

CLAIMS

WHAT IS CLAIMED IS:

1. Use of a therapeutic agent in preparing a medicament for treating or reducing the likelihood of developing a disease or condition in a subject in need thereof by modulating expression of a target protein in a cell of the subject, the use comprising: contacting the cell of the subject with the therapeutic agent or a vector encoding the therapeutic agent, wherein the cell comprises a pre-mRNA that is transcribed from a target gene and that encodes the target protein, the pre-mRNA comprising an alternatively-spliced coding exon (ASCE), wherein an alternative processed mRNA that is produced by splicing out of the ASCE during processing of the pre-mRNA undergoes non-sense mediated RNA decay, wherein the therapeutic agent promotes inclusion of the ASCE during the processing of the pre-mRNA, thereby increasing a level of a processed mRNA that is processed from the pre-mRNA and that comprises the ASCE.
2. The use of claim 1, wherein the expression of the target protein is increased in the cell.
3. The use of claim 1 or 2, wherein the target gene is selected from the group consisting of: *PKD1*, *ABCA4*, *FUS*, *CEL*, and *NSD1*.
4. The use of any one of claims 1-3, wherein the therapeutic agent
 - (a) binds to a targeted portion of the pre-mRNA encoding the target protein;
 - (b) modulates binding of a factor involved in splicing of the ASCE; or
 - (c) a combination of (a) and (b).
5. The use of claim 4, wherein the targeted region is located in (a) an intronic region between the ASCE and a canonical exonic region upstream of the ASCE of the pre-mRNA encoding the target protein, or (b) an intronic region between the ASCE and a canonical exonic region downstream of the ASCE of the pre-mRNA encoding the target protein.
6. The use of claim 4, wherein the targeted portion: (a) comprises at least a portion of the ASCE; or (b) comprises at least a portion of an intronic region upstream or downstream of the ASCE.
7. The use of claim 4, wherein the targeted portion does not comprise a 5' exon-intron junction of the ASCE or a 3' exon-intron junction of the ASCE.

8. The use of claim 4, wherein the targeted portion is within the ASCE.
9. The use of claim 4, wherein the targeted portion comprises about 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 26, 27, 28, 29, 30, or more consecutive nucleotides of the ASCE.
10. The use of any one of claims 1-9, wherein the targeted portion of the pre-mRNA is within the ASCE selected from the group consisting of: GRCh38/ hg38: chr16 2092954 2093093; GRCh38/ hg38: chr1 94111438 94111579; GRCh38/ hg38: chr16 31186802 31186836; GRCh38/ hg38: chr9 133066530 133066660; and GRCh38/ hg38: chr5 177238237 177238507.
11. The use of any one of claims 1-10, wherein the target protein is NSD1, and wherein the use causes a modification of a histone protein in the cell, optionally wherein the histone protein is Histone H3.
12. The use of any one of claim 1-11, wherein the alternative processed mRNA that is produced by splicing out of the ASCE during processing of the pre-mRNA comprises a premature termination codon (PTC).
13. The use of any one of claims 1-12, wherein the agent is an antisense oligomer (ASO).
14. The use of any one of claims 1-13, wherein the disease or condition is associated with haploinsufficiency of a gene encoding the target protein, and wherein the subject has a first allele encoding a functional target protein, and a second allele from which the target protein is not produced or produced at a reduced level, or a second allele encoding a nonfunctional target protein or a partially functional target protein.
15. The use of any one of claims 1-14, wherein the disease or condition is selected from the group consisting of: Polycystic Kidney Disease 1 with or without Polycystic Liver Disease; Autosomal Dominant Polycystic Kidney Disease; Age-related macular degeneration-2; Stargardt Disease 1; Amyotrophic Lateral Sclerosis; Amyotrophic Lateral Sclerosis 6 with or without Frontotemporal Dementia; Tremor, Hereditary Essential, 4; Frontotemporal Dementia; Maturity-Onset Diabetes Of The Young, Type 8, with Exocrine Dysfunction; Maturity-Onset Diabetes Of The Young; Sotos Syndrome 1; and Beckwith-Wiedemann Syndrome.