hCPS1-ASO-238	0.8325	0.1677
hCPS1-ASO-50	1.2992	0.2852	hCPS1-ASO-119	1.4687	0.3357	hCPS1-ASO-239	1.2847	0.3268
hCPS1-ASO-51	1.0101	0.2333	hCPS1-ASO-120	1.4309	0.2206	hCPS1-ASO-240	1.0368	0.1643
hCPS1-ASO-52	1.2026	0.2065	hCPS1-ASO-121	1.5330	0.4945	hCPS1-ASO-241	1.0348	0.2319
hCPS1-ASO-53	1.3176	0.2462	hCPS1-ASO-122	2.1728	1.0205	hCPS1-ASO-242	1.2009	0.3035
hCPS1-ASO-54	1.2888	0.1512	hCPS1-ASO-123	1.3792	0.2117	hCPS1-ASO-243	0.8364	0.1646
hCPS1-ASO-55	0.9070	0.0979	hCPS1-ASO-124	1.6351	0.2666	hCPS1-ASO-244	0.9177	0.1890
hCPS1-ASO-56	2.2957	0.4780	hCPS1-ASO-125	1.9894	0.2327	hCPS1-ASO-245	0.9563	0.2149
hCPS1-ASO-57	1.3780	0.1587	hCPS1-ASO-126	1.8741	0.1928	hCPS1-ASO-246	1.0945	0.1746
hCPS1-ASO-58	1.1027	0.1230	hCPS1-ASO-127	1.9805	0.5252	hCPS1-ASO-247	1.1518	0.1876

hCPS1-ASO-59	1.2449	0.2215	hCPS1-ASO-128	1.7071	0.2968	hCPS1-ASO-248	1.1365	0.2040
hCPS1-ASO-60	1.4067	0.1655	hCPS1-ASO-129	1.8255	0.4447	hCPS1-ASO-249	0.9208	0.2208
hCPS1-ASO-61	1.2124	0.0876	hCPS1-ASO-130	1.9578	0.6166	hCPS1-ASO-250	1.1458	0.2996
hCPS1-ASO-62	0.9895	0.1303	hCPS1-ASO-131	1.3484	0.2757	hCPS1-ASO-251	0.8471	0.1852
hCPS1-ASO-63	2.3654	0.4539	hCPS1-ASO-132	1.4400	0.3570	hCPS1-ASO-252	0.7147	0.0925
hCPS1-ASO-64	1.1365	0.1718	hCPS1-ASO-133	1.4004	0.1358	hCPS1-ASO-253	0.6961	0.1808
hCPS1-ASO-65	0.8489	0.1813	hCPS1-ASO-134	1.5631	0.1290	hCPS1-ASO-254	0.8060	0.1913
hCPS1-ASO-66	1.2409	0.1946	hCPS1-ASO-135	1.6723	0.4246	hCPS1-ASO-255	0.8039	0.1878
hCPS1-ASO-67	0.9222	0.1245	hCPS1-ASO-136	1.6023	0.3159	hCPS1-ASO-256	0.7368	0.0548
hCPS1-ASO-68	1.3275	0.1510	hCPS1-ASO-137	1.5022	0.2462	hCPS1-ASO-257	0.9517	0.2562
hCPS1-ASO-69	1.0944	0.2374	hCPS1-ASO-138	1.9038	0.5748	hCPS1-ASO-258	1.0658	0.3429
hCPS1-ASO-70	1.5761	0.1388	hCPS1-ASO-139	1.6131	0.1660	hCPS1-ASO-259	0.8157	0.2459
hCPS1-ASO-71	1.3363	0.1613	hCPS1-ASO-140	1.6504	0.2242	hCPS1-ASO-260	1.1626	0.2553
hCPS1-ASO-72	1.0412	0.1404	hCPS1-ASO-141	1.8803	0.2397	hCPS1-ASO-261	0.9754	0.1961
hCPS1-ASO-73	1.3314	0.2056	hCPS1-ASO-142	3.0769	0.3542	hCPS1-ASO-262	1.3364	0.3546
hCPS1-ASO-74	1.2915	0.1170	hCPS1-ASO-143	1.9543	0.5131	hCPS1-ASO-263	1.0346	0.1123
hCPS1-ASO-75	1.2395	0.0952	hCPS1-ASO-144	3.5634	0.5168	hCPS1-ASO-264	0.6237	0.0401
hCPS1-ASO-76	1.0942	0.2650	hCPS1-ASO-145	2.8153	0.5824	hCPS1-ASO-265	0.7730	0.1091
hCPS1-ASO-1b	1.1870	0.1452	hCPS1-ASO-146	1.5756	0.0004	hCPS1-ASO-266	0.8882	0.1967
hCPS1-ASO-1c	1.4590	0.2142	hCPS1-ASO-147	1.8075	0.1998	hCPS1-ASO-267	0.7796	0.2146
hCPS1-ASO-1d	1.0277	0.1069	hCPS1-ASO-148	1.6902	0.0950	hCPS1-ASO-268	0.9467	0.1832
hCPS1-ASO-1e	1.0992	0.1400	hCPS1-ASO-149	1.5828	0.0817	hCPS1-ASO-269	0.9570	0.1712
hCPS1-ASO-1f	1.6978	0.4026	hCPS1-ASO-150	1.6598	0.1305	hCPS1-ASO-270	0.8511	0.1498
hCPS1-ASO-1g	4.4990	0.6087	hCPS1-ASO-151	1.7341	0.2274	hCPS1-ASO-271	0.9859	0.1688
hCPS1-ASO-2	4.3014	0.9287	hCPS1-ASO-152	1.7582	0.2844	hCPS1-ASO-272	0.7428	0.0842
hCPS1-ASO-3	2.2218	0.1531	hCPS1-ASO-153	1.8459	0.3518	hCPS1-ASO-273	0.8121	0.1444
hCPS1-ASO-9a	1.0275	0.1642	hCPS1-ASO-154	1.5900	0.4826	hCPS1-ASO-274	0.7497	0.1493

hCPS1-ASO-10a	1.1384	0.2750	hCPS1-ASO-155	1.3183	0.0726	hCPS1-ASO-275	0.7799	0.1717
hCPS1-ASO-11a	1.1334	0.1617	hCPS1-ASO-156	0.9952	0.1123	hCPS1-ASO-276	0.8826	0.1542
hCPS1-ASO-12a	0.8162	0.0866	hCPS1-ASO-157	1.2972	0.1294	hCPS1-ASO-277	0.8896	0.2650
hCPS1-ASO-13a	1.5297	0.1882	hCPS1-ASO-158	1.7248	0.2074	hCPS1-ASO-278	0.4696	0.0748
hCPS1-ASO-14a	0.9744	0.0844	hCPS1-ASO-159	1.7892	0.3807	hCPS1-ASO-279	1.3629	0.1492
hCPS1-ASO-15a	0.9225	0.1756	hCPS1-ASO-160	1.6078	0.2263	hCPS1-ASO-280	1.9970	0.4340
hCPS1-ASO-7a	0.6872	0.0821	hCPS1-ASO-161	1.0960	0.6012	hCPS1-ASO-281	1.9249	0.2595
hCPS1-ASO-4a	1.5925	0.1816	hCPS1-ASO-162	1.5522	0.6413	hCPS1-ASO-282	1.4252	0.4261
hCPS1-ASO-5a	2.1196	0.3491	hCPS1-ASO-163	1.1633	0.0408	hCPS1-ASO-283	4.4672	1.1138
hCPS1-ASO-6a	1.8529	0.9210	hCPS1-ASO-164	1.3349	0.1053	hCPS1-ASO-284	5.0837	1.5527
hCPS1-ASO-8a	1.5270	0.8361	hCPS1-ASO-165	1.6669	0.2143	hCPS1-ASO-285	4.7339	0.3981
hCPS1-ASO-9b	0.8992	0.0590	hCPS1-ASO-166	1.3915	0.2569	hCPS1-ASO-286	1.5091	0.3739
hCPS1-ASO-10b	0.9770	0.0428	hCPS1-ASO-167	1.7175	0.2493	hCPS1-ASO-287	1.3469	0.3479
hCPS1-ASO-11b	1.6000	0.2631	hCPS1-ASO-168	1.1979	0.1337	hCPS1-ASO-288	1.6093	0.2169
hCPS1-ASO-12b	0.9917	0.1514	hCPS1-ASO-169	1.3335	0.2080	hCPS1-ASO-289	0.9802	0.3187
hCPS1-ASO-13b	1.1117	0.1612	hCPS1-ASO-170	1.0882	0.3444	hCPS1-ASO-290	1.6650	0.1183
hCPS1-ASO-14b	0.8017	0.0536	hCPS1-ASO-171	1.2852	0.1472	hCPS1-ASO-291	1.7705	0.4831
hCPS1-ASO-15b	0.8779	0.0632	hCPS1-ASO-172	1.3309	0.1877	hCPS1-ASO-292	1.8768	0.3481
hCPS1-ASO-7b	0.9488	0.0891	hCPS1-ASO-173	1.3430	0.2467	hCPS1-ASO-293	1.8295	0.3331
hCPS1-ASO-4b	0.9687	0.1444	hCPS1-ASO-174	1.2633	0.2020	hCPS1-ASO-294	4.2131	0.7748
hCPS1-ASO-5b	0.9448	0.1081	hCPS1-ASO-175	1.6397	0.3383	hCPS1-ASO-295	0.8242	0.1736
hCPS1-ASO-6b	0.8277	0.0428	hCPS1-ASO-176	1.3926	0.5390	hCPS1-ASO-296	1.7239	0.4255
hCPS1-ASO-8b	0.9161	0.1199	hCPS1-ASO-177	1.4242	0.2749	hCPS1-ASO-297	2.0747	0.4485
hCPS1-ASO-77	4.1549	0.9198	hCPS1-ASO-178	1.4453	0.2574	hCPS1-ASO-298	1.1081	0.1802
hCPS1-ASO-78	2.2972	0.1418	hCPS1-ASO-179	1.2086	0.0863	hCPS1-ASO-299	5.1515	0.9679
hCPS1-ASO-79	2.4319	0.2248	hCPS1-ASO-180	1.2183	0.1814	hCPS1-ASO-300	4.8213	0.9887
hCPS1-ASO-80	2.7917	0.6061	hCPS1-ASO-181	1.3878	0.1419	hCPS1-ASO-301	3.3943	0.6421

hCPS1-ASO-1h	1.1727	0.1382	hCPS1-ASO-182	1.3813	0.1038	hCPS1-ASO-302	1.8365	0.4610
hCPS1-ASO-1i	1.4355	0.1558	hCPS1-ASO-183	1.2326	0.1733	hCPS1-ASO-303a	1.3137	0.2222
hCPS1-ASO-1j	1.2027	0.0988	hCPS1-ASO-184	1.3169	0.3607	hCPS1-ASO-303b	1.7427	0.3256
hCPS1-ASO-1k	1.1188	0.0499	hCPS1-ASO-185	1.4697	0.2622	hCPS1-ASO-304a	2.2107	0.3595
hCPS1-ASO-1l	1.3171	0.1662	hCPS1-ASO-186	1.2855	0.3984	hCPS1-ASO-304b	2.0165	0.7982
hCPS1-ASO-1m	1.1873	0.1099	hCPS1-ASO-187	1.3655	0.2214	hCPS1-ASO-305a	1.8751	0.3138
hCPS1-ASO-1n	1.1683	0.1096	hCPS1-ASO-188	1.3777	0.1068	hCPS1-ASO-305b	2.9614	0.4636
hCPS1-ASO-1o	1.3191	0.1220	hCPS1-ASO-189	1.2786	0.1922	hCPS1-ASO-306a	2.9192	0.8811
hCPS1-ASO-1p	1.9562	0.0841	hCPS1-ASO-190	1.0252	0.0880	hCPS1-ASO-306b	3.4468	1.3494
hCPS1-ASO-1q	1.2673	0.1820	hCPS1-ASO-191	1.2291	0.1588	hCPS1-ASO-307a	1.3314	0.3165
hCPS1-ASO-1r	1.5857	0.1339	hCPS1-ASO-192	1.4614	0.2198	hCPS1-ASO-307	1.2205	0.1267
hCPS1-ASO-1s	2.5762	0.3147	hCPS1-ASO-193	1.4984	0.4280	hCPS1-ASO-308a	1.2918	0.2042
hCPS1-ASO-1t	2.4333	0.2508	hCPS1-ASO-194	0.9625	0.3146	hCPS1-ASO-308	1.1019	0.1488
hCPS1-ASO-1u	2.9405	0.2842	hCPS1-ASO-195	1.4616	0.2171	hCPS1-ASO-309a	1.9776	0.5046
hCPS1-ASO-1v	1.9457	0.2076	hCPS1-ASO-196	1.3635	0.0990	hCPS1-ASO-309b	1.4482	0.2178
hCPS1-ASO-82a	2.5019	0.3142	hCPS1-ASO-197	1.5088	0.2155	hCPS1-ASO-309c	1.8643	0.3592
hCPS1-ASO-83a	1.6054	0.1333	hCPS1-ASO-198	1.5691	0.1943	hCPS1-ASO-310a	2.1756	0.8122
hCPS1-ASO-83b	1.3049	0.1062	hCPS1-ASO-199	0.8877	0.2414	hCPS1-ASO-310b	2.1692	0.3493
hCPS1-ASO-84a	1.6594	0.1400	hCPS1-ASO-200	0.9393	0.1766	hCPS1-ASO-310c	1.5170	0.2149
hCPS1-ASO-84b	1.6155	0.2525	hCPS1-ASO-201	0.8805	0.1631	hCPS1-ASO-310d	1.7083	0.2543
hCPS1-ASO-85a	3.1551	0.2265	hCPS1-ASO-202	0.9079	0.1671	hCPS1-ASO-311a	3.7975	0.7950
hCPS1-ASO-1	1.2847	0.4866	hCPS1-ASO-203	0.8525	0.1637	hCPS1-ASO-311b	2.2173	0.2349
						hCPS1-ASO-311c	3.8806	0.8311

[0244] hCPS1-ASO-1a and hCPS1-ASO1g were tested in hepatocytes at increasing concentrations. 0.156 to 5 uM ASO was incubated with hepatocytes as described above. As shown in **Table 5**, both hCPS1-ASO-1a and hCPS1-ASO1g induced a dose dependent increase in CPS1 mRNA.

Table 5			
Name	FC	SD	Dose (uM)
hCPS1-ASO-1a	1.6220	0.0932	0.156
hCPS1-ASO-1a	1.9973	0.2021	0.313
hCPS1-ASO-1a	2.4574	0.1968	0.625
hCPS1-ASO-1a	3.7565	0.4598	1.25
hCPS1-ASO-1a	4.9565	0.7826	2.5
hCPS1-ASO-1a	4.9868	0.4258	5
hCPS1-ASO-1g	1.5646	0.0907	0.156
hCPS1-ASO-1g	1.7147	0.1318	0.313
hCPS1-ASO-1g	1.9748	0.3676	0.625
hCPS1-ASO-1g	3.3634	0.7101	2.5
hCPS1-ASO-1g	3.7516	0.7574	5

[0245] Additional chemical modifications were made to selected ASOs. The chemical modifications are provided in **FIG. 14**. Hepatocytes were incubated with 1.25 to 5 uM of the selected ASO as described above. The highest CSP1 mRNA fold change (FC) and standard deviation (SD) is provided in **Table 6**.

Table 6			
Name	FC	DS	Dose (uM)
hCPS1-ASO-1a	5.5803	0.9290	5uM
hCPS1-ASO-1b	1.1870	0.1452	5uM
hCPS1-ASO-1c	1.4590	0.2142	5uM
hCPS1-ASO-1d	1.0277	0.1069	5uM
hCPS1-ASO-1e	1.0992	0.1400	5uM
hCPS1-ASO-1f	1.6978	0.4026	5uM
hCPS1-ASO-1g	4.4990	0.6087	5uM
hCPS1-ASO-2	4.3014	0.9287	5uM
hCPS1-ASO-3	2.2218	0.1531	5uM
hCPS1-ASO-1h	1.1727	0.1382	1
hCPS1-ASO-1i	1.4355	0.1558	5uM
hCPS1-ASO-1j	1.2027	0.0988	5uM
hCPS1-ASO-1k	1.1188	0.0499	0.2
hCPS1-ASO-1l	1.3171	0.1662	5uM
hCPS1-ASO-1m	1.1873	0.1099	5uM
hCPS1-ASO-1n	1.1683	0.1096	1
hCPS1-ASO-1o	1.3191	0.1220	5uM
hCPS1-ASO-1p	1.9562	0.0841	5uM
hCPS1-ASO-1q	1.2673	0.1820	0.2
hCPS1-ASO-1r	1.5857	0.1339	5

hCPS1-ASO-1s	2.5762	0.3147	5
hCPS1-ASO-1t	2.4333	0.2508	5
hCPS1-ASO-1u	2.9405	0.2842	5
hCPS1-ASO-1v	1.9457	0.2076	5
hCPS1-ASO-82a	2.5019	0.3142	5
hCPS1-ASO-82a	2.5546	0.1486	5
hCPS1-ASO-86a	1.2337	0.1193	1.25
hCPS1-ASO-86b	1.3452	0.4155	2.5
hCPS1-ASO-87a	1.7071	0.3347	5
hCPS1-ASO-88a	1.4598	0.2254	5
hCPS1-ASO-89a	1.1069	0.2738	5
hCPS1-ASO-91a	1.9014	0.3037	5
hCPS1-ASO-91b	3.0003	0.6407	2.5
hCPS1-ASO-91c	1.8697	0.2390	2.5
hCPS1-ASO-91d	2.2671	0.0950	2.5
hCPS1-ASO-91e	3.2286	0.3834	2.5
hCPS1-ASO-91f	1.6813	0.1274	1.25
hCPS1-ASO-91g	2.8205	0.0827	2.5
hCPS1-ASO-91h	3.1424	0.1637	2.5
hCPS1-ASO-91i	3.7109	0.4564	1.25
hCPS1-ASO-91j	5.0641	0.2305	5uM
hCPS1-ASO-279a	1.3629	0.1492	5uM
hCPS1-ASO-280a	1.9970	0.4340	5uM
hCPS1-ASO-281a	1.9249	0.2595	5uM
hCPS1-ASO-282a	1.4252	0.4261	5uM
hCPS1-ASO-283a	4.4672	1.1138	5uM
hCPS1-ASO-284a	5.0837	1.5527	5uM
hCPS1-ASO-285a	4.7339	0.3981	5uM
hCPS1-ASO-286a	1.5091	0.3739	5uM
hCPS1-ASO-287a	1.3469	0.3479	5uM
hCPS1-ASO-288a	1.6093	0.2169	5uM
hCPS1-ASO-289a	0.9802	0.3187	5uM
hCPS1-ASO-290a	1.6650	0.1183	5uM
hCPS1-ASO-291a	1.7705	0.4831	5uM
hCPS1-ASO-292a	1.8768	0.3481	5uM
hCPS1-ASO-293a	1.8295	0.3331	5uM
hCPS1-ASO-294a	4.2131	0.7748	5uM
hCPS1-ASO-295a	0.8242	0.1736	5uM
hCPS1-ASO-296a	1.7239	0.4255	5uM
hCPS1-ASO-297a	2.0747	0.4485	5uM

hCPS1-ASO-298a	1.1081	0.1802	5uM
hCPS1-ASO-299a	5.1515	0.9679	5uM
hCPS1-ASO-300a	4.8213	0.9887	5uM
hCPS1-ASO-301a	3.3943	0.6421	5uM
hCPS1-ASO-302a	1.8365	0.4610	5uM
hCPS1-ASO-303a	1.3137	0.2222	5uM
hCPS1-ASO-303b	1.7427	0.3256	5uM
hCPS1-ASO-304a	2.2107	0.3595	5uM
hCPS1-ASO-304b	2.0165	0.7982	5uM
hCPS1-ASO-305a	1.8751	0.3138	5uM
hCPS1-ASO-305b	2.9614	0.4636	5uM
hCPS1-ASO-306a	2.9192	0.8811	5uM
hCPS1-ASO-306b	3.4468	1.3494	5uM
hCPS1-ASO-307a	1.3314	0.3165	5uM
hCPS1-ASO-307b	1.2205	0.1267	5uM
hCPS1-ASO-308a	1.2918	0.2042	5uM
hCPS1-ASO-308b	1.1019	0.1488	5uM
hCPS1-ASO-309a	1.9776	0.5046	5uM
hCPS1-ASO-309b	1.4482	0.2178	5uM
hCPS1-ASO-309c	1.8643	0.3592	5uM
hCPS1-ASO-310a	2.1756	0.8122	5uM
hCPS1-ASO-310b	2.1692	0.3493	5uM
hCPS1-ASO-310c	1.5170	0.2149	5uM
hCPS1-ASO-310d	1.7083	0.2543	5uM
hCPS1-ASO-311a	3.7975	0.7950	5uM
hCPS1-ASO-311b	2.2173	0.2349	5uM
hCPS1-ASO-311c	3.880599933	0.8311	5uM
hCPS1-ASO-312a	1.284688861	0.4866	5uM

[0246] In sum, 109 initial ASOs targeting CPS1 RR44 were made, of which 76 ASOs comprising 69 gapmers and 7 steric ASOs passed the first pass screen. These 76 ASOs were selected for tiling, and 9 ASOs, comprising 4 gapmers and 5 sterics were selected from this screen. A further 24 ASOs comprising 12 gapmers and 12 mixmers with additional chemistries were made via fine tuning. hCPS1-ASO-1g (SEQ ID NO: 22) was selected for further characterization. PO bonds, a GalNAc moiety and additional 5meC moieties were added for *in vivo* studies, resulting in hCPS1-ASO-1x (SEQ ID NO: 409).

Example 2: Synthesis and characterization of additional CPS1 regRNA-targeting ASOs

[0247] Two additional regRNAs, RR89 and RR90, were identified. ASOs targeting the new regRNA were synthesized and tested at 5 uM in hepatocytes as described above. The CPS1 mRNA fold increase after treatment with these ASOs is provided in **Table 7** below.

Table 7							
RR	Name	FC	SD	RR	Name	FC	SD
RR89	hCPS1-ASO-317	1.5775	0.8135	RR90	hCPS1-ASO-405	1.2012	0.2487
RR89	hCPS1-ASO-318	1.5826	0.7218	RR90	hCPS1-ASO-406	1.2865	0.2028
RR89	hCPS1-ASO-319	1.5962	0.4788	RR90	hCPS1-ASO-407	1.1295	0.2439
RR89	hCPS1-ASO-320	1.4931	0.7690	RR90	hCPS1-ASO-408	1.0533	0.2725
RR89	hCPS1-ASO-321	1.6746	0.6312	RR90	hCPS1-ASO-409	0.8087	0.1096
RR89	hCPS1-ASO-322	2.0095	0.7188	RR90	hCPS1-ASO-410	1.3942	0.5000
RR89	hCPS1-ASO-323	2.0440	1.0473	RR90	hCPS1-ASO-411	1.3583	0.3396
RR89	hCPS1-ASO-324	2.3892	0.8168	RR90	hCPS1-ASO-412	1.6266	0.7518
RR89	hCPS1-ASO-325	1.5915	0.7186	RR90	hCPS1-ASO-413	1.2538	0.4311
RR89	hCPS1-ASO-326	2.1136	1.1464	RR90	hCPS1-ASO-414	1.1461	0.3094
RR89	hCPS1-ASO-327	1.9483	0.9495	RR90	hCPS1-ASO-415	0.9143	0.0766
RR89	hCPS1-ASO-328	1.6812	0.5726	RR90	hCPS1-ASO-416	1.1560	0.1866
RR89	hCPS1-ASO-329	1.8316	0.9072	RR90	hCPS1-ASO-417	1.0591	0.2657
RR89	hCPS1-ASO-330	2.0059	0.8976	RR90	hCPS1-ASO-418	1.3887	0.3178
RR89	hCPS1-ASO-331	1.8741	0.7026	RR90	hCPS1-ASO-419	1.3402	0.4910
RR89	hCPS1-ASO-332	2.1500	0.7416	RR90	hCPS1-ASO-420	1.5140	0.3829
RR89	hCPS1-ASO-333	1.5499	0.5157	RR90	hCPS1-ASO-421	1.0943	0.2253
RR89	hCPS1-ASO-334	1.5552	0.4804	RR90	hCPS1-ASO-422	1.1711	0.1122
RR89	hCPS1-ASO-335	1.9576	0.5176	RR90	hCPS1-ASO-423	0.9694	0.1022
RR89	hCPS1-ASO-336	1.8716	0.6998	RR90	hCPS1-ASO-424	1.2236	0.1582
RR89	hCPS1-ASO-337	1.8125	0.8488	RR90	hCPS1-ASO-425	1.2610	0.1906
RR89	hCPS1-ASO-338	2.0401	0.7645	RR90	hCPS1-ASO-426	1.3614	0.2645
RR89	hCPS1-ASO-339	2.2799	1.3896	RR90	hCPS1-ASO-427	1.0732	0.1397
RR89	hCPS1-ASO-340	2.4647	1.1151	RR90	hCPS1-ASO-428	1.0589	0.2379
RR89	hCPS1-ASO-341	1.6513	0.6047	RR90	hCPS1-ASO-429	0.8780	0.1622
RR89	hCPS1-ASO-342	3.0261	1.3769	RR90	hCPS1-ASO-430	1.1569	0.1560
RR89	hCPS1-ASO-343	1.6381	0.7347	RR90	hCPS1-ASO-431	1.1585	0.1097
RR89	hCPS1-ASO-344	1.5409	0.4495	RR90	hCPS1-ASO-432	1.2950	0.2285
RR89	hCPS1-ASO-345	2.0952	1.0805	RR90	hCPS1-ASO-433	1.0298	0.2219
RR89	hCPS1-ASO-346	2.3178	1.3366	RR90	hCPS1-ASO-434	1.3012	0.0903
RR89	hCPS1-ASO-347	1.4951	0.6377	RR90	hCPS1-ASO-435	1.0841	0.1667
RR89	hCPS1-ASO-348	1.6709	0.5697	RR90	hCPS1-ASO-436	1.1873	0.2434
RR89	hCPS1-ASO-349	1.1956	0.5132	RR90	hCPS1-ASO-437	0.8902	0.4503
RR89	hCPS1-ASO-350	1.3203	0.7134	RR90	hCPS1-ASO-438	1.1951	0.1350
RR89	hCPS1-ASO-351	1.7942	1.1274	RR90	hCPS1-ASO-439	0.8887	0.0839

RR89	hCPS1-ASO-352	1.5520	0.9718	RR90	hCPS1-ASO-440	1.0615	0.1012
RR89	hCPS1-ASO-353	1.7568	1.2231	RR90	hCPS1-ASO-441	0.8649	0.0311
RR89	hCPS1-ASO-354	1.8507	1.1719	RR90	hCPS1-ASO-442	0.9772	0.1905
RR89	hCPS1-ASO-355	1.5305	0.8114	RR90	hCPS1-ASO-443	0.8815	0.2444
RR89	hCPS1-ASO-356	1.7731	0.9631	RR90	hCPS1-ASO-444	1.3442	0.1924
RR89	hCPS1-ASO-357	1.2436	0.7147	RR90	hCPS1-ASO-445	0.8889	0.0616
RR89	hCPS1-ASO-358	1.6246	1.3366	RR90	hCPS1-ASO-446	1.3171	0.2598
RR89	hCPS1-ASO-359	1.5335	1.0744	RR90	hCPS1-ASO-447	1.0407	0.0687
RR89	hCPS1-ASO-360	1.9214	1.5074	RR90	hCPS1-ASO-448	1.1217	0.1056
RR89	hCPS1-ASO-361	1.4754	0.9292	RR90	hCPS1-ASO-449	1.1537	0.3244
RR89	hCPS1-ASO-362	1.6906	1.0116	RR90	hCPS1-ASO-450	1.3109	0.2590
RR89	hCPS1-ASO-363	1.3134	0.7014	RR90	hCPS1-ASO-451	1.5129	0.6513
RR89	hCPS1-ASO-364	1.7029	0.7542	RR90	hCPS1-ASO-452	1.2111	0.1128
RR89	hCPS1-ASO-365	1.6591	0.7996	RR90	hCPS1-ASO-453	1.0163	0.1088
RR89	hCPS1-ASO-366	1.6470	1.0509	RR90	hCPS1-ASO-454	1.3094	0.3247
RR89	hCPS1-ASO-367	1.8307	1.2695	RR90	hCPS1-ASO-455	1.1397	0.2210
RR89	hCPS1-ASO-368	1.6084	0.9115	RR90	hCPS1-ASO-456	1.0946	0.1733
RR89	hCPS1-ASO-369	1.3892	0.8035	RR90	hCPS1-ASO-457	1.0506	0.1601
RR89	hCPS1-ASO-370	1.5032	0.7262	RR90	hCPS1-ASO-458	1.2491	0.2422
RR89	hCPS1-ASO-371	1.4850	0.5957	RR90	hCPS1-ASO-459	1.3670	0.2012
RR89	hCPS1-ASO-372	1.5812	0.5242	RR90	hCPS1-ASO-460	1.3623	0.1823
RR89	hCPS1-ASO-373	1.6841	0.7860	RR90	hCPS1-ASO-461	1.0625	0.2351
RR89	hCPS1-ASO-374	1.4621	0.9788	RR90	hCPS1-ASO-462	1.2013	0.4743
RR89	hCPS1-ASO-375	1.6176	1.1216	RR90	hCPS1-ASO-463	1.0886	0.1494
RR89	hCPS1-ASO-376	1.3686	0.7403	RR90	hCPS1-ASO-464	1.1047	0.2209
RR89	hCPS1-ASO-377	1.2268	0.8146	RR90	hCPS1-ASO-465	1.1645	0.1735
RR89	hCPS1-ASO-378	1.6610	1.1474	RR90	hCPS1-ASO-466	1.4413	0.3431
RR89	hCPS1-ASO-379	1.4860	0.8718	RR90	hCPS1-ASO-467	1.2275	0.0838
RR89	hCPS1-ASO-380	1.5339	0.5719	RR90	hCPS1-ASO-468	1.3235	0.1612
RR89	hCPS1-ASO-381	1.3295	0.5757	RR90	hCPS1-ASO-469	0.8282	0.2019
RR89	hCPS1-ASO-382	1.9644	0.7430	RR90	hCPS1-ASO-470	0.9232	0.2007
RR89	hCPS1-ASO-383	1.8440	1.1617	RR90	hCPS1-ASO-471	1.3966	0.5929
RR89	hCPS1-ASO-384	1.5065	0.9131	RR90	hCPS1-ASO-472	1.0118	0.3935
RR89	hCPS1-ASO-385	1.5340	0.7326	RR90	hCPS1-ASO-473	0.9936	0.0465
RR89	hCPS1-ASO-386	1.6840	0.7312	RR90	hCPS1-ASO-474	1.3558	0.1254
RR89	hCPS1-ASO-387	1.3766	0.5754	RR90	hCPS1-ASO-475	1.2423	0.2156
RR89	hCPS1-ASO-388	1.4547	0.5771	RR90	hCPS1-ASO-476	1.9336	1.7330
RR89	hCPS1-ASO-389	1.3246	0.8197	RR90	hCPS1-ASO-477	0.9444	0.2228
RR89	hCPS1-ASO-390	2.5864	1.2608	RR90	hCPS1-ASO-478	1.3043	0.4730
RR89	hCPS1-ASO-391	1.5723	0.9236	RR90	hCPS1-ASO-479	1.0763	0.2153
RR89	hCPS1-ASO-392	1.4165	1.0256	RR90	hCPS1-ASO-480	1.0685	0.0883
RR89	hCPS1-ASO-393	1.6100	0.9882	RR90	hCPS1-ASO-481	1.0366	0.2728
RR89	hCPS1-ASO-394	1.2672	0.8009	RR90	hCPS1-ASO-482	1.3154	0.2555

RR89	hCPS1-ASO-395	1.6338	0.5694	RR90	hCPS1-ASO-483	1.2040	0.0888
RR89	hCPS1-ASO-396	1.5087	0.7520	RR90	hCPS1-ASO-484	1.4609	0.3332
RR89	hCPS1-ASO-397	1.7948	0.8470	RR90	hCPS1-ASO-485	1.4426	0.3264
RR89	hCPS1-ASO-398	1.6142	0.8862	RR90	hCPS1-ASO-486	1.1654	0.3570
RR89	hCPS1-ASO-399	1.6498	0.8071	RR90	hCPS1-ASO-487	1.2836	0.1139
RR89	hCPS1-ASO-400	1.3005	0.7143	RR90	hCPS1-ASO-488	1.1598	0.5098
RR89	hCPS1-ASO-401	1.2663	0.6460	RR90	hCPS1-ASO-489	1.1434	0.1147
RR89	hCPS1-ASO-402	1.3756	0.5260	RR90	hCPS1-ASO-490	1.1133	0.1801
RR89	hCPS1-ASO-403	0.9677	0.3162	RR90	hCPS1-ASO-491	1.1545	0.0996
RR89	hCPS1-ASO-404	1.3644	0.4530	RR90	hCPS1-ASO-492	1.8287	0.8381

Example 3: *In vivo* characterization of selected ASOs in Non-human primates

[0248] Male cynomolgus monkeys (NHP), 2~4 years old, were subcutaneously injected with either 20 mg/kg or 50 mg/kg of hCPS1-ASO-1x on Day 0, and repeated doses were given to some groups on Day 21. Three NHPs were randomly assigned as one group. PBS was administered to one group as a negative control. Ammonia challenge and ureagenesis assay in NHPs were performed in an overnight fasted state prior to the ammonia challenge. 200 mg/kg of $^{15}\text{NH}_4\text{Cl}$ solution was subcutaneously injected into NHPs and multiple blood draws were performed over 0-120 min and immediately plasmas were obtained by centrifugation.

[0249] hCPS1-ASO-1x decreased ammonia production in NHPs by a statistically significant amount as compared to PBS only treatment by Day 27. **FIG. 17** provides the ammonia AUC both over time and per dose.

[0250] A second *in vivo* NHP study was performed to assess the efficacy with a lower dose of hCPS1-ASO-1x. Female cynomolgus monkeys (NHP), 2~4 years old, were subcutaneously injected with either 5 mg/kg or 15 mg/kg of hCPS1-ASO-1x on Day 1, and repeated doses were given on Day 36. Each group was consisted with three NHPs. One group was administered with PBS as a negative control. Ammonia challenge and ureagenesis assay in NHPs were performed in an overnight fasted state prior to the ammonia challenge. 200 mg/kg of $^{15}\text{NH}_4\text{Cl}$ solution was subcutaneously injected into NHPs and several blood draws were performed over 0-120 min and immediately plasmas were obtained by centrifugation. ^{13}C -ureagenesis assay was performed in an overnight fasted state prior to sodium acetate delivery. 55 mg/kg of ^{13}C -sodium acetate was provided by oral gavage and multiple blood draws were performed over 0-240 min and plasmas were immediately obtained by centrifugation. **FIG. 18** shows that hCPS1-ASO-1x decreased ammonia in NHPs after a single dose of 5 mg/kg for up to 5 weeks (shown are ammonia levels

on day 22 and Day 36). In addition, urea levels increased in the ASOs treated NHPs up to 29 days post dose. **FIG. 19** provides the ammonia AUC quantification on Days 22, 29 and 36.

[0251] Combination of hCPS1-ASO-1x with ^{13}C -sodium acetate treatment enhanced ureagenesis in NHPs at day 43 as compared to hCPS1-ASO-1x alone (**FIG. 20**).

[0252] In sum, upregulation of CPS1 increased the output of the urea cycle in mouse, NHP, and human hepatocytes, both *in vitro* and *in vivo*. Increasing CPS1 mRNA in the mouse OTC^{def} model via ASO treatment also increased the metabolism of ammonia to urea and the NHP data and humanized mouse liver data support this finding.

INCORPORATION BY REFERENCE

[0253] Unless stated to the contrary, the entire disclosure of each of the patent documents and scientific articles referred to herein is incorporated by reference for all purposes.

EQUIVALENTS

[0254] The invention may be embodied in other specific forms without departing from the spirit or essential characteristics thereof. The foregoing embodiments are therefore to be considered in all respects illustrative rather than limiting the invention described herein. Scope of the invention is thus indicated by the appended claims rather than by the foregoing description, and all changes that come within the meaning and range of equivalency of the claims are intended to be embraced therein.

WHAT IS CLAIMED IS:

1. An antisense oligonucleotide (ASO) complementary to at least 8 contiguous nucleotides of a regulatory RNA (regRNA) of Carbamoyl-Phosphate Synthetase 1 (CPS1), wherein the regRNA has a nucleotide sequence selected from the group consisting of SEQ ID NO: 49, 50, 69-79 and 89-90.
2. The ASO of claim 1, wherein the ASO is complementary to a sequence in the regRNA that is no more than 200 nucleotides from the 3' end of the regRNA.
3. The ASO of claim 1, wherein the ASO is complementary to a sequence in the regRNA that is no more than 200 nucleotides from the 5' end of the regRNA.
4. The ASO of claim 1 or 2, wherein the regulatory RNA has a nucleotide sequence of SEQ ID NO: 49, and the ASO comprises a nucleotide sequence of SEQ ID NO: 1.
5. The ASO of any one of claim 1, 2, or 4, wherein the regulatory RNA has a nucleotide sequence of SEQ ID NO: 49, and the ASO comprises a nucleotide sequence of SEQ ID NO: 2.
6. The ASO of any one of claim 1, 2, or 4, wherein the regulatory RNA has a nucleotide sequence of SEQ ID NO: 49, and the ASO comprises a nucleotide sequence selected from the group consisting of SEQ ID NOs: 1-3.
7. The ASO of claim 1 or 2, wherein the regulatory RNA has a nucleotide sequence of SEQ ID NO: 50, and the ASO comprises a nucleotide sequence selected from the group consisting of SEQ ID NOs: 4-15.
8. The ASO of claim 1-3, wherein the regulatory RNA has a nucleotide sequence of SEQ ID NO: 89, and the ASO comprises a nucleotide sequence selected from the group consisting of SEQ ID NOs: 487-574.
9. The ASO of claim 1-3, wherein the regulatory RNA has a nucleotide sequence of SEQ ID NO: 90, and the ASO comprises a nucleotide sequence selected from the group consisting of SEQ ID NOs: 575-662.

10. The ASO of any one of claims 1-9, wherein the ASO is no more than 50, 40, 30, or 25 nucleotides in length.
11. The ASO of any one of claims 1-10, wherein the ASO comprises a polynucleotide comprising one or more chemical modifications.
12. The ASO of claim 11, wherein at least 3, 4, or 5 nucleotides at the 5' end and at least 3, 4, or 5 nucleotides at the 3' end of the ASO comprise ribonucleotides with one or more chemical modifications.
13. The ASO of claim 11 or 12, wherein the one or more chemical modifications comprise a nucleotide sugar modification comprising one or more of 2'-O—C1-4alkyl such as 2'-O-methyl (2'-OMe), 2'-deoxy (2'-H), 2'-O—C1-3alkyl-O—C1-3alkyl such as 2'-methoxyethyl ("2'-MOE"), 2'-fluoro ("2'-F"), 2'-amino ("2'-NH₂"), 2'-arabinosyl ("2'-arabino") nucleotide, 2'-F-arabinosyl ("2'-F-arabino") nucleotide, 2'-locked nucleic acid ("LNA") nucleotide, 2'-amido bridge nucleic acid (AmNA), 2'-unlocked nucleic acid ("ULNA") nucleotide, a sugar in L form ("L-sugar"), 4'-thioribosyl nucleotide, constrained ethyl (cET), 2'-fluoro-arabino (FANA), or thiomorpholino.
14. The ASO of any one of claims 11-13, wherein the one or more chemical modifications comprise an internucleotide linkage modification comprising one or more of phosphorothioate ("PS" or (P(S))), phosphoramidate (P(NR₁R₂)) such as dimethylaminophosphoramidate (P(N(CH₃)₂)), phosphonocarboxylate (P(CH₂)_nCOOR) such as phosphonoacetate "PACE" (P(CH₂COO—)), thiophosphonocarboxylate ((S)P(CH₂)_nCOOR) such as thiophosphonoacetate "thioPACE" ((S)P(CH₂COO—)), alkylphosphonate (P(C1-3alkyl)) such as methylphosphonate —P(CH₃), boranophosphonate (P(BH₃)), or phosphorodithioate (P(S)₂).
15. The ASO of any one of claims 11-14, wherein the one or more chemical modifications comprise a nucleobase modification comprising one or more of 2-thiouracil ("2-thioU"), 2-thiocytosine ("2-thioC"), 4-thiouracil ("4-thioU"), 6-thioguanine ("6-thioG"), 2-aminoadenine ("2-aminoA"), 2-aminopurine, pseudouracil, hypoxanthine, 7-deazaguanine, 7-deaza-8-azaguanine, 7-deazaadenine, 7-deaza-8-azaadenine, 5-methylcytosine ("5-methylC"), 5-methyluracil ("5-methylU"), 5-hydroxymethylcytosine, 5-hydroxymethyluracil, 5,6-

dehydrouracil, 5-propynylcytosine, 5-propynyluracil, 5-ethynylcytosine, 5-ethynyluracil, 5-allyluracil ("5-allylU"), 5-allylcytosine ("5-allylC"), 5-aminoallyluracil ("5-aminoallylU"), 5-aminoallyl-cytosine ("5-aminoallylC"), an abasic nucleotide, Z base, P base, Unstructured Nucleic Acid ("UNA"), isoguanine ("isoG"), isocytosine ("isoC") a glycerol nucleic acid (GNA), glycerol nucleic acid (GNA), or thiophosphoramidate morpholinos (TMOs).

16. The ASO of any one of claims 11-15, wherein the one or more chemical modifications comprise 2'-O-methoxyethyl, 5-methyl cytidine, locked nucleic acid (LNA), and phosphorothioate internucleotide bond.

17. The ASO of any one of claims 11-16, wherein the ASO comprises 8 or more contiguous nucleotides of unmodified DNA flanked by at least 3 nucleotides of modified ribonucleotides at each of the 5' end and the 3' end.

18. The ASO of claim 17, wherein the ASO comprises the nucleotide sequence and/or chemical modification of any one of SEQ ID NO: 16, 22-27, 31-39, 400, 403-415, 417-432, 435-480, or 482-486.

19. The ASO of claim 17 or 18, wherein the ASO comprises the nucleotide sequence and/or chemical modification of SEQ ID NO: 409.

20. The ASO of claim 17 or 18, wherein the ASO further comprises at least one phosphorothioate internucleotide bond.

21. The ASO of claim 20, wherein the ASO comprises the nucleotide sequence of SEQ ID NOs: 403-406, 409-415, 417-424, 470, 473, 477, 480, or 486.

22. The ASO of claim 17, wherein the chemical modification is cET.

23. The ASO of claim 22, wherein the ASO comprises the nucleotide sequence of SEQ ID NOs: 425-432 or 435-442.

24. The ASO of claim 17, wherein the chemical modification is LNA.

25. The ASO of claim 24, wherein the ASO comprises the nucleotide sequence of SEQ ID NOs: 443-458.
26. The ASO of claim 17, wherein the chemical modification is LNA and 2'-O-methoxyethyl.
27. The ASO of claim 26, wherein the ASO comprises the nucleotide sequence of SEQ ID NOs: 400, 408, 460, 462, 464-466, 468, 469, 471, 472, 475, 476, or 479.
28. The ASO of any one of claims 11-16, wherein the ASO does not comprise 8 or more contiguous nucleotides of unmodified DNA.
29. The ASO of any one of claims 11-16, wherein the ASO does not comprise an unmodified ribonucleotide.
30. The ASO of any one of claims 11-16 or 29, wherein the ASO does not comprise a deoxyribonucleotide.
31. The ASO of any one of claims 11-16, 29, or 30, wherein the length of the ASO is $2 \times n + 4$ nucleotides (n is an integer of 8 or greater), wherein the nucleotides at positions $2 \times m$ are ribonucleotides modified by LNA (m is an integer from 1 to n) and the remaining nucleotides are ribonucleotides modified by 2'-O-methoxyethyl.
32. The ASO of claim 35, wherein the ASO comprises the nucleotide sequence of SEQ ID NOs: 393 or 394.
33. The ASO of any one of claims 11-16, 29, or 30, wherein the length of the ASO is $3 \times n + 2$ nucleotides (n is an integer of 4 or greater), wherein the nucleotides at positions $3 \times m$ are ribonucleotides modified by LNA (m is an integer from 1 to n) and the remaining nucleotides are ribonucleotides modified by 2'-O-methoxyethyl.
34. The ASO of claim 33, wherein the ASO comprises the nucleotide sequence of SEQ ID NOs: 392 or 395.

35. The ASO of any one of claims 11-16, 29, or 30, wherein the length of the ASO is $3 \times n + 2$ nucleotides (n is an integer of 6 or greater), wherein the nucleotides at positions $3 \times m$ are ribonucleotides modified by LNA (m is an integer from 1 to n) and the five nucleotides at the 3' and 5' positions are ribonucleotides modified by 2'-O-methoxyethyl.
36. The ASO of claim 35, wherein the ASO comprises the nucleotide sequence of SEQ ID NO: 19 or 20.
37. The ASO of any one of claims 11-16, 29, or 30, wherein the length of the ASO is $4 \times n$ nucleotides (n is an integer of 3 or greater), wherein the nucleotides at positions $4 \times m$ are ribonucleotides modified by LNA (m is an integer from 1 to n) and the five nucleotides at the 3' and 5' positions are ribonucleotides modified by 2'-O-methoxyethyl.
38. The ASO of claim 37, wherein the ASO comprises the nucleotide sequence of SEQ ID NO: 21.
39. The ASO of any one of claims 11-16, 29, or 30, wherein the length of the ASO is $4 \times n + 4$ nucleotides (n is an integer of 3 or greater), wherein the nucleotides at positions $4 \times m$ are ribonucleotides modified by LNA (m is an integer from 1 to n) and the remaining nucleotides are ribonucleotides modified by 2'-O-methoxyethyl.
40. The ASO of claim 39, wherein the ASO comprises the nucleotide sequence of SEQ ID NOs: 396 or 397.
41. The ASO of any one of claims 11-16, 29, or 30, wherein each ribonucleotide of the ASO is modified by 2'-O-methoxyethyl.
42. The ASO of claim 41, wherein the ASO comprises the nucleotide sequence of any one of SEQ ID NOs: 17, 28-30, and 40-48.
43. The ASO of any one of claims 11-16, 29, or 30, wherein each nucleotide of the ASO is a ribonucleotide modified by 2'-O-methoxyethyl.
44. The ASO of claim 43, wherein the ASO comprises the nucleotide sequence of any one of SEQ ID NOs: 17, 28-30, and 40-48.

45. The ASO of any one of claims 11-44, wherein each cytidine in the ASO is modified by 5-methyl.
46. The ASO of any one of claims 11-16, wherein the length of the ASO is $5 \times n + 5$ nucleotides (n is an integer of 3 or greater), wherein the nucleotides at positions $5 \times m$ are ribonucleotides modified by LNA (m is an integer from 1 to n) and the nucleotides at the remaining positions are ribonucleotides modified by 2'-O-methoxyethyl.
47. The ASO of claim 46, wherein the ASO comprises the nucleotide sequence of SEQ ID NOs: 398 or 399.
48. The ASO of any one of claims 11-47, wherein the ASO further comprises a GalNAc moiety, optionally a GalNAc3 moiety.
49. The ASO of any one of claims 11-48, wherein the ASO further comprises a biotin or cholesterol moiety.
50. The ASO of any one of claims 11-49, wherein each cytidine in the ASO is modified by 5-methyl.
51. The ASO of any one of claims 1-50, wherein the regRNA is an enhancer RNA (eRNA).
52. A pharmaceutical composition comprising the ASO of any one of claims 1-51 and a pharmaceutically acceptable carrier or excipient carrier.
53. A method of increasing transcription of CPS1 in a human cell, the method comprising contacting the cell with the ASO of any one of claims 1-51 or the pharmaceutical composition of claim 52.
54. The method of claim 53, wherein the cell is a hepatocyte.
55. The method of claim 53 or 54, wherein the ASO increases the amount of the regulatory RNA in the cell as compared to a cell that has not been contacted with the ASO or the pharmaceutical composition.

56. The method of any one of claims 53-55, wherein the ASO increases the stability of the regulatory RNA in the cell as compared to a cell that has not been contacted with the ASO or the pharmaceutical composition.
57. A method of treating a urea cycle disorder, the method comprising administering to a subject in need thereof an effective amount of the ASO of any one of claims 1-51 or the pharmaceutical composition of claim 52.
58. The method of claim 57, wherein the urea cycle disorder is CPS1-deficiency.
59. The method of claim 57 or 58, wherein the urea cycle disorder is hyperammonemia.
60. The method of any one of claims 57-59, wherein the ASO increases the amount of the regulatory RNA in a cell of the subject as compared to a cell that has not been contacted with the ASO or the pharmaceutical composition.
61. The method of any one of claims 57-60, wherein the ASO increases the stability of the regulatory RNA in a cell of the subject as compared to a cell that has not been contacted with the ASO or the pharmaceutical composition.
62. The method of claim 60 or 61, wherein the cell is a hepatocyte.