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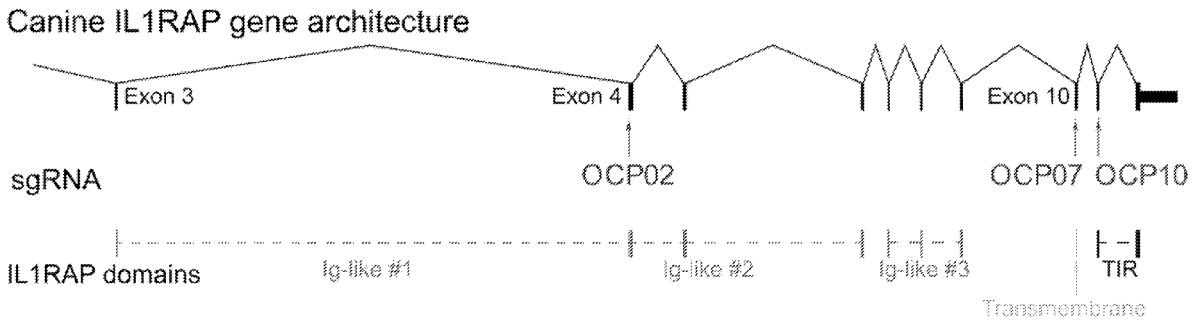


FIG. 2A

(57) Abstract: Provided herein are compositions and methods for ablating intracellular signaling through specific cell surface receptors as means of treatment for various conditions of a pro- inflammatory character. In some aspects, the compositions and methods are to prevent the progression of osteoarthritis and other arthritides and to treat osteoarthritis and other arthritides in a mammalian joint. In some aspects, the compositions and method are for treating or preventing localized nociception, inflammation, degeneration, or morphological changes associated with back or spine conditions or disorders.

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TRANSMEMBRANE RECEPTOR GENE EDITING

CROSS REFERENCE TO RELATED APPLICATIONS

[0001] This application claims priority to U.S. Provisional Patent Application No. 63/301,033, filed January 19, 2022, U.S. Provisional Patent Application No. 63/303,479, filed January 26, 2022, and U.S. Provisional Patent Application No. 63/390,222, filed July 18, 2022, the contents of which are hereby incorporated by reference herein, in their entireties, for all purposes.

BACKGROUND OF THE INVENTION

[0002] Receptor-ligand interactions are responsible for transmission of various signals across the plasma membrane of a receptor-expressing cell. In most instances, a circulating ligand will bind to a particular receptor anchored into cellular membrane (with or without co-receptors), which, by different mechanisms and often through activity of the receptor's cytoplasmic domain, results in the transduction of signaling pathways from the cell surface to the interior. Such signaling events can, in turn, impact a variety of cellular activities, including modulation of expression of various gene products that can further impact cellular functions.

[0003] The ubiquity of the receptor-ligand paradigm in cellular biology means that numerous diseases, illnesses, and conditions are caused, wholly or in part, by aberrant or excessive signaling through various cellular receptors, and various approaches have been utilized to address this. Small and large molecules can be used to disrupt receptor-ligand interactions, though issues of off-target effects and potential immunogenicity remain.

[0004] More recently, genetic approaches have been explored to either transiently reduce (i.e., knockdown), e.g., in the case of siRNA, or permanently ablate (i.e., genetic knockout), the expression of a given ligand or receptor. In both instances, such reduction or ablation can result in 'leakiness.' For example, a lower-affinity receptor may bind ligand present in excess in the absence of the native receptor, or conversely, unoccupied receptors may bind other ligands in absence of its native ligand. In either instance, this leakiness can result in additional issues at the organismal level. Therefore, more advanced genetic tools are needed to address the myriad of diseases, illnesses and conditions without the leakiness observed with traditional genetic knockdown or knockout.

BRIEF SUMMARY OF THE INVENTION

[0005] Provided herein are compositions and methods for silencing the signaling functionality of one or more cellular receptors in an animal in need thereof to treat a disease, illness or condition caused by aberrant or excessive signaling through said receptor.

[0006] In some embodiments, receptor signaling is silenced by CRISPR editing of the gene encoding the receptor. In some embodiments, the CRISPR editing results in ablation of a transmembrane domain (e.g., generation of soluble decoy receptor). In some embodiments, the CRISPR editing results in ablation of a cytoplasmic domain (e.g., generation of a membrane-bound decoy receptor). In some embodiments, the CRISPR editing results targetes the extracellular domain (e.g., generation of a complete knock out).

[0007] In contrast to complete ablation or transient knockdown of gene expression of a receptor or ligand, which has been associated with potentially important off-target effects and leakiness, the targeting of a receptor's transmembrane domain or cytoplasmic domain, as described herein, comprises a novel approach for blocking intracellular signaling of one or more receptor-ligand interactions without the issues of excess ligand or unoccupied receptors to contribute to more deleterious outcomes.

BRIEF DESCRIPTION OF THE DRAWINGS

[0008] The presently disclosed embodiments will be further explained with reference to the attached drawings. The drawings shown are not necessarily to scale, with emphasis instead generally being placed upon illustrating the principles of the presently disclosed embodiments.

[0009] Figure 1 illustrates the exons to be edited by CRISPR methods herein described to generate the indicated type of interference (e.g., genetic knockout, soluble decoy receptor, or membrane-bound decoy receptor) for the indicated exemplary gene targets.

[0010] Figures 2A and 2B illustrate the different types of CRISPR edits to (A) canine IL1RAP gene and (B) human TNFRSF4 gene. For cIL1RAP, the splicing map at top indicates which exons are edited with sgRNA shown, aligned with the corresponding domains in the full length cIL1RAP protein, such that OCP02 edits in the ectodomain, OCP07 edits in the transmembrane domain, and OCP10 edits in the TIR domain (bottom). For TNFRSF4, the splicing map at bottom is labeled with the encoded protein domains and

aligned with the sgRNA binding sites and the interference type generated. For instance, those sgRNAs that generate soluble decoy receptors cluster within the area encoding the transmembrane domain, while those generating transmembrane decoy receptors cluster within the encoded cytoplasmic domain and ablate the TRAF binding sites. In either case, synthesis of the ectodomain is unimpacted, allowing binding of the ligand.

[0011] Figures 3A and 3B illustrate a non-exhaustive list of disease states associated with IL1R1 and IL1RAP activity.

[0012] Figures 4A and 4B illustrate a non-exhaustive list of disease states associated with (A) IL6R and (B) IL6ST activity.

[0013] Figure 5 illustrates a non-exhaustive list of disease states associated with TNFRSF1A activity.

[0014] Figure 6 illustrates a non-exhaustive list of disease states associated with TNFRSF1B activity.

[0015] Figure 7 illustrates a non-exhaustive list of disease states associated with TNFRSF3 activity.

[0016] Figure 8 illustrates a non-exhaustive list of disease states associated with TNFRSF4 activity.

[0017] Figure 9 illustrates a non-exhaustive list of disease states associated with TNFRSF11A activity.

[0018] Figures 10A and 10B illustrate a non-exhaustive list of disease states associated with (A) TGFRB1 and (B) TGFBR2 activity.

[0019] Figures 11A and 11B illustrate the design of exemplary sgRNAs that target canine IL1R1, including (A) a summary of select sgRNAs based on off-target risks, on-target efficacy, and frameshift likelihood and (B) AlphaFold2 models of wild-type and decoy IL1R1 receptors, as predicted to be generated by OCR13 and OCR14.

[0020] Figure 12 illustrates the in vitro performance of the tested sgRNA candidates that target canine IL1RAP, as deduced from Sanger traces. ND, not determined.

[0021] Figures 13A, 13B, 13C, and 13D illustrate the effect of various Cas9 variants on the in-vitro editing performance of select candidate sgRNAs that target canine IL1R1.

[0022] Figures 14A and 14B illustrate the design of exemplary sgRNAs that target canine IL1RAP, including (A) a summary of select sgRNAs based on off-target risks, on-target efficiency and frameshift likelihood and (B) AlphaFold2-predicted models of the 3D structure of normal and OCP07-edited IL1RAP.

[0023] Figure 15 illustrates the in vitro performance of the tested sgRNA candidates that target canine IL1RAP, as deduced from Sanger traces.

[0024] Figures 16A, 16B, 16C illustrate (A) select sgRNAs targeting IL1RAP for testing and their editing efficacy with wildtype Cas9, (B) the effect of the indicated Cas9 variants on editing efficacy in canine monocytes and (C) a comparison of editing efficacy between AR-Cas9 and WT-Cas9 in canine synovial fibroblasts.

[0025] Figures 17A, 17B, and 17C illustrate the editing efficacy of the indicated IL1RAP-directed sgRNAs in (A) canine monocytes, (B) canine chondrocytes and (C) canine synovial fibroblasts.

[0026] Figure 18 illustrates the impact of IL1R1 editing on silencing transcriptional induction of PTGS2 in response to 4 hours exposure to IL1β in canine synoviocytes.

[0027] Figure 19 illustrates the impact of IL1R1 editing on silencing transcriptional induction of IL6 in response to 4 hours exposure to IL1β in canine synoviocytes.

[0028] Figure 20 illustrates the experimental design underlying transcriptome analyses, among other assays. Generally, IL1β treatment will induce pro-inflammatory signaling exclusively through the IL1 receptor, whereas MSU crystals and LPS trigger inflammation by different means (in addition to inducing IL1 signaling).

[0029] Figures 21A and 21B illustrate the transcriptional upregulation of PTGS2 (COX-2) in wild type control and IL1RAP- edited canine monocytes at (A) 4 and (B) 24 hours of exposure to LPS (1 ug/ml), IL1β (100 pM), MSU crystals (400 ug/ml), and PBS (1X).

[0030] Figure 22A and 22B illustrate the impact of IL1RAP editing on silencing transcriptional induction of PTGS2 in (A) canine chondrocytes and (B) canine synoviocytes in response to 4 hours exposure to IL1β.

[0031] Figures 23A and 23B illustrate luciferase activity levels (RLU) of (A) canine synovial fibroblasts at 8 hours and (B) canine chondrocytes at 24 hours post exposure to luciferase mRNA containing LNPs at the indicated concentration.

[0032] Figures 24A and 24B illustrate results of synovial fluid cytology assays collected (A) at baseline and (B) at 4 weeks after injection of saline, low dose LNP formulation A and low-dose LNP formulation B.

[0033] Figures 25A, 25B, 25C, 25D, 25E, 25F, 25G, and 25H collectively illustrate, for control and IL1RAP-edited cells, (A) a principal component analysis plot of normalized gene counts following IL1β or MSU treatment. Two heatmaps of select gene expression as result of (B) IL1β or (C) MSU treatment, and Venn diagrams of upregulated or downregulated genes following (D, E) IL1β or (F, G) MSU treatment. (H) Transcriptome analysis of the top 500 IL1β-responsive genes in IL1RAP-edited canine monocytes DH82.

[0034] Figures 26A, 26B, 26C, 26D, 26E, and 26F collectively illustrate SEQ ID NOs: 680-824 (A-D) the crRNA sequences generated by the bioinformatic methods herein described that target human IL1R1 to generate a genetic knockout, a soluble decoy receptor, a membrane-bound decoy receptor, or other form and (E-H) additional information regarding the choromosome 2 genomic coordinates (assembly hg38) of the bound DNA, DNA strand targeted, exon targeted, and several predicted performance metrics.

[0035] Figures 27A, 27B, 27C, 27D, 27E, 27F, 27G, and 27H collectively illustrate SEQ ID NOs: 825-892 and SEQ ID NOs: 3336-3420 (A-D) the crRNA sequences generated by the bioinformatic methods herein described that target canine IL1R1 to generate a genetic knockout, a soluble decoy receptor, or a membrane-bound decoy receptor, or other form and (E-H) additional information includes the chromosome 10 genomic coordinates (assembly canFam3) of the bound DNA, the DNA strand targeted, the exon targeted, and several predicted performance metrics.

[0036] Figures 28A, 28B, and 28C collectively illustrate SEQ ID NOs: 893-967, the crRNA sequences generated by the bioinformatic methods herein described that target equine IL1R1 to generate (A) a genetic knockout, (B) a soluble decoy receptor, or (C) a membrane-bound decoy receptor. Additional information includes the chromosome 15 genomic coordinates (assembly equCab3) of the bound DNA, the DNA strand targeted, the exon targeted, and several predicted performance metrics.

[0037] Figures 29A, 29B, and 29C collectively illustrate SEQ ID NOs: 968-1039, the crRNA sequences generated by the bioinformatic methods herein described that target feline IL1R1 to generate (A) a genetic knockout, (B) a soluble decoy receptor, or (C) a membrane-bound decoy receptor. Additional information includes the chromosome A3 genomic

coordinates (assembly felCat9) of the bound DNA, the DNA strand targeted, the exon targeted, and several predicted performance metrics.

[0038] Figures 30A, 30B, 30C, 30D, 30E, 30F, 30G, and 30H collectively illustrate SEQ ID NOs: 1040-1203, (A-D) the crRNA sequences generated by the bioinformatic methods herein described that target human IL1RAP to generate a genetic knockout, a soluble decoy receptor, a membrane-bound decoy receptor or other form and (E-H) additional information regarding the chromosome 3 genomic coordinates (assembly hg38) of the bound DNA, DNA strand targeted, exon targeted, and several predicted performance metrics.

[0039] Figures 31A, 31B, 31C, 31D, 31E, and 31F collectively illustrate SEQ ID NOs: 1204-1271 and SEQ ID NOs: 3421-3490 (A-C) the crRNA sequences generated by the bioinformatic methods herein described that target canine IL1RAP to generate a genetic knockout, a soluble decoy receptor, a membrane-bound decoy receptor, or other form and (D-F) additional information includes the chromosome 34 genomic coordinates (assembly canFam3) of the bound DNA, the DNA strand targeted, the exon targeted, and several predicted performance metrics.

[0040] Figures 32A, 32B, and 32C collectively illustrate SEQ ID NOs: 1272-1348, the crRNA sequences generated by the bioinformatic methods herein described that target equine IL1RAP to generate (A) a genetic knockout, (B) a soluble decoy receptor, or (C) a membrane-bound decoy receptor. Additional information includes the chromosome 19 genomic coordinates (assembly equCab3) of the bound DNA, the DNA strand targeted, the exon targeted, and several predicted performance metrics.

[0041] Figures 33A, 33B, and 33C collectively illustrate SEQ ID NOs: 1349-1424, the crRNA sequences generated by the bioinformatic methods herein described that target feline IL1RAP to generate (A) a genetic knockout, (B) a soluble decoy receptor, or (C) a membrane-bound decoy receptor. Additional information includes where the chromosome C2 genomic coordinates (assembly felCat9) bound, DNA strand targeted, exon targeted, and several predicted performance metrics.

[0042] Figures 34A, 34B, 34C, 34D, 34E, and 34F collectively illustrate SEQ ID NOs: 1425-1546, (A-C) the crRNA sequences generated by the bioinformatic methods herein described that target human TGFBR1 to generate a genetic knockout, a soluble decoy receptor, a membrane-bound decoy receptor or other form and (D-F) additional information

regarding the chromosome 9 genomic coordinates (assembly hg38) of the bound DNA, DNA strand targeted, exon targeted, and several predicted performance metrics.

[0043] Figures 35A, 35B, 35C, 35D, 35E, 35F, 35G, and 35H collectively illustrate SEQ ID NOs: 1547-1745, (A-E) the crRNA sequences generated by the bioinformatic methods herein described that target human TGFBR2 to generate a genetic knockout, a soluble decoy receptor, a membrane-bound decoy receptor or other form and (F-J) additional information regarding the chromosome 3 genomic coordinates (assembly hg38) of the bound DNA, DNA strand targeted, exon targeted, and several predicted performance metrics.

[0044] Figures 36A, 36B, 36C, 36D, 36E, 36F, 36G, 36H, 36I, and 36J collectively illustrate SEQ ID NOs: 1746-1968, (A-E) the crRNA sequences generated by the bioinformatic methods herein described that target human IL6R to generate a genetic knockout, a soluble decoy receptor, a membrane-bound decoy receptor or other form and (F-J) additional information regarding the chromosome 1 genomic coordinates (assembly hg38) of the bound DNA, DNA strand targeted, exon targeted, and several predicted performance metrics.

[0045] Figures 37A, 37B, 37C, 37D, 37E, 37F, 37G, 37H, 37I, and 37J collectively illustrate SEQ ID NOs: 1969-2178, (A-E) the crRNA sequences generated by the bioinformatic methods herein described that target human IL6ST to generate a genetic knockout, a soluble decoy receptor, a membrane-bound decoy receptor or other form and (F-J) additional information regarding the chromosome 5 genomic coordinates (assembly hg38) of the bound DNA, DNA strand targeted, exon targeted, and several predicted performance metrics.

[0046] Figures 38A, 38B, 38C, 38D, 38E, 38F, 38G, 38H, 38I, and 38J collectively illustrate SEQ ID NOs: 2179-2395, (A-E) the crRNA sequences generated by the bioinformatic methods herein described that target human TNFRSF1A to generate a genetic knockout, a soluble decoy receptor, a membrane-bound decoy receptor or other form (F-J) additional information regarding the chromsome 12 genomic coordinates (assembly hg38) of the bound DNA, DNA strand targeted, exon targeted, and several predicted performance metrics.

[0047] Figures 39A, 39B, 39C, 39D, 39E, 39F, 39G, 39H, 39I, and 39J collectively illustrate SEQ ID NOs: 2396-2642, (A-E) the crRNA sequences generated by the bioinformatic methods herein described that target human TNFRSF1B to generate a genetic

knockout, a soluble decoy receptor, a membrane-bound decoy receptor or other form and (F-J) additional information regarding the chromsome 1 genomic coordinates (assembly hg38) of the bound DNA, DNA strand targeted, exon targeted, and several predicted performance metrics.

[0048] Figures 40A, 40B, 40C, 40D, 40E, 40F, 40G, 40H, 40I, and 40J collectively illustrate SEQ ID NOs: 2643-2866, (A-E) the crRNA sequences generated by the bioinformatic methods herein described that target human TNFRSF3 to generate a genetic knockout, a soluble decoy receptor, a membrane-bound decoy receptor or other form and (F-J) additional information regarding the chromsome 12 genomic coordinates (assembly hg38) of the bound DNA, DNA strand targeted, exon targeted, and several predicted performance metrics.

[0049] Figures 41A, 41B, 41C, 41D, 41E, 41F, 41G, and 41H collectively illustrate SEQ ID NOs: 2867-3041, (A-D) the crRNA sequences generated by the bioinformatic methods herein described that target human TNFRSF4 to generate a genetic knockout, a soluble decoy receptor, a membrane-bound decoy receptor or other form and (E-H) additional information regarding the chromsome 1 genomic coordinates (assembly hg38) of the bound DNA, DNA strand targeted, exon targeted, and several predicted performance metrics.

[0050] Figures 42A, 42B, 42C, 42D, 42E, 42F, 42G, 42H, 42I, 42J, 42K, and 42L collectively illustrate SEQ ID NOs: 3042-3335, (A-F) the crRNA sequences generated by the bioinformatic methods herein described that target human TNFRSF11A to generate a genetic knockout, a soluble decoy receptor, a membrane-bound decoy receptor or other form and (G-L) additional information regarding the chromsome 18 genomic coordinates (assembly hg38) of the bound DNA, DNA strand targeted, exon targeted, and several predicted performance metrics.

[0051] Figures 43A and 43B illustrate (A) a schematic view showing the targeted domains of TGFBR1 and the orientation of various sgRNAs predicted to generate knockouts, membrane-bound decoy receptors, and soluble decoy receptors (ECD: Extracellular Domain; TMD: Transmembrane Domain; ICD: Intracellular Domain; GSM: GS rich Motif); and (B) a set of parameters considered for designing sgRNAs against TGFBR1, as well as example crRNA sequences.

[0052] Figures 44A and 44B illustrate (A) a schematic view showing the targeted domains of TGFBR2 and the orientation of various sgRNAs predicted to generate knockouts,

membrane-bound decoy receptors, and soluble decoy receptors (ECD: Extracellular Domain; TMD: Transmembrane Domain; ICD: Intracellular Domain; GSM: GS rich Motif); and (B) a set of parameters considered for designing sgRNAs against TGFBR2, as well as example crRNA sequences.

[0053] Figures 45A and 45B show a summary of the efficiency for editing the human TGFBR1 gene in THP-1 cells using the identified guides and (A) wild type SpCas9 or (B)ARCas9.

[0054] Figures 46A and 46B show a summary of the efficiency for editing the human TGFBR2 gene in THP-1 cells using the identified guides and (A) wild type SpCas9 or (B)ARCas9.

[0055] Figures 47A, 47B, 47C, and 47D illustrate relative levels of (A, C) TGFB1 and (B, D) TIMP1 gene expression in THP-1 cells that are unedited (WT) or edited to knock out TGFB1 (OHTG), TGFBR1 (OHTIR), or TGFBR2 (OHTIIR) following challenge by LPS (panels A and B) or TGF-beta (panels C and D) for 6 hours.

[0056] Figures 48A, 48B, 48C, 48D, 48E, 48F, 48G, 48H, 48I, 48J, and 48K collectively illustrate human-directed crRNA sequences targeting (A) hIL1R1 (SEQ ID NOs: 3491-3513), (B) hIL1RAP (SEQ ID NOs: 3514-3543), (C) hIL6R (SEQ ID NOs: 3544-3566), (D) hIL6ST (SEQ ID NOs: 3567-3606), (E) hTNFRSF1A (SEQ ID NOs: 3607-3647), (F) hTNFRSF1B (SEQ ID NOs: 3648-3692), (G) hTNFRSF3 (SEQ ID NOs: 3693-3713), (H) hTNFRSF4 (SEQ ID NOs: 3714-3740), (I) hTNFRSF11A (SEQ ID NOs: 3741-3788), (J) hTGFBR1 (SEQ ID NOs: 3789-3813), and (K) hTGFBR2 (SEQ ID NOs: 3814-3865) for use in sgRNAs to validate in vitro editing with different modes of delivery.

DETAILED DESCRIPTION OF THE INVENTION

I. Introduction

[0057] Provided herein are compositions and methods for silencing the signaling functionality of one or more cellular receptors in an animal in need thereof to treat a disease, illness or condition caused by aberrant or excessive signaling through said receptor.

[0058] In some embodiments, receptor signaling is silenced by CRISPR editing of the gene encoding the receptor. In some embodiments, the CRISPR editing results in ablation of a transmembrane domain (i.e., generation of a soluble decoy receptor). In some embodiments,

the CRISPR editing results in ablation of a cytoplasmic domain (i.e., generation of a membrane-bound decoy receptor).

II. Definitions

[0059] Unless defined otherwise, all technical and scientific terms used herein have the same meaning as is commonly understood by one of skill in the art to which this invention belongs. All patents and publications referred to herein are incorporated by reference in their entireties.

[0060] The terms "Interleukin 1 receptor type 1" or "IL1R1" refer to the genes (NCBI Gene ID: 3554 [human], NCBI Gene ID: 481328 [canine], NCBI Gene ID: 100009699 [equine], NCBI Gene ID: 101080705 [feline]) or an encoded gene product (e.g., UniProt: P14778; NP_001307909.1 [human], XP_038536135.1 [canine], NP_001075263.2 [equine], XP_023107327.2 [feline]), as well as sequence variants, proteins harboring conservative amino acid substitutions, and glycoforms thereof. Canonically, the proteins encoded by the genes listed above are capable of binding all forms of the pro-inflammatory cytokine interleukin 1 (IL1 or IL1) to mediate interleukin-1-dependent activation of NF-kappa-B, MAPK and other signaling pathways. This intracellular signaling involves the recruitment of adapter molecules such as TOLLIP, MYD88, and IRAK1 or IRAK2 via TIR-TIR interactions with the cytoplasmic domains of receptor/coreceptor subunits. IL1R1 can also bind the Interleukin 1 receptor antagonist (IL1Ra or IL1Ra or IL1RN), which prevents association with IL1RAP to form a signaling-competent complex. In some instances, and merely for the sake of disambiguation, a prefix is added when referring to the protein or gene of a particular species (with *h*, *c*, *e*, and *f*, referring to the human, canine, equine, and feline forms, respectively).

[0061] In certain embodiments, any region of an IL1R1 gene (e.g., 5' untranslated region [UTR], exon 1, exon 2, exon 3, exon 4, exon 5, exon 6, exon 7, exon 8, exon 9, exon 10, exon 11, exon 12, exon 13, exon 14, exon 15, exon 16, exon 17, exon 18, exon 19, exon 20, exon 21, any intervening intronic regions, intron/exon junctions, the 3' UTR, or polyadenylation signal) is targeted by an RNA-guided nuclease to alter the gene. In some embodiments, the IL1R1 gene targeted by an RNA-guided nuclease is from a mammal. In some embodiments, the IL1R1 gene targeted by an RNA-guided nuclease is from a human (hIL1R1). In some embodiments, the IL1R1 gene targeted by an RNA-guided nuclease is from a dog (cIL1R1). In some embodiments, the IL1R1 gene targeted by an RNA-guided nuclease is from a horse

(eIL1R1). In some embodiments, the IL1R1 gene targeted by an RNA-guided nuclease is from a cat (fIL1R1).

[0062] The terms "Interleukin 1 Receptor Accessory Protein," "IL1RAP," or "IL1RAP" refer to the genes (NCBI Gene ID: 3556 [human], NCBI Gene ID: 488126 [canine], NCBI Gene ID: 100068726 [equine], NCBI Gene ID: 101094125 [feline]) or an encoded gene product (e.g., UniProt: Q9NPH3; NP_002173.1 [human], XP_038318680.1 [canine], XP_001498597.2 [equine], XP_044893081.1 [feline]), as well as sequence variants, proteins harboring conservative amino acid substitutions, and glycoforms thereof. Canonically, the proteins encoded by the genes listed above are capable of associating with IL1R1 bound to IL1 to form the high affinity interleukin-1 receptor complex that mediates interleukin-1-dependent activation of NF-kappa-B and other signaling pathways through the recruitment of adapter molecules such as TOLLIP, MYD88, and IRAK1 or IRAK2 via TIR-TIR interactions with the cytoplasmic domains of receptor/coreceptor subunits. In some instances, and merely for the sake of disambiguation, a prefix is added when referring to the protein or gene of a particular species (with *h*, *c*, *e*, and *f*, referring to the human, canine, equine, and feline forms, respectively).

[0063] In certain embodiments, any region of an IL1RAP gene (e.g., 5' untranslated region [UTR], exon 1, exon 2, exon 3, exon 4, exon 5, exon 6, exon 7, exon 8, exon 9, exon 10, exon 11, exon 12, exon 13, exon 14, exon 15, exon 16, exon 17, any intervening intronic regions, intron/exon junctions, the 3' UTR, or polyadenylation signal) is targeted by an RNA-guided nuclease to alter the gene (*see*, e.g., Fig. 2A). In some embodiments, the IL1RAP gene targeted by an RNA-guided nuclease is from a mammal. In some embodiments, the IL1RAP gene targeted by an RNA-guided nuclease is from a human (hIL1RAP). In some embodiments, the IL1RAP gene targeted by an RNA-guided nuclease is from a dog (cIL1RAP). In some embodiments, the IL1RAP gene targeted by an RNA-guided nuclease is from a horse (eIL1RAP). In some embodiments, the IL1RAP gene targeted by an RNA-guided nuclease is from a cat (fIL1RAP).

[0064] The term "interleukin-1 receptor complex" or "IL1R complex" refers to any number of the protein receptors that comprises the family of transmembrane protein receptors responsible for transmitting or modulating intracellular signaling via binding of the pro-inflammatory cytokine interleukin 1 (IL1). These members include IL1R1, IL1R2, which primarily functions as a decoy receptor, IL1RAP, and IL1RL1, which can complex with other family members in the IL33 or IL36 signaling system.

[0065] The terms "Transforming Growth Factor Beta Receptor 1" or "TGFBR1" refer to the genes (NCBI Gene ID: 7046 [human], NCBI Gene ID: 481628 [canine], NCBI Gene ID: 100034117 [equine], NCBI Gene ID: 101094057 [feline]) or an encoded gene product (e.g., UniProt: P36897; NP_004603.1 [human], XP_038538191.1 [canine], XP_023485510.1 [equine], XP_023098269.1 [feline]), as well as sequence variants, proteins harboring conservative amino acid substitutions, and glycoforms thereof. Canonically, the proteins encoded by the genes listed above are transmembrane serine/threonine kinases forming, with TGFBR2, the native receptor for the TGF-beta cytokines TGFB1, TGFB2 and TGFB3. When bound to its ligand, TGFBR1 is phosphorylated by TGFBR2, activating intracellular signaling regulating multiple physiological and pathological processes through release of SMAD2, which can then translocate to the nucleus or activation of other cytoplasmic signaling mediators. In some instances, and merely for the sake of disambiguation, a prefix is added when referring to the protein or gene of a particular species (with *h*, *c*, *e*, and *f*, referring to the human, canine, equine, and feline forms, respectively).

[0066] In certain embodiments, any region of an TGFBR1 gene (e.g., 5' untranslated region [UTR], exon 1, exon 2, exon 3, exon 4, exon 5, exon 6, exon 7, exon 8, exon 9, exon 10, exon 11, exon 12, any intervening intronic regions, intron/exon junctions, the 3' UTR, or polyadenylation signal) is targeted by an RNA-guided nuclease to alter the gene. In some embodiments, the TGFBR1 gene targeted by an RNA-guided nuclease is from a mammal. In some embodiments, the TGFBR1 gene targeted by an RNA-guided nuclease is from a human (hTGFBR1). In some embodiments, the TGFBR1 gene targeted by an RNA-guided nuclease is from a dog (cTGFBR1). In some embodiments, the TGFBR1 gene targeted by an RNA-guided nuclease is from a horse (eTGFBR1). In some embodiments, the TGFBR1 gene targeted by an RNA-guided nuclease is from a cat (fTGFBR1).

[0067] The terms "Transforming Growth Factor Beta Receptor 2" or "TGFBR2" refer to the genes (NCBI Gene ID: 7048 [human], NCBI Gene ID: 477039 [canine], NCBI Gene ID: 100033860 [equine], NCBI Gene ID: 101091725 [feline]) or an encoded gene product (e.g., UniProt: P37173; NP_003233.4 [human], XP_038288013.1 [canine], XP_023475502.1 [equine], XP_023116415.1 [feline]), as well as sequence variants, proteins harboring conservative amino acid substitutions, and glycoforms thereof Canonically, the proteins encoded by the genes listed above are transmembrane serine/threonine kinases forming, with TGFBR2, the native receptor for the TGF-beta cytokines TGFB1, TGFB2 and TGFB3. When bound to its ligand, TGFBR1 is phosphorylated by TGFBR2, activating intracellular

signaling regulating multiple physiological and pathological processes through release of SMAD2, which can then translocate to the nucleus or activation of other cytoplasmic signaling mediators. In some instances, and merely for the sake of disambiguation, a prefix is added when referring to the protein or gene of a particular species (with *h*, *c*, *e*, and *f*, referring to the human, canine, equine, and feline forms, respectively).

[0068] In certain embodiments, any region of an TGFBR2 gene (e.g., 5' untranslated region [UTR], exon 1, exon 2, exon 3, exon 4, exon 5, exon 6, exon 7, exon 8, exon 9, exon 10, any intervening intronic regions, intron/exon junctions, the 3' UTR, or polyadenylation signal) is targeted by an RNA-guided nuclease to alter the gene. In some embodiments, the TGFBR2 gene targeted by an RNA-guided nuclease is from a mammal. In some embodiments, the TGFBR2 gene targeted by an RNA-guided nuclease is from a human (hTGFBR2). In some embodiments, the TGFBR2 gene targeted by an RNA-guided nuclease is from a dog (cTGFBR2). In some embodiments, the TGFBR2 gene targeted by an RNA-guided nuclease is from a horse (eTGFBR2). In some embodiments, the TGFBR2 gene targeted by an RNA-guided nuclease is from a cat (fTGFBR2).

[0069] The terms "Interleukin-6 Receptor" or "IL6R" refer to the genes (NCBI Gene ID: 3560 [human], NCBI Gene ID: 612271 [canine], NCBI Gene ID: 102148787 [equine], NCBI Gene ID: 101085689 [feline]) or an encoded gene product (e.g., UniProt: P08887; CAA41231.1 [human], XP_038527979.1 [canine], XP_023496854.1 [equine], XP_023103841.2 [feline]), as well as sequence variants, proteins harboring conservative amino acid substitutions, and glycoforms thereof. Canonically, the proteins encoded by the genes listed above are transmembrane proteins capable of binding to interleukin-6, its native ligand. This binding event triggers intracellular signaling events that result in pro-inflammatory responses. *See generally*, Wolf, J., et al. (2014). *Cytokine*, 70(1), 11-20. In some instances, and merely for the sake of disambiguation, a prefix is added when referring to the protein or gene of a particular species (with *h*, *c*, *e*, and *f*, referring to the human, canine, equine, and feline forms, respectively).

[0070] In certain embodiments, any region of an IL6R gene (e.g., 5' untranslated region [UTR], exon 1, exon 2, exon 3, exon 4, exon 5, exon 6, exon 7, exon 8, exon 9, exon 10, exon 11, exon 12, exon 13, exon 14, exon 15, any intervening intronic regions, intron/exon junctions, the 3' UTR, or polyadenylation signal) is targeted by an RNA-guided nuclease to alter the gene. In some embodiments, the IL6R gene targeted by an RNA-guided nuclease is from a mammal. In some embodiments, the IL6R gene targeted by an RNA-guided nuclease

is from a human (hIL6R). In some embodiments, the IL6R gene targeted by an RNA-guided nuclease is from a dog (cIL6R). In some embodiments, the IL6R gene targeted by an RNA-guided nuclease is from a horse (eIL6R). In some embodiments, the IL6R gene targeted by an RNA-guided nuclease is from a cat (fIL6R).

[0071] The terms "Interleukin-6 Cytokine Family Signal Transducer," "GP130," or "IL6ST" refer to the genes (NCBI Gene ID: 3572 [human], NCBI Gene ID: 403545 [canine], NCBI Gene ID: 100051700 [equine], NCBI Gene ID: 101089832 [feline]) or an encoded gene product (e.g., UniProt: P40189; NP_001177910.1 [human], NP_001273950.1 [canine], XP_023481030.1 [equine], XP_011281205.1 [feline]), as well as sequence variants, proteins harboring conservative amino acid substitutions, and glycoforms thereof. Canonically, the proteins encoded by the genes listed above are signal transducers shared by many cytokines, including interleukin 6 (IL6), ciliary neurotrophic factor (CNTF), leukemia inhibitory factor (LIF), and oncostatin M (OSM) and function as a part of the cytokine receptor complex. Activation of this protein is dependent upon the binding of cytokines to their receptors (e.g., IL6 to IL6R). Knockout studies in mice suggest that this gene plays a critical role in regulating myocyte apoptosis. *See generally*, Martínez-Pérez, C., et al. (2021). *Journal of Personalized Medicine*, 11(7), 618. In some instances, and merely for the sake of disambiguation, a prefix is added when referring to the protein or gene of a particular species (with *h*, *c*, *e*, and *f*, referring to the human, canine, equine, and feline forms, respectively

[0072] In certain embodiments, any region of an IL6ST gene (e.g., 5' untranslated region [UTR], exon 1, exon 2, exon 3, exon 4, exon 5, exon 6, exon 7, exon 8, exon 9, exon 10, exon 11, exon 12, exon 13, exon 14, exon 15, exon 16, exon 17, exon 18, exon 19, exon 20, any intervening intronic regions, intron/exon junctions, the 3' UTR, or polyadenylation signal) is targeted by an RNA-guided nuclease to alter the gene. In some embodiments, the IL6ST gene targeted by an RNA-guided nuclease is from a mammal. In some embodiments, the IL6ST gene targeted by an RNA-guided nuclease is from a human (hIL6ST). In some embodiments, the IL6ST gene targeted by an RNA-guided nuclease is from a dog (cIL6ST). In some embodiments, the IL6ST gene targeted by an RNA-guided nuclease is from a horse (eIL6ST). In some embodiments, the IL6ST gene targeted by an RNA-guided nuclease is from a cat (fIL6ST).

[0073] The terms "Tumor Necrosis Factor Receptor 1" or "TNFRSF1A" refer to the genes (NCBI Gene ID: 7132 [human], NCBI Gene ID: 403634 [canine], NCBI Gene ID: 100059548 [equine], NCBI Gene ID: 493957 [feline]) or an encoded gene product (e.g.,

UniProt: P19438; NP_001056.1 [human], XP_038295153.1 [canine], XP_023498787.1 [equine], NP_001009361.1 [feline]), as well as sequence variants, proteins harboring conservative amino acid substitutions, and glycoforms thereof. Canonically, the proteins encoded by the genes listed above are transmembrane receptor proteins capable of binding Tumor Necrosis Factor Alpha (TNFA) or lymphotoxin alpha (LTA), its principal ligand. Upon binding to TNFA, the receptor trimerizes and is activated, transmitting intracellular signaling cascades with role in various processes, including apoptosis and inflammation. *See generally*, Ward-Kavanagh, L. K., et al. (2016). *Immunity*, 44(5), 1005-1019. In some instances, and merely for the sake of disambiguation, a prefix is added when referring to the protein or gene of a particular species (with *h*, *c*, *e*, and *f*, referring to the human, canine, equine, and feline forms, respectively).

[0074] In certain embodiments, any region of an TNFRSF1A gene (e.g., 5' untranslated region [UTR], exon 1, exon 2, exon 3, exon 4, exon 5, exon 6, exon 7, exon 8, exon 9, exon 10, exon 11, any intervening intronic regions, intron/exon junctions, the 3' UTR, or polyadenylation signal) is targeted by an RNA-guided nuclease to alter the gene. In some embodiments, the TNFRSF1A gene targeted by an RNA-guided nuclease is from a mammal. In some embodiments, the TNFRSF1A gene targeted by an RNA-guided nuclease is from a human (hTNFRSF1A). In some embodiments, the TNFRSF1A gene targeted by an RNA-guided nuclease is from a dog (cTNFRSF1A). In some embodiments, the TNFRSF1A gene targeted by an RNA-guided nuclease is from a horse (eTNFRSF1A). In some embodiments, the TNFRSF1A gene targeted by an RNA-guided nuclease is from a cat (fTNFRSF1A).

[0075] The terms "Tumor Necrosis Factor Receptor 2" or "TNFRSF1B" refer to the genes (NCBI Gene ID: 7133 [human], NCBI Gene ID: 487437 [canine], NCBI Gene ID: 100055840 [equine], NCBI Gene ID: 101080392 [feline]) or an encoded gene product (e.g., UniProt: P20333; XP_011540362.1 [human], XP_038387905.1 [canine], XP_023491528.1 [equine], XP_023113905.2 [feline]), as well as sequence variants, proteins harboring conservative amino acid substitutions, and glycoforms thereof. Canonically, the proteins encoded by the genes listed above are transmembrane receptor proteins capable of binding TNFA or LTA and are implicated in pro-survival pathways through downstream activation of NFkB pathway. *See generally*, Ward-Kavanagh, L. K., et al. (2016). *Immunity*, 44(5), 1005-1019. In some instances, and merely for the sake of disambiguation, a prefix is added when referring to the protein or gene of a particular species (with *h*, *c*, *e*, and *f*, referring to the human, canine, equine, and feline forms, respectively).

[0076] In certain embodiments, any region of an TNFRSF1B gene (e.g., 5' untranslated region [UTR], exon 1, exon 2, exon 3, exon 4, exon 5, exon 6, exon 7, exon 8, exon 9, exon 10, exon 11, exon 13, any intervening intronic regions, intron/exon junctions, the 3' UTR, or polyadenylation signal) is targeted by an RNA-guided nuclease to alter the gene. In some embodiments, the TNFRSF1B gene targeted by an RNA-guided nuclease is from a mammal. In some embodiments, the TNFRSF1B gene targeted by an RNA-guided nuclease is from a human (hTNFRSF1B). In some embodiments, the TNFRSF1B gene targeted by an RNA-guided nuclease is from a dog (cTNFRSF1B). In some embodiments, the TNFRSF1B gene targeted by an RNA-guided nuclease is from a horse (eTNFRSF1B). In some embodiments, the TNFRSF1B gene targeted by an RNA-guided nuclease is from a cat (fTNFRSF1B).

[0077] The terms "Lymphotoxin Beta Receptor" or "TNFRSF3" refer to the genes (NCBI Gene ID: 4055 [human], NCBI Gene ID: 486728 [canine], NCBI Gene ID: 100059650 [equine], NCBI Gene ID: 101081146 [feline]) or an encoded gene product (e.g., UniProt: P36941; NP_001257916.1 [human], XP_038295148.1 [canine], XP_001492220.3 [equine], XP_003988366.4 [feline]), as well as sequence variants, proteins harboring conservative amino acid substitutions, and glycoforms thereof. Canonically, the proteins encoded by the genes listed above play a role in signaling during the development of lymphoid and other organs, lipid metabolism, immune response, and programmed cell death. Major ligands of this receptor include lymphotoxin alpha/beta and tumor necrosis factor ligand superfamily member 14 (TNFSF14). Activity of this receptor has also been linked to carcinogenesis. *See generally*, Seymour, R., et al. (2006). *Veterinary Pathology*, 43(4), 401-423. In some instances, and merely for the sake of disambiguation, a prefix is added when referring to the protein or gene of a particular species (with *h*, *c*, *e*, and *f*, referring to the human, canine, equine, and feline forms, respectively).

[0078] In certain embodiments, any region of an TNFRSF3 gene (e.g., 5' untranslated region [UTR], exon 1, exon 2, exon 3, exon 4, exon 5, exon 6, exon 7, exon 8, exon 9, exon 10, exon 11, exon 12, any intervening intronic regions, intron/exon junctions, the 3' UTR, or polyadenylation signal) is targeted by an RNA-guided nuclease to alter the gene. In some embodiments, the TNFRSF3 gene targeted by an RNA-guided nuclease is from a mammal. In some embodiments, the TNFRSF3 gene targeted by an RNA-guided nuclease is from a human (hTNFRSF3). In some embodiments, the TNFRSF3 gene targeted by an RNA-guided nuclease is from a dog (cTNFRSF3). In some embodiments, the TNFRSF3 gene targeted by

an RNA-guided nuclease is from a horse (eTNFRSF3). In some embodiments, the TNFRSF3 gene targeted by an RNA-guided nuclease is from a cat (fTNFRSF3).

[0079] The terms "OX40 Receptor," "OX40," "CD134," or "TNFRSF4" refer to the genes (NCBI Gene ID: 7293 [human], NCBI Gene ID: 489600 [canine], NCBI Gene ID: 100066167 [equine], NCBI Gene ID: 493665 [feline]) or an encoded gene product (e.g., UniProt: P43489; XP_011540377.1 [human], XP_038520220.1 [canine], XP_001503612.3 [equine], NP_001009200.1 [feline]), as well as sequence variants, proteins harboring conservative amino acid substitutions, and glycoforms thereof. Canonically, the proteins encoded by the genes listed above specifically bind to OX40 ligand (OX40L) and are predominantly expressed on lymphocytes. The result of this binding is transient downstream intracellular signaling mediated via TRAF2 and other effector proteins that often occurs in response to the presence of antigen. *See generally*, Ward-Kavanagh, L. K., et al. (2016). *Immunity*, 44(5), 1005-1019. In some instances, and merely for the sake of disambiguation, a prefix is added when referring to the protein or gene of a particular species (with *h*, *c*, *e*, and *f*, referring to the human, canine, equine, and feline forms, respectively).

[0080] In certain embodiments, any region of an TNFRSF4 gene (e.g., 5' untranslated region [UTR], exon 1, exon 2, exon 3, exon 4, exon 5, exon 6, exon 7, any intervening intronic regions, intron/exon junctions, the 3' UTR, or polyadenylation signal) is targeted by an RNA-guided nuclease to alter the gene. In some embodiments, the TNFRSF4 gene targeted by an RNA-guided nuclease is from a mammal. In some embodiments, the TNFRSF4 gene targeted by an RNA-guided nuclease is from a human (hTNFRSF4). In some embodiments, the TNFRSF4 gene targeted by an RNA-guided nuclease is from a dog (cTNFRSF4). In some embodiments, the TNFRSF4 gene targeted by an RNA-guided nuclease is from a horse (eTNFRSF4). In some embodiments, the TNFRSF4 gene targeted by an RNA-guided nuclease is from a cat (fTNFRSF4).

[0081] The terms "TNF Receptor Superfamily Member 11A" or "TNFRSF11A" refer to the genes (NCBI Gene ID: 8792 [human], NCBI Gene ID: 483957 [canine], NCBI Gene ID: 100056617 [equine], NCBI Gene ID: 101090651 [feline]) or an encoded gene product (e.g., UniProt: Q9Y6Q6; NP_001257878.1 [human], XP_038509502.1 [canine], XP_023503703.1 [equine], XP_023096972.1 [feline]), as well as sequence variants, proteins harboring conservative amino acid substitutions, and glycoforms thereof. Canonically, the proteins encoded by the genes listed above are transmembrane proteins capable of interacting with n various TRAF family proteins, through which the receptors induce the activation of NF-

kappa B and MAPK8/JNK pathways. This receptor, with its ligand, is an important regulator of the interaction between T cells and dendritic cells and is also an essential mediator for bone metabolism and development. *See generally*, Xue, J. Y., et al. (2021). *Journal of Bone and Mineral Metabolism*, 39(1), 45-53. In some instances, and merely for the sake of disambiguation, a prefix is added when referring to the protein or gene of a particular species (with *h*, *c*, *e*, and *f*, referring to the human, canine, equine, and feline forms, respectively).

[0082] In certain embodiments, any region of an TNFRSF11A gene (e.g., 5' untranslated region [UTR], exon 1, exon 2, exon 3, exon 4, exon 5, exon 6, exon 7, exon 8, exon 9, exon 10, exon 11, exon 12, any intervening intronic regions, intron/exon junctions, the 3' UTR, or polyadenylation signal) is targeted by an RNA-guided nuclease to alter the gene. In some embodiments, the TNFRSF11A gene targeted by an RNA-guided nuclease is from a mammal. In some embodiments, the TNFRSF11A gene targeted by an RNA-guided nuclease is from a human (hTNFRSF11A). In some embodiments, the TNFRSF11A gene targeted by an RNA-guided nuclease is from a dog (cTNFRSF11A). In some embodiments, the TNFRSF11A gene targeted by an RNA-guided nuclease is from a horse (eTNFRSF11A). In some embodiments, the TNFRSF11A gene targeted by an RNA-guided nuclease is from a cat (fTNFRSF11A).

[0083] The term "treatment" refers to obtaining a desired pharmacologic and/or physiologic effect. The effect may be prophylactic in terms of completely or partially preventing a disease or symptom thereof and/or may be therapeutic in terms of a partial or complete cure for a disease and/or adverse effect attributable to the disease. For example, a composition, method, or system of the present disclosure may be administered as a prophylactic treatment to a subject that has a predisposition for a given condition (e.g., arthritis). "Treatment", as used herein, covers any treatment of a disease in a mammal, particularly in a human, canine, feline, or equine, and includes: (a) preventing the disease from occurring in a subject which may be predisposed to the disease but has not yet been diagnosed as having it; (b) inhibiting the disease, *i.e.*, arresting its development or progression; and (c) relieving the disease, *i.e.*, causing regression of the disease and/or relieving one or more disease symptoms.

[0084] "Treatment" is also meant to encompass delivery of an agent in order to provide for a pharmacologic effect, even in the absence of a disease or condition. For example, "treatment" encompasses delivery of a composition that can elicit an immune response or confer immunity in the absence of a disease condition, *e.g.*, in the case of a vaccine. It is

understood that compositions and methods of the present disclosure are applicable to treat all mammals, including, but not limited to human, canine, feline, equine, and bovine subjects.

[0085] The term "therapeutically effective" refers to the amount of a composition or combination of compositions as described herein that is sufficient to effect the intended application including, but not limited to, disease treatment. A therapeutically effective amount may vary depending upon the intended application (*in vitro* or *in vivo*), or the subject and disease condition being treated (*e.g.*, the weight, age and gender of the subject), the severity of the disease condition, or the manner of administration. The term also applies to a dose that will induce a particular response in target cells (*e.g.*, the reduction of platelet adhesion and/or cell migration). The specific dose will vary depending on the particular composition(s) chosen, the dosing regimen to be followed, whether the composition is administered in combination with other compositions or compounds, timing of administration, the tissue to which it is administered, and the physical delivery system in which the composition is carried.

[0086] The term "joint disease" is defined as measurable abnormalities in the cells or tissues of the joint that could lead to illness, for example, metabolic and molecular derangements triggering anatomical and/or physiological changes in the joint. Including, but not limited to, radiographic detection of joint space narrowing, subchondral sclerosis, subchondral cysts, and osteophyte formation.

[0087] "Joint illness" is defined in human subjects as symptoms that drive the subject to seek medical intervention, for example, subject reported pain, stiffness, swelling, or immobility. For non-human mammals, "joint illness" is defined, for example, as lameness, observable changes in gait, weight bearing, allodynia, or exploratory behavior.

[0088] A "back or spine condition or disorder" includes, but is not limited to, low back pain, neck pain, discogenic disorders, adolescent idiopathic scoliosis, adult degenerative scoliosis, cervical degenerative disc disease, cervical disc herniation, cervical myelopathy, cervical stenosis, compression fractures, degenerative spondylolisthesis, isthmic spondylolisthesis, low back sprains and strains, lumbar degenerative disc disease, lumbar disc herniation, lumbar stenosis, neck sprain (whiplash) and strain, neck strain, osteoporosis, and whiplash. Generally, such disorders or conditions contribute to or cause localized nociception, inflammation, or morphological changes (e.g., fibrosis, degeneration, osteolysis, osteogenesis) at the cervical, thoracic, lumbar or sacral spine, or surrounding tissues.

[0089] "Low back pain" is defined as measurable or discernible pain or discomfort (either chronic or sporadic) in a given subject, encompassing at least the lumbar-spinal region of a mammal. The pain may present as being localized to the lower back (e.g., muscle ache) or as shooting, burning, stinging, and/or radiating sensations throughout the subject's back and/or extremities. The pain may be idiopathic or may be associated with one or more (diagnosed or undiagnosed) underlying conditions including, but not limited to, chronic inflammation, arthritis, osteoporosis, trauma (e.g., post-surgical), neuropathies, musculo-skeletal abnormalities (e.g., slipped discs or spinal stenosis), herniated nucleus pulposus (HNP), annular ligament tears, facet joint arthritis, radicular nerve compression, and/or degenerative disorders.

[0090] "Neck pain" is defined as measurable or discernable pain or discomfort associated with the cervical spine or adjacent ligaments, muscles, and/or tendons. The pain may manifest as localized pain in the neck or shooting, stinging, burning, and/or radiating sensations throughout the back or extremities, including, but not limited to, the subject's head, shoulders, arms, legs, and/or back. Neck pain may be idiopathic or associated with one or more (diagnosed or undiagnosed) underlying conditions, including, but not limited to, rheumatoid arthritis, osteoporosis, fibromyalgia, chronic inflammation, herniated disc, spondylosis, spinal stenosis, whiplash, and/or degenerative disorders.

[0091] The terms "polynucleotide," "nucleotide," and "nucleic acid" are used interchangeably herein to refer to all forms of nucleic acid, oligonucleotides, including deoxyribonucleic acid (DNA) and ribonucleic acid (RNA). Polynucleotides include genomic DNA, cDNA and antisense DNA, and spliced or unspliced mRNA, rRNA, tRNA, lncRNA, RNA antagomirs, and inhibitory DNA or RNA (RNAi, e.g., small or short hairpin (sh)RNA, microRNA (miRNA), aptamers, small or short interfering (si)RNA, trans-splicing RNA, or antisense RNA). Polynucleotides also include non-coding RNA, which include for example, but are not limited to, RNAi, miRNAs, lncRNAs, RNA antagomirs, aptamers, and any other non-coding RNAs known to those of skill in the art. Polynucleotides include naturally occurring, synthetic, and intentionally altered or modified polynucleotides as well as analogues and derivatives. The term "polynucleotide" also refers to a polymeric form of nucleotides of any length, including deoxyribonucleotides or ribonucleotides, or analogs thereof, and is synonymous with nucleic acid sequence. A polynucleotide may comprise modified nucleotides, such as methylated nucleotides and nucleotide analogs, and may be interrupted by non-nucleotide components. If present, modifications to the nucleotide

structure may be imparted before or after assembly of the polymer. The term polynucleotide, as used herein, refers interchangeably to double- and single-stranded molecules. Unless otherwise specified or required, any embodiment as described herein encompassing a polynucleotide encompasses both the double-stranded form and each of two complementary single-stranded forms known or predicted to make up the double-stranded form. Polynucleotides can be single, double, or triplex, linear or circular, and can be of any length. In discussing polynucleotides, a sequence or structure of a particular polynucleotide may be described herein according to the convention of providing the sequence in the 5' to 3' direction.

[0092] The term "gene" or "nucleotide sequence encoding a polypeptide" refers to the segment of DNA involved in producing a polypeptide chain. The DNA segment may include regions preceding and following the coding region (leader and trailer) involved in the transcription / translation of the gene product and the regulation of the transcription / translation, as well as intervening sequences (introns) between individual coding segments (exons). For example, a gene includes a polynucleotide containing at least one open reading frame capable of encoding a particular protein or polypeptide after being transcribed and translated.

[0093] The terms "extracellular domain" and "ectodomain" may be used interchangeably and, when referring to transmembrane cellular receptors, is defined as the portion of the protein that is exposed to the extracellular environment and is able to engage with and/or bind a ligand.

[0094] The terms "cytoplasmic domain" and "intracellular domain" may be used interchangeably and, when referring to transmembrane receptors, define the portion of the protein that is exposed to the cytoplasm. In many instances, these portions of the proteins comprise signaling domains to recruit and associate with various intracellular factors. Following engagement with a ligand via the extracellular domain, the interaction effects changes that may result in new association, dissociation or recruitment of various cytoplasmic factors that aid in transducing a signal.

[0095] The term "transmembrane domain," which may be abbreviated as "TM," as it refers to transmembrane receptors, is defined as the portion of the protein is embedded within the plasma membrane (i.e., not exposed to either the extracellular environment or the cytosol). Transmembrane domains are generally of a more hydrophobic character than either the

extracellular or cytoplasmic portions and often adopt higher order helical structures. Though its primary role is an anchor, ligand-induced conformational changes to particular receptors have been shown to impact the transmembrane domain such that it is integral to the subsequent intracellular signaling.

[0096] The term "receptor" refers to a protein capable of binding another cognate protein (i.e., its ligand) with high affinity. This receptor-ligand interaction may be 1:1, or result in multimerization, wherein numerous proteins aggregate to bind one or more ligands. Receptors are generally present at the cell surface, such that they may most efficiently encounter a ligand and initiate intracellular signaling.

[0097] The term "intracellular signaling" refers to cellular changes that result due to events occurring at the cell surface. Typically, a soluble ligand binds its receptor at the cell surface, which can induce changes in the receptor, such that associated intracellular factors are also affected. These factors may then impact others within the cell, and this cascade continues until, in many cases, a particular factor is able to alter gene expression in the nucleus in response to the stimulus at the surface.

[0098] The term "RNA-guided nuclease" refers to an enzyme capable of breaking the backbone of, for example, a DNA molecule. The activity of RNA-guided nucleases is directed by a nucleic acid molecule (i.e., guide RNA). Once properly oriented to form a functional ribonucleoprotein complex, the enzyme locates a specific position within a target nucleic acid (e.g., a gene or locus) via sequence complementarity with a portion of the guide RNA. Non-exhaustive examples of RNA-guided nucleases include Cas9, Cas12 and Cas12a (previously known as Cpf1).

[0099] The term "Cas9" refers to an RNA-guided, double-stranded DNA-binding nuclease protein or nickase protein, or a variant thereof and may be used to refer to either naturally-occurring or recombinant Cas9 nucleases variants (e.g., ES-Cas9, HF-Cas9, PE-Cas9, and AR-Cas9). The wildtype Cas9 nuclease has two functional domains, *e.g.*, RuvC and HNH, that simultaneously cut both strands of double stranded DNA, resulting in a double-strand break. Cas9 enzymes described herein may comprise a HNH or HNH-like nuclease domain and/or a RuvC or RuvC-like nuclease domain without impacts on the ability to induce double-strand breaks in genomic DNA (e.g., at a target locus) when both functional domains are active. The Cas9 enzyme may comprise one or more catalytic domains of a Cas9 protein derived from bacteria belonging to the group consisting of *Corynebacter*, *Sutterella*,

Legionella, *Treponema*, *Filifactor*, *Eubacterium*, *Streptococcus*, *Lactobacillus*, *Mycoplasma*, *Bacteroides*, *Flaviivola*, *Flavobacterium*, *Sphaerochaeta*, *Azospirillum*, *Gluconacetobacter*, *Neisseria*, *Roseburia*, *Parvibaculum*, *Staphylococcus*, *Nitratifractor*, and *Campylobacter*. In some embodiments, the two catalytic domains are derived from different bacteria species.

[00100] As used herein, "PAM" refers to a Protospacer Adjacent Motif and is necessary for an RNA-guided nuclease to bind a target nucleic acid. In many instances, the PAM directly abuts the complementary sequence in the target. Naturally-occurring Cas9, for example, molecules recognize specific PAM sequences (see, e.g., Table 1). In some embodiments, a Cas9 molecule has the same PAM specificities as a naturally occurring Cas9 molecule. In other embodiments, a Cas9 molecule has a PAM specificity not associated with a naturally occurring Cas9 molecule. In other embodiments, a Cas9 molecule's PAM specificity is not associated with the naturally occurring Cas9 molecule to which it has the closest sequence homology. For example, a naturally occurring Cas9 molecule can be altered such that the PAM sequence recognition is altered to decrease off target sites, improve specificity, or eliminate a PAM recognition requirement. In an embodiment, a Cas9 molecule may be altered (e.g., to lengthen a PAM recognition sequence, improve Cas9 specificity to high level of identity, to decrease off target sites, and/or increase specificity). In an embodiment, the length of the PAM recognition sequence is at least 4, 5, 6, 7, 8, 9, 10 or 15 amino acids in length. In some embodiments, a Cas9 molecule may be altered to ablate PAM recognition.

[00101] The terms "guide RNA," "gRNA" or "sgRNA" may be used interchangeably and refer to an RNA molecule, preferably a synthetic RNA molecule, composed of a targeting (crRNA) sequence and scaffold. These molecules, once loaded onto a functional RNA-guided nuclease can direct sequence-specific cleavage of a target nucleic acid.

[00102] An sgRNA can be administered or formulated, e.g., as a synthetic RNA, or as a nucleic acid comprising a sequence encoding the gRNA, which is then expressed in the target cells. As would be evident to one of ordinary skill in the art, various tools may be used in the design and/or optimization of an sgRNA in order to, for example, increase specificity and/or precision of genomic editing at a particular site.

[00103] In general, candidate sgRNAs may be designed and identified by first locating suitable PAMs within a genomic sequence. Then additional calculations may be utilized to predict on-target and off-target efficiencies. Available web-based tools to aid in the initial design and modeling of candidate sgRNAs include, without limitation, CRISPRseek,

CRISPR Design Tool, Cas-OFFinder, E-CRISP, ChopChop, CasOT, CRISPR direct, CRISPOR, BREAKING-CAS, CrispRGold, and CCTop. See, e.g., Safari, F. et al. (2017). Current Pharmaceutical Biotechnology, 18(13):1038-54, which is incorporated by reference herein in its entirety for all purposes. Such tools are also described, for example, in PCT Publication No. WO2014093701A1 and Liu, G. et al. (2020). Computational approaches for effective CRISPR guide RNA design and evaluation. Computational and Structural Biotechnology Journal, 18: 35-44, each of which is incorporated by reference herein in its entirety for all purposes. Candidate sgRNAs may be further assessed by experimental screening or other methodologies.

[00104] The terms "CRISPR RNA" or "crRNA" refer to the portion of an sgRNA molecule with complementarity to the target nucleic acid.

[00105] The phrase "pharmaceutically acceptable" refers to those compounds, materials, compositions, and/or dosage forms that are, within the scope of sound medical judgment, suitable for use in contact with the tissues of human beings and animals without excessive toxicity, irritation, allergic response, or other problems or complications commensurate with a reasonable benefit/risk ratio.

[00106] The terms "pharmaceutically acceptable carrier" or "pharmaceutically acceptable excipient" are intended to include any and all solvents, dispersion media, coatings, antibacterial and antifungal agents, isotonic and absorption delaying agents, and inert ingredients. The use of such pharmaceutically acceptable carriers or pharmaceutically acceptable excipients for active pharmaceutical ingredients is well known in the art. Except insofar as any conventional pharmaceutically acceptable carrier or pharmaceutically acceptable excipient is incompatible with the active pharmaceutical ingredient, its use in the therapeutic compositions of the disclosure is contemplated. Additional active pharmaceutical ingredients, such as other drugs, can also be incorporated into the described compositions and methods.

[00107] The term "pharmaceutically acceptable excipient" is intended to include vehicles and carriers capable of being co-administered with a compound to facilitate the performance of its intended function. The use of such media for pharmaceutically active substances is well known in the art. Examples of such vehicles and carriers include solutions, solvents, dispersion media, delay agents, emulsions and the like. Any other conventional carrier

suitable for use with the multi-binding compounds also falls within the scope of the present disclosure.

[00108] As used herein, the term "a", "an", or "the" generally is construed to cover both the singular and the plural forms.

[00109] The terms "about" and "approximately" mean within a statistically meaningful range of a value. Such a range can be within an order of magnitude, preferably within 50%, more preferably within 20%, more preferably still within 10%, and even more preferably within 5% of a given value or range. The allowable variation encompassed by the terms "about" or "approximately" depends on the particular system under study, and can be readily appreciated by one of ordinary skill in the art. Moreover, as used herein, the terms "about" and "approximately" mean that compositions, amounts, formulations, parameters, shapes and other quantities and characteristics are not and need not be exact, but may be approximate and/or larger or smaller, as desired, reflecting tolerances, conversion factors, rounding off, measurement error and the like, and other factors known to those of skill in the art. In general, a dimension, size, formulation, parameter, shape or other quantity or characteristic is "about" or "approximate," whether or not expressly stated to be such. It is noted that embodiments of very different sizes, shapes and dimensions may employ the described arrangements.

[00110] The term "substantially" as used herein can refer to a majority of, or mostly, as in at least about 50%, 60%, 70%, 80%, 90%, 95%, 96%, 97%, 98%, 99%, 99.5%, 99.9%, 99.99%, or at least about 99.999% or more.

[00111] The transitional terms "comprising," "consisting essentially of," and "consisting of," when used in the appended claims, in original and amended form, define the claim scope with respect to what unrecited additional claim elements or steps, if any, are excluded from the scope of the claim(s). The term "comprising" is intended to be inclusive or open-ended and does not exclude any additional, unrecited element, method, step or material. The term "consisting of" excludes any element, step or material other than those specified in the claim and, in the latter instance, impurities ordinary associated with the specified material(s). The term "consisting essentially of" limits the scope of a claim to the specified elements, steps or material(s) and those that do not materially affect the basic and novel characteristic(s) of the claimed methods and compositions. All compositions, methods, and kits described herein that embody the present disclosure can, in alternate embodiments, be more specifically

defined by any of the transitional terms "comprising," "consisting essentially of," and "consisting of."

III. Methods

A. CRISPR

[00112] Unless otherwise defined, all technical and scientific terms used herein have the same meaning as commonly understood by one of ordinary skill in the art to which this disclosure belongs. Although methods and materials similar or equivalent to those described herein may be used in the practice or testing of the present disclosure, suitable methods and materials are described below. All publications, patent applications, patents, and other references mentioned herein are incorporated by reference in their entirety. In addition, the materials, methods, and examples are illustrative only and not intended to be limiting.

[00113] In one aspect, the present disclosure encompasses compositions relating to clustered regularly interspaced short palindromic repeats (CRISPR) and CRISPR-associated RNA-guided nucleases and associated methods, components, and compositions (hereafter, CRISPR/Cas systems). Such systems minimally require at least one isolated or non-naturally-occurring RNA-guided nuclease (e.g., a Cas9 protein) and at least one isolated or non-naturally-occurring guide RNA (e.g., an sgRNA) to effectuate augmentation of a nucleic acid sequence (e.g., genomic DNA).

[00114] In some embodiments, a CRISPR/Cas system effectuates the alteration of a targeted gene or locus in a eukaryotic cell by effecting an alteration of the sequence at a target position (e.g., by creating an insertion or deletion (collectively, an indel) resulting in loss-of-function of (i.e., knocking out) the affected gene or allele; e.g., a nucleotide substitution resulting in a truncation, nonsense mutation, or other type of loss-of-function of an encoded product of, for example, one or more IL1R1, IL1RAP, TGFBR1, TGFBR2, IL6R, IL6ST, TNFRSF1A, TNFRSF1B, TNFRSF3, TNFRSF4, or TNFRSF11A gene (i.e., mRNA or protein); a deletion of one or more nucleotides resulting in a truncation, nonsense mutation, or other type of loss-of-function of an encoded product of, for example, one or more IL1R1, IL1RAP, TGFBR1, TGFBR2, IL6R, IL6ST, TNFRSF1A, TNFRSF1B, TNFRSF3, TNFRSF4, or TNFRSF11A gene; e.g., loss-of-function of the encoded mRNA or protein by a single nucleotide, double nucleotide, or other frame-shifting deletion, or a deletion resulting in a premature stop codon; or an insertion resulting in a truncation, nonsense mutation, or other type of loss-of-function of an encoded gene product, such as an encoded gene product

of, for example, one or more IL1R1, IL1RAP, TGFBR1, TGFBR2, IL6R, IL6ST, TNFRSF1A, TNFRSF1B, TNFRSF3, TNFRSF4, or TNFRSF11A gene (i.e., mRNA or protein); e.g., a single nucleotide, double nucleotide, or other frame-shifting insertions, or an insertion resulting in a premature stop codon. In some embodiments, a CRISPR/Cas system of the present disclosure provides for the alteration of a gene and/or encoded product of a gene, such that the altered product has a resultant loss-of-function and becomes a dominant negative or decoy (e.g., a transmembrane receptor incapable of initiating intracellular signaling or a soluble receptor).

[00115] In one aspect, CRISPR/Cas systems effectuate changes to the sequence of a nucleic acid through nuclease activity. For example, in the case of genomic DNA, the RNA-guided-nuclease locates a target position within a targeted gene or locus by sequence complementarity with the target genomic sequence (e.g., CRISPR RNA (crRNA) or a complementary component of a synthetic single guide RNA (sgRNA)) and cleaves the genomic DNA upon recognition of a particular, nuclease-specific motif called the protospacer adjacent motif (PAM). See generally, Collias, D., & Beisel, C. L. (2021). Nature Communications, 12(1), 1-12.

[00116] Nuclease activity (i.e., cleavage) induces a double-strand break (DSB) in the case of genomic DNA. Endogenous cellular mechanisms of DSB repair, namely non-homologous end joining (NHEJ), microhomology-mediated end joining (MMEJ), and homologous recombination, result in erroneous repair at a given target position with some calculable frequency as a result of interference from said components of the CRISPR/Cas system, thereby introducing substitutions or indels into the genomic DNA. See generally Scully, R., et al. (2019). Nature Reviews Molecular Cell Biology, 20(11), 698-714. At some frequency, these indels and/or substitutions may result in frameshifts, nonsense mutations (i.e., early stop codons) or truncations that impact the availability of gene products, such as mRNA and/or protein. In certain embodiments, the CRISPR/Cas system may induce a homology-directed repair (HDR) mechanism leading to insertions of non-random sequences at a target position through the use of templates (e.g., an HDR template) provided to the cell as part of the system along with the nuclease and gRNA. See Bloh, K., & Rivera-Torres, N. (2021). International Journal of Molecular Sciences, 22(8), 3834.

[00117] In general, the minimum requirements of the CRISPR/Cas system will be dependent upon the nuclease (i.e., Cas protein) provided therewith. To this extent, these bacterially-

derived nucleases have been functionally divided into Types I, III, and V, which all fall into Class 1 and Types II, IV, and VI that are grouped into Class 2.

[00118] *Class 1 CRISPR/Cas systems:*

[00119] The exact components, compositions, and methods for effectuating a change in a targeted nucleic acid sequence using a Class 1 CRISPR/Cas system will vary, but should minimally include: a nuclease (selected from at least Types I, and III), at least one guide RNA selected from 1) sgRNA or 2) a combination of crRNA and tracrRNA. These CRISPR/Cas systems have been categorized together as Class 1 CRISPR/Cas systems due to their similarities in requirements and mode of action within a eukaryotic cell. To this end, compositions, components, and methods among Class 1 constituents may be considered functionally interchangeable, and the following details, provided merely for exemplary purposes, do not represent an exhaustive list of class members:

[00120] Cas3 (see Table 1) is the prototypical Type I DNA nuclease that functions as the effector protein as part of a larger complex (the Cascade complex comprising Cse1, Cse2,), that is capable of genome editing. See generally He, L., et al. (2020). Genes, 11(2), 208. Unlike other CRISPR/Cas systems, Type I systems localize to the DNA target without the Cas3 nuclease via the Cascade complex, which then recruits Cas3 to cleave DNA upon binding and locating the 3' PAM. The Cascade complex is also responsible for processing crRNAs such that they can be used to guide it to the target position. Because of this functionality, Cascade has the ability to process multiple arrayed crRNAs from a single molecule. See . Luo, M. (2015). Nucleic Acids Research, 43(1), 674-681. As such, Type I system may be used to edit multiple targeted genes or loci from a single molecule.

[00121] Because the natural Cas3 substrate is ssDNA, its function in genomic editing is thought to be as a nickase; however, when targeted in tandem, the resulting edit is a result of blunt end cuts to opposing strands to approximate a blunt-cutting endonuclease, such as Cas9. See Pickar-Oliver, A., & Gersbach, C. A. (2019). Nature Reviews Molecular Cell Biology, 20(8), 490-507.

[00122] Like Type I nucleases, the Type III system relies upon a complex of proteins to effect nucleic acid cleavage. Particularly, Cas10 possesses the nuclease activity to cleave ssDNA in prokaryotes. See Tamulaitis, G. Trends in Microbiology, 25(1), 49-61 (2017). Interestingly, this CRISPR/Cas system, native to archaea, exhibits dual specificity and targets both ssDNA and ssRNA. Aside from this change, the system functions much like Type I in

that the crRNA targets an effector complex (similar to Cascade) in a sequence-dependent manner. Similarly, the effector complex processes crRNAs prior to association. The dual nature of this nuclease makes its applications to genomic editing potentially more powerful, as both genomic DNA and, in some cases, mRNAs with the same sequence may be targeted to silence particular targeted genes.

[00123] *Class 2 CRISPR/Cas systems:*

[00124] The exact components, compositions, and methods for effectuating a change in a targeted nucleic acid sequence using a Class 2 CRISPR/Cas system will vary but should minimally include: a nuclease (selected from at least Types II, and V), at least one guide RNA selected from 1) sgRNA or 2) a combination of crRNA and tracrRNA. These CRISPR/Cas systems have been categorized together as Class 2 CRISPR/Cas systems due to their similarities in requirements and mode of action within a eukaryotic cell. To this end, compositions, components, and methods among Class 2 constituents may be considered functionally interchangeable, and the following details, provided merely for exemplary purposes, do not represent an exhaustive list of class members:

[00125] Type II nucleases are the best-characterized CRISPR/Cas systems, particularly the canonical genomic editing nuclease Cas9 (see Table 1). Multiple Cas9 proteins, derived from various bacterial species, have been isolated. The primary distinction between these nucleases is the PAM, a required recognition site within the targeted dsDNA. After association with a gRNA molecule, the crRNA (or targeting domain of a sgRNA) orients the nuclease at the proper position, but the protein's recognition of the PAM is what induces a cleavage event near that site, resulting in a blunt DSB.

[00126] In addition to the naturally-derived Cas9 proteins, several engineered variants have similarly been reported. These range from Cas9 with enhanced specific (i.e., less off-target activity), such as espCas9. Others have been catalytically modified via point mutations in the RuvC (e.g., D10A) and HNH (e.g., H840A) domains such that they induce only single-strand breaks (i.e., Cas9 nickases). See Frock, R. et al. (2015). Nature Biotechnology, 33(2), 179-186. These have also been shown to be less error-prone in editing. Such mitigation of off-target effects becomes paramount when selecting for a desired insertion (i.e., a knock in mutation, in which a desired nucleotide sequence is introduced into a target nucleic acid molecule) rather than a deletion. Indeed, less off-target effects may aid in the preferred DNA

repair mechanism (HDR, in most instances for knock in mutations). See generally Naeem, M., et al. (2020). Cells, 9(7), 1608.

[00127] Additional exemplary further engineered variants of canonical Cas proteins (e.g., mutants, chimeras, and include the following (each of which are hereby incorporated by reference in their entireties for all purposes): WO2015035162A2, WO2019126716A1, WO2019126774A1, WO2014093694A1, WO2014150624A1, US20190225955A1, US Pat. No. 11427818, US Pat. No. 11242542, US Pat. No. 11098297, US Pat. No. 10876100, US Pat. No. 10767193, US Pat. No. 10494621, and US Pat. No. 10100291.

[00128] For the avoidance of doubt, SpCas9 collectively refers to any one of the group consisting of espCas9 (also referred to herein as ES-Cas9 or esCas9), HF-Cas9, PE-Cas9, ARCas9 (also referred to as AR-Cas9).

[00129] Like the canonical Cas9 systems, Type V nucleases only require a synthetic sgRNA with a targeting domain complementary to a genomic sequence to carry out genomic editing. These nucleases contain a RuvC domain but lack the HNH domain of Type II nucleases. Further, Cas12, for example, leaves a staggered cut in the dsDNA substrate distal to the PAM, as compared to Cas9's blunt cut next to the PAM. Both Cas12a, also known as Cpf1, and Cas12b, also known as C2c1 (see Table 1), act as part of larger complex of two gRNA-associated nucleases that acts on dsDNA as a quaternary structure, nicking each strand simultaneously. See Zetsche, B. et al. (2015). Cell, 163(3):759-771; see also Liu, L. et al. (2017). Molecular Cell, 65(2):310-322. Additionally, Cas12b (C2c1) is a highly accurate nuclease with little tolerance for mismatches. See Yang, H. et al. (2016). Cell, 167(7):1814-1828.e12.

[00130] Table 1. Exemplary list of Cas nucleases and their requirements

Nuclease (Species)	PAM (5'→3')	Type of end generated (nucleic acid target)	Spacer length (nt)
Cas9 (*S. pyogenes*)	NGG	Blunt (dsDNA)	20
Cas9 (*S. aureus*)	NNGRRT	Blunt (dsDNA)	20
Cas9 (*C. jejuni*)	NNNNRYAC	Blunt (dsDNA)	22
Cas9 (*S. thermophilus*)	NNAGAAW	Blunt (dsDNA)	20
Cas9 (*N. meningitidis*)	NNNNGATT	Blunt (dsDNA)	24
Cas9 (*F. novicida*)	NGG	Blunt (dsDNA)	21

Cas12a (*L. bacterium*)	TTTV	5' staggered (dsDNA/ssDNA)	23-25
Cas12a (*Acidaminococcus sp.*)	TTTN	5' staggered (dsDNA/ssDNA)	24
Cas3 (E. coli)	CTT/CCT/CAT/CTC	None/blunt (ssDNA)	32

[00131] See generally Wang, J., Zhang, C., & Feng, B. (2020). Journal of Cellular and Molecular Medicine, 24(6), 3256-3270, where N=any nucleotide; R=any purine (A or G); Y=any pyrimidine (C or T); W=A or T ; V=A, C or G.

[00132] In one aspect, the CRISPR/Cas system of the present disclosure comprises at least one RNA-guided nuclease (e.g. a Cas protein) derived from one or more of the following selected bacterial genera: *Corynebacterium, Sutterella, Legionella, Treponema, Filifactor, Eubacterium, Streptococcus, Lactobacillus, Mycoplasma, Bacteroides, Flavobacterium, Spirochaeta, Azospirillum, Gluconacetobacter, Neisseria, Roseburia, Parvibaculum, Nitratifractor, Campylobacter, Pseudomonas, Streptomyces, Staphylococcus, Francisella, Acidaminococcus, Lachnospiraceae, Leptotrichia,* and *Prevotella.* In some embodiments, the Cas protein is derived from Deltaproteobacteria or Planctomycetes bacterial species.

[00133] Some aspects of the present disclosure provide strategies, methods, compositions, and treatment modalities for altering a targeted sequence within a gene locus (e.g., altering the sequence of wild type and/or of a mutant sequence within a cell or within a mammal) by insertion or deletion of one or more nucleotides mediated by an RNA-guided nuclease and one or more guide RNAs (gRNAs), resulting in loss of function of the targeted gene product. In some embodiments, the loss of function results in "knocking out" the gene of interest (i.e., generation of a "knock out") by ablating gene expression. In some embodiments, the loss function results in a non-functional gene product (i.e., a gene product without all functionality of the wildtype gene product). In some embodiments, the loss of function results in expression of gene product with different characteristics (e.g., different binding affinity or different cellular localization).

[00134] In certain embodiments, the targeted gene is selected from IL1R1, IL1RAP, TGFBR1, TGFBR2, IL6R, IL6ST, TNFRSF1A, TNFRSF1B, TNFRSF3, TNFRSF4, TNFRSF11A, and combinations thereof. In some embodiments, any region of the targeted gene (e.g., a promoter region, a 5' untranslated region, a 3' untranslated region, an exon, an intron, or an exon/intron border) is targeted by an RNA-guided nuclease to alter the gene. In

some embodiments, a non-coding region of the targeted gene (e.g., an enhancer region, a promoter region, an intron, 5' UTR, 3' UTR, polyadenylation signal) is targeted to alter the gene.

[00135] *CRISPR guide RNAs:*

[00136] In one aspect, the CRISPR/Cas system of the present disclosure further provides a gRNA molecule (e.g., an isolated or non-naturally occurring RNA molecule) that interacts with the RNA-guided nuclease. In certain embodiments, the gRNA is an sgRNA comprising a crRNA sequence comprising a nucleotide sequence which is complementary to a sequence in a target nucleic acid. In some embodiments, the sgRNA further comprises an RNA scaffolding portion (i.e. tracrRNA) that interacts with the RNA-guided nuclease, such that the crRNA is positioned to scan a target nucleic acid for complementarity. In some embodiments, the system is further, optionally, comprised of an oligonucleotide—an HDR template with homology to either side of the target position. See Bloh, K., & Rivera-Torres, N. (2021). International Journal of Molecular Sciences, 22(8):3834.

[00137] In an embodiment, the RNA-guided nuclease and sgRNA are configured to orient an associated nuclease such that a cleavage event, (e.g., a double strand break or a single strand break) occurs sufficiently close to a complementary sequence in the targeted nucleic acid, thereby facilitating an alteration in the nucleic acid sequence. In some embodiments, the crRNA is 20 nucleotides in length. In some embodiments, the crRNA is 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 26, 27, 28, 29, or 30 nucleotides in length.

[00138] In some embodiments, the crRNA orients the RNA-guided nuclease such that a cleavage event occurs within 1, 2, 3, 4, 5, 10, 15, 20, 25, 30, 35, 40, 45, 50, 55, 60, 65, 70, 75, 80, 85, 90, 95, 100, 125, 150, 175, or 200 nucleotides away from the complementary sequence in the targeted nucleic acid. The double- or single-strand break may be positioned upstream or downstream of the complementary sequence in the targeted nucleic acid. In some embodiments, the cleavage event occurs within a targeted gene. In some embodiments, the cleavage event occurs upstream of a targeted gene.

[00139] In certain embodiments, a second gRNA molecule, comprising a second crRNA orients a second RNA-guided nuclease, such that a cleavage event occurs sufficiently close to a complementary sequence in the targeted nucleic acid, thereby facilitating an alteration in the nucleic acid sequence. In some embodiments, the first gRNA and the second gRNA promote a cleavage event within a single targeted gene. In some embodiments, the first

gRNA and the second gRNA promote a cleavage event within different targeted genes. In some embodiments, the second crRNA is 20 nucleotides in length. In some embodiments, the second crRNA is 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 26, 27, 28, 29, or 30 nucleotides in length.

[00140] In some embodiments, the second crRNA orients the RNA-guided nuclease such that a cleavage event occurs within 1, 2, 3, 4, 5, 10, 15, 20, 25, 30, 35, 40, 45, 50, 55, 60, 65, 70, 75, 80, 85, 90, 95, 100, 125, 150, 175, or 200 nucleotides away from the complementary sequence in the targeted nucleic acid. The double- or single-strand break may be positioned upstream or downstream of the complementary sequence in the targeted nucleic acid. In some embodiments, the cleavage event occurs within a targeted gene. In some embodiments, the cleavage event occurs upstream of a targeted gene.

[00141] In some embodiments, the targeting domains of the first gRNA and the second gRNA are configured such that a cleavage event is positioned, independently for each of the gRNA molecules, within 1, 2, 3, 4, 5, 10, 15, 20, 25, 30, 35, 40, 45, 50, 55, 60, 65, 70, 75, 80, 85, 90, 95, 100, 125, 150, 175, or 200 nucleotides of the others cleavage event. In some embodiments, the first gRNA and the second gRNA molecules alter the targeted nucleic acid sequences simultaneously. In some embodiments, the first gRNA and the second gRNA molecules alter the targeted nucleic acid sequences sequentially.

[00142] In some embodiments, a single-strand break is accompanied by a second single-strand break, positioned by the crRNA of a first gRNA and a second gRNA, respectively. For example, the crRNA may orient the associated RNA-guided nucleases such that a cleavage event, (e.g., the two single-strand breaks), are positioned within 1, 2, 3, 4, 5, 10, 15, 20, 25, 30, 35, 40, 45, 50, 55, 60, 65, 70, 75, 80, 85, 90, 95, 100, 125, 150, 175, or 200 nucleotides of one another. In some embodiments, a first crRNA and a second crRNA are configured to orient associated RNA-guided nucleases such that, for example, two single-strand breaks occurs at the same position, or within 1, 2, 3, 4, 5, 10, 15, 20, 25, 30, 35, 40, 45, 50 nucleotides of one another, on opposing strands of genomic DNA, thereby essentially approximating a double strand break.

[00143] In some embodiments, the nucleic acid encoding one or more crRNAs is selected from any of SEQ ID NOs: 680-1039. In some embodiments, the nucleic acid encoding one or more crRNAs target hIL1R1 and is selected from any of SEQ ID NOs: 680-824. In some embodiments, the nucleic acid encoding one or more crRNAs target cIL1R1 and is selected

from any of SEQ ID NOs: 825-892 and SEQ ID NOs: 3336-3420. In some embodiments, the nucleic acid encoding one or more crRNAs target eIL1R1 and is selected from any of SEQ ID NOs: 893-967. In some embodiments, the nucleic acid encoding one or more crRNAs target fIL1R1 and is selected from any of SEQ ID NOs: 968-1039.

[00144] In some embodiments, the nucleic acid encoding one or more crRNAs is selected from any of SEQ ID NOs: 1040-1424. In some embodiments, the nucleic acid encoding one or more crRNAs target hIL1RAP and is selected from any of SEQ ID NOs: 1040-1203. In some embodiments, the nucleic acid encoding one or more crRNAs target cIL1RAP and is selected from any of SEQ ID NOs: 1204-1271 and SEQ ID NOs: 3421-3490. In some embodiments, the nucleic acid encoding one or more crRNAs target eIL1RAP and is selected from any of SEQ ID NOs: 1272-1348. In some embodiments, the nucleic acid encoding one or more crRNAs target fIL1RAP and is selected from any of SEQ ID NOs: 1349-1424.

[00145] In some embodiments, the nucleic acid encoding one or more crRNAs is selected from any of SEQ ID NOs: 1425-1546. In some embodiments, the nucleic acid encoding one or more crRNAs target hTGFBR1 and is selected from any of SEQ ID NOs: 1425-1546.

[00146] In some embodiments, the nucleic acid encoding one or more crRNAs is selected from any of SEQ ID NOs: 1547-1745. In some embodiments, the nucleic acid encoding one or more crRNAs target hTGFBR2 and is selected from any of SEQ ID NOs: 1547-1745.

[00147] In some embodiments, the nucleic acid encoding one or more crRNAs is selected from any of SEQ ID NOs: 1746-1968. In some embodiments, the nucleic acid encoding one or more crRNAs target hIL6R and is selected from any of SEQ ID NOs: 1746-1968.

[00148] In some embodiments, the nucleic acid encoding one or more crRNAs is selected from any of SEQ ID NOs: 1969-2178. In some embodiments, the nucleic acid encoding one or more crRNAs target hIL6ST and is selected from any of SEQ ID NOs: 1969-2178.

[00149] In some embodiments, the nucleic acid encoding one or more crRNAs is selected from any of SEQ ID NOs: 2179-2395. In some embodiments, the nucleic acid encoding one or more crRNAs target hTNFRSF1A and is selected from any of SEQ ID NOs: 2179-2395.

[00150] n some embodiments, the nucleic acid encoding one or more crRNAs is selected from any of SEQ ID NOs: 2396-2642. In some embodiments, the nucleic acid encoding one or more crRNAs target hTNFRSF1B and is selected from any of SEQ ID NOs: 2396-2642.

[00151] n some embodiments, the nucleic acid encoding one or more crRNAs is selected from any of SEQ ID NOs: 2643-2866. In some embodiments, the nucleic acid encoding one or more crRNAs target hTNFRSF3 and is selected from any of SEQ ID NOs: 2643-2866.

[00152] n some embodiments, the nucleic acid encoding one or more crRNAs is selected from any of SEQ ID NOs: 2867-3041. In some embodiments, the nucleic acid encoding one or more crRNAs target hTNFRSF4 and is selected from any of SEQ ID NOs: 2867-3041.

[00153] n some embodiments, the nucleic acid encoding one or more crRNAs is selected from any of SEQ ID NOs: 3042-3335. In some embodiments, the nucleic acid encoding one or more crRNAs target hTNFRSF11A and is selected from any of SEQ ID NOs: 3042-3335.

[00154] In some embodiments a nucleic acid encodes a second sgRNA molecule. In some embodiments, a nucleic acid encodes a third sgRNA molecule. In some embodiments, a nucleic acid encodes a fourth sgRNA molecule.

[00155] In certain embodiments, a nucleic acid may comprise (a) a sequence encoding a first sgRNA, comprising a crRNA that is complementary with a sequence in a targeted gene, (b) a sequence encoding a second sgRNA, comprising a crRNA that is complementary with a sequence in a second targeted gene, and (c) a sequence encoding an RNA-guided nuclease (e.g., Cas9). Optionally, (d) and (e) are sequences encoding a third sgRNA and a fourth sgRNA, respectively. In some embodiments, the second targeted gene is the same as the first targeted gene. In other embodiments, the second targeted gene is different from the first targeted gene. In some embodiments, (a), (b), and (c) are encoded within the same nucleic acid molecule (e.g., the same vector). In some embodiments, (a) and (b) are encoded within the same nucleic acid molecule. In some embodiments, (a), (b) and (d) are encoded within the same nucleic acid molecule. In some embodiments, (a), (b) and (e) are encoded within the same nucleic acid molecule. In some embodiments, (a), (b), (d) and (e) are encoded within the same nucleic acid molecule. In some embodiments, (a), (b), and (c) are encoded within separate nucleic acid molecules. When more than two sgRNAs are used, any combination of (a), (b), (c), (d) and (e) may be encoded within a single or separate nucleic acid molecules.

[00156] In one aspect, the nucleic acid molecules (i.e., those encoding (a), (b), (c), (d) or (e)) are delivered to a target cell (i.e., any combination of the encoded RNA-guided nuclease of (c) and at least one encoded gRNA molecule of (a), (b), (d), or (e) contact a target cell). In some embodiments, said nucleic acid molecules are delivered to a target cell in vivo. In other

embodiments, said nucleic acid molecules are delivered to a target cell ex vivo. In some embodiments, said nucleic acid molecules are delivered to a target cell in vitro. In certain embodiments, said nucleic acid molecules are delivered to a target cell as DNA. In other embodiments, said nucleic acid molecules are delivered to a target cell as RNA (e.g., mRNA). In some embodiments, the products of said nucleic acid molecules are delivered as an assembled ribonucleoprotein (RNP).

[00157] In some embodiments, contacting a target cell comprises delivering said RNA-guided nuclease of (c), as a protein with at least one said nucleic acid molecules selected from (a), (b), (d), and (e). In some embodiments, contacting a target cell comprises delivering said encoded RNA-guided nuclease of (c), as DNA with at least one said nucleic acid molecules selected from (a), (b), (d), and (e). In some embodiments, contacting a target cell comprises delivering said encoded RNA-guided nuclease of (c), as mRNA with at least one said nucleic acid molecules selected from (a), (b), (d), and (e).

[00158] In certain embodiments, CRISPR components are delivered to a target cell via nanoparticles. Exemplary nanoparticles that may be used with all CRISPR/Cas systems disclosed herein include, at least, lipid nanoparticles or liposomes, hydrogel nanoparticles, metalorganic nanoparticles, gold nanoparticles, magnetic nanoparticles and virus-like particles. See generally Xu, C. F. et al. (2021). Advanced Drug Delivery Reviews, 168:3-29.

B. TALEN

[00159] In one aspect, the present disclosure contemplates use of methods, components, and compositions relating to Transcription Activator-Like Effector Nucleases (TALENs) to effectuate augmentation of a `nucleic acid sequence (e.g., a targeted gene.

[00160] TALE stands for "Transcription Activator-Like Effector" proteins, which include TALENs ("Transcription Activator-Like Effector Nucleases"). A method of using a TALE system for gene editing may also be referred to herein as a TALE method. TALEs are naturally occurring proteins from the plant pathogenic bacteria genus *Xanthomonas*, and contain DNA-binding domains composed of a series of 33–35-amino-acid repeat domains that each recognizes a single base pair. TALE specificity is determined by two hypervariable amino acids that are known as the repeat-variable di-residues (RVDs). Modular TALE repeats are linked together to recognize contiguous DNA sequences. A specific RVD in the DNA-binding domain recognizes a base in the target locus, providing a structural feature to assemble predictable DNA-binding domains. The DNA binding domains of a TALE are

fused to the catalytic domain of a type IIS FokI endonuclease to make a targetable TALE nuclease. To induce site-specific mutation, two individual TALEN arms, separated by a 14-20 base pair spacer region, bring FokI monomers in close proximity to dimerize and produce a targeted double-strand break.

[00161] Several large, systematic studies utilizing various assembly methods have indicated that TALE repeats can be combined to recognize virtually any user-defined sequence. Custom-designed TALE arrays are also commercially available through Cellectis Bioresearch (Paris, France), Transposagen Biopharmaceuticals (Lexington, KY, USA), and Life Technologies (Grand Island, NY, USA). TALE and TALEN methods suitable for use in the present disclosure are described in U.S. Patent Application Publication Nos. US 2011/0201118 A1; US 2013/0117869 A1; US 2013/0315884 A1; US 2015/0203871 A1 and US 2016/0120906 A1, the disclosures of which are incorporated by reference herein.

[00162] Non-limiting examples of genes that may be silenced or inhibited by permanently gene-editing via a TALE method include IL1R1, IL1RAP, TGFBR1, TGFBR2, IL6R, IL6ST, TNFRSF1A, TNFRSF1B, TNFRSF3, TNFRSF4, TNFRSF11A, and combinations thereof. Non-limiting examples of genes that may be augmented such that their resultant products function as decoys or dominant negatives by permanently gene-editing via a TALE method include IL1R1, IL1RAP, TGFBR1, TGFBR2, IL6R, IL6ST, TNFRSF1A, TNFRSF1B, TNFRSF3, TNFRSF4, TNFRSF11A, and combinations thereof. Non-limiting examples of genes that may be enhanced by permanently gene-editing via a TALE method include IL1R1, IL1RAP, TGFBR1, TGFBR2, IL6R, IL6ST, TNFRSF1A, TNFRSF1B, TNFRSF3, TNFRSF4, TNFRSF11A, and combinations thereof. In an aspect, the disclosure provides compositions for up-regulation of protein receptors (including wildtype or genetically edited), including those that bind to anti-inflammatory cytokines via a TALE method.

[00163] Examples of systems, methods, and compositions for altering the expression of a target gene sequence by a TALE method, and which may be used in accordance with embodiments of the present disclosure, are described in U.S. Patent No. 8,586,526, which is incorporated by reference herein.

C. Zinc-finger nucleases (ZFN)

In one aspect, the present disclosure contemplates use of methods, components, and compositions relating to zinc-finger nucleases (ZFNs) to effectuate augmentation of a nucleic acid sequence (e.g., a targeted gene).

[00164] An individual zinc finger contains approximately 30 amino acids in a conserved ββα configuration. Several amino acids on the surface of the α-helix typically contact 3 bp in the major groove of DNA, with varying levels of selectivity. Zinc fingers have two protein domains. The first domain is the DNA binding domain, which includes eukaryotic transcription factors and contain the zinc finger. The second domain is the nuclease domain, which includes the FokI restriction enzyme and is responsible for the catalytic cleavage of DNA.

[00165] The DNA-binding domains of individual ZFNs typically contain between three and six individual zinc finger repeats and can each recognize between 9 and 18 base pairs. If the zinc finger domains are specific for their intended target site then even a pair of 3-finger ZFNs that recognize a total of 18 base pairs can, in theory, target a single locus in a mammalian genome. One method to generate new zinc-finger arrays is to combine smaller zinc-finger "modules" of known specificity. The most common modular assembly process involves combining three separate zinc fingers that can each recognize a 3 base pair DNA sequence to generate a 3-finger array that can recognize a 9 base pair target site. Alternatively, selection-based approaches, such as oligomerized pool engineering (OPEN) can be used to select for new zinc-finger arrays from randomized libraries that take into consideration context-dependent interactions between neighboring fingers. Engineered zinc fingers are available commercially; Sangamo Biosciences (Richmond, CA, USA) has developed a propriety platform (CompoZr®) for zinc-finger construction in partnership with Sigma–Aldrich (St. Louis, MO, USA).

[00166] Non-limiting examples of genes that may be silenced or inhibited by permanently gene-editing via a zinc finger method include IL1R1, IL1RAP, TGFBR1, TGFBR2, IL6R, IL6ST, TNFRSF1A, TNFRSF1B, TNFRSF3, TNFRSF4, TNFRSF11A, and combinations thereof. Non-limiting examples of genes that may be augmented such that their resultant products function as decoys or dominant negatives by permanently gene-editing via a zinc finger method include IL1R1, IL1RAP, TGFBR1, TGFBR2, IL6R, IL6ST, TNFRSF1A, TNFRSF1B, TNFRSF3, TNFRSF4, TNFRSF11A, and combinations thereof. Non-limiting examples of genes that may be enhanced by permanently gene-editing via a zinc finger method include IL1R1, IL1RAP, TGFBR1, TGFBR2, IL6R, IL6ST, TNFRSF1A, TNFRSF1B, TNFRSF3, TNFRSF4, TNFRSF11A, and combinations thereof. In an aspect, the disclosure provides compositions for up-regulation of protein receptors (including wildtype or genetically edited), including those that bind to anti-inflammatory cytokines via a zinc finger method.

[00167] Examples of systems, methods, and compositions for altering the expression of a target gene sequence by a zinc finger method, which may be used in accordance with embodiments of the present disclosure, are described in U.S. Patent Nos. 6,534,261, 6,607,882, 6,746,838, 6,794,136, 6,824,978, 6,866,997, 6,933,113, 6,979,539, 7,013,219, 7,030,215, 7,220,719, 7,241,573, 7,241,574, 7,585,849, 7,595,376, 6,903,185, and 6,479,626, which are incorporated by reference herein.

[00168] Other examples of systems, methods, and compositions for altering the expression of a target gene sequence by a zinc finger method, which may be used in accordance with embodiments of the present disclosure, are described in Beane, *et al.*, *Mol. Therapy*, **2015,** 23 1380-1390, the disclosure of which is incorporated by reference herein.

IV. Joint Disease or Illness

A. Introduction

[00169] As described herein, embodiments of the present disclosure provide compositions and methods for improving joint function and treating joint disease. In particular embodiments, compositions and methods are provided to gene-edit synovial fibroblasts, synoviocytes, chondrocytes, tissue (resident) macrophages, or other cells to reduce pro-inflammatory signaling mediated by the binding of inflammatory cytokines—including, but not limited to, IL1α, IL1β, TNFα, IL6, IL8, IL18, IL33, matrix metalloproteinases (MMPs), TGFβ1, TGFβ2, and combinations thereof—to their cognate receptor(s). Some embodiments are used for treating various forms of arthritis and other inflammatory joint diseases. Some embodiments are further useful for treating canine lameness due to osteoarthritis. Some embodiments are further useful for treating equine lameness due to joint disease. Some embodiments are further useful for treating feline lameness due to joint disease. Some embodiments are also useful for treating post-traumatic arthritis, gout, pseudogout, psoriatic arthritis, and other inflammation-mediated or immune-mediated joint diseases.

[00170] Treatment of osteoarthritis, degenerative joint disease, and other joint dysfunctions is complex, and few long-term options exist for either symptomatic relief or restoring joint function. Osteoarthritis (OA) is the leading cause of disability due to pain. See, Neogi, T. (2013). Osteoarthritis Cartilage, 21(9):1145-53. OA and similar diseases impact all mammal species, including working animals, domestic pets, and their owners. The common mechanistic thread among joint diseases is the presence of acute of chronic inflammation, which is driven by increased levels of pro-inflammatory cytokine signaling. Joint diseases

tend to take a progressive course that encompasses discomfort, pain, and—especially in the case of OA—disability, depending on the degree of disease progression.

[00171] Psoriatic arthritis (PsA) is another chronic inflammatory joint disease, in which the joint symptoms are accompanied by skin lesions, such as those commonly associated with psoriasis. See, Boehncke, W. et al. (2014). British Journal of Dermatology, 170(4):772-786. Like other forms of arthritis, such as OA, PsA is caused by pro-inflammatory signaling of a host of cytokines, including IL1. Indeed, PsA morbidity has been shown to correlate with single nucleotide polymorphisms (SNPs) that impact the activity of the IL1 gene locus. See, Rahman, P. et al. (2006). Arthritis and Rheumatism, 54(7):2321–2325. These studies also implicate inflammatory cytokine signaling, in general, and IL1 more specifically, in disease progression.

[00172] Gout is a chronic inflammatory condition that affects joints. The underlying cause is monosodium urate (MSU) crystal deposition and the resultant host response, particularly in joint structures (as well as subcutaneous tissues and other sites). See, Dalbeth, N., & Stamp, L. (2014). Annals of the Rheumatic Diseases, 73(9):1598-1600. The clinical manifestations include recurrent acute flares of severe inflammatory arthritis and tendinobursitis. IL1 and other pro-inflammotory mediators are a major contributor to this host response. See, Dinarello, C. A. (2014). Molecular Medicine, 20(1):S43-S58. To this end, effective blockade of these signaling pathways may provide relief to gout patients.

[00173] The current standard of care for many joint disease patients includes anti-inflammatory medications (e.g., NSAIDs) or anti-rheumatics (e.g., methotrexate [inhibitor of AICAR] or adalimumab [anti-TNF alpha monoclonal antibody]). See, Friedman, B., & Cronstein, B. (2019). Joint Bone Spine, 86(3):301–307. All of these treatments require repeated dosing for continued effectiveness, which may lead to toxicity issues or tolerance over time. As such, new methods and compositions to treat joint disease and illness are acutely needed to treat these chronic conditions.

[00174] In one aspect, the compositions and methods herein described are directed to treat joint disease or illness in a mammal in need thereof. In some embodiments, the joint disease or illness is osteoarthritis. In some embodiments, the joint disease or illness is psoriatic arthritis. In some embodiments, the joint disease or illness is gout.

[00175] Among the advantages of the present disclosure over treatments currently available for mammals afflicted with one or more joint disease or illness include the period of relief

from symptoms. Upon genetic editing of a cell within a joint, pro-inflammatory signaling is silenced through the targeted gene for the life of that cell and any mitotic progeny. By contrast, biologic treatments require periodic dosing, which may magnify the impact of the host of potentially severe side effects. Among various genetic approaches, the present disclosure is also superior due to, among other reasons, a resistance to leakiness by virtue of modifying a protein receptor, rather than ablating expression of a ligand, which may result in compensatory effects (e.g., buildup of other factors due to lack of negative feedback).

[00176] In some embodiments, the present disclosure includes a method for the treatment or prevention of a joint disease or condition in a subject in need thereof, the method comprising administering, to a joint of the subject, a pharmaceutical composition comprising a therapeutically effective amount of a Clustered Regularly Interspaced Short Palindromic Repeats (CRISPR) gene-editing system, the system comprising (i) a CRISPR Associated (Cas) protein; and (ii) at least one guide RNA targeting an IL1R1 gene, IL1RAP gene, TGFBR1 gene, TGFBR2 gene, IL6R gene, IL6ST gene, TNFRSF1A gene, TNFRSF1B gene, TNFRSF3 gene, TNFRSF4 gene, or TNFRSF11A gene or a combination thereof. In some embodiments, the joint disease or condition is osteoarthritis. In some embodiments, the joint disease or condition is psoriatic arthritis. In some embodiments, the joint disease or condition is gout.

[00177] In some embodiments, the present disclosure includes a method for the treatment or prevention of an arthritis. Non-limiting examples of arthritis the can be treated using the compositions and methods described herein include post-tramatic arthritis, osteoarthritis (a degenerative condition that affects the joints, most commonly the hips, knees, and hands), rheumatoid arthritis (an autoimmune disorder that causes inflammation in the joints and surrounding tissue), psoriatic arthritis (a type of arthritis that occurs in people with psoriasis, a skin condition characterized by scaly red patches), gout (a type of arthritis caused by the buildup of uric acid crystals in the joints), lupus (a chronic autoimmune disorder that can cause inflammation and damage to the joints, as well as other organs), ankylosing spondylitis (a type of arthritis that primarily affects the spine, causing inflammation and stiffness), reactive arthritis (a type of arthritis that occurs as a reaction to an infection in the body), septic arthritis (a type of arthritis caused by an infection in the joint), juvenile idiopathic arthritis (a form of arthritis that affects children under the age of 16), and fibromyalgia (a chronic pain disorder that can cause widespread pain and stiffness, including in the joints).

[00178] In some embodiments, the present disclosure includes a method for the treatment or prevention of pseudogout, Crystal arthropathies (caused by the formation of crystals in the joints, such as gout and pseudogout), or CPPD disease (calcium pyrophosphate deposition disease) also called chondroclacinosis.

[00179] In some embodiments, the present disclosure includes a method for the treatment or prevention of rheumatoid arthritis, psoriasis, asthma, inflammatory bowel disease, multiple sclerosis, Alzheimer's disease, Type 2 diabetes, cardiovascular disease, or cancer. In some embodiments, these disorders are treated by administering a CRISPR composition, as described herein, targeting an IL1 receptor, e.g., IL1R1 or IL1AP.

B. Osteoarthritis

[00180] In one aspect, the present disclosure encompasses treatments for osteoarthritis (OA). In some embodiments, OA treatment comprises a therapeutically effective amount of a Clustered Regularly Interspaced Short Palindromic Repeats (CRISPR) gene-editing system, the system comprising: (i) a CRISPR Associated (Cas) protein; and (ii) at least one guide RNA targeting IL1R1. In some embodiments, the OA treatment comprises a CRISPR gene-editing system targeting hIL1R1. In some embodiments, the OA treatment comprises a CRISPR gene-editing system targeting cIL1R1. In some embodiments, the OA treatment comprises a CRISP gene-editing system R targeting eIL1R1. In some embodiments, the OA treatment comprises a CRISPR gene-editing system targeting fIL1R1.

[00181] In some embodiments, the CRISPR gene-editing system for the treatment of OA comprises one or more sgRNAs targeting exon 1 of hIL1R1. In some embodiments, the CRISPR gene-editing system for the treatment of OA comprises one or more sgRNAs targeting exon 2 of hIL1R1. In some embodiments, the CRISPR gene-editing system for the treatment of OA comprises one or more sgRNAs targeting exon 3 of hIL1R1. In some embodiments, the CRISPR gene-editing system for the treatment of OA comprises one or more sgRNAs targeting exon 4 of hIL1R1. In some embodiments, the CRISPR gene-editing system for the treatment of OA comprises one or more sgRNAs targeting exon 5 of hIL1R1. In some embodiments, the CRISPR gene-editing system for the treatment of OA comprises one or more sgRNAs targeting exon 6 of hIL1R1. In some embodiments, the CRISPR gene-editing system for the treatment of OA comprises one or more sgRNAs targeting exon 7 of hIL1R1. In some embodiments, the CRISPR gene-editing system for the treatment of OA

comprises one or more sgRNAs targeting exon 8 of hIL1R1. In some embodiments, the CRISPR gene-editing system for the treatment of OA comprises one or more sgRNAs targeting exon 9 of hIL1R1. In some embodiments, the CRISPR gene-editing system for the treatment of OA comprises one or more sgRNAs targeting exon 10 of hIL1R1. In some embodiments, the CRISPR gene-editing system for the treatment of OA comprises one or more sgRNAs targeting exon 11 of hIL1R1. In some embodiments, the CRISPR gene-editing system for the treatment of OA comprises one or more sgRNAs targeting exon 12 of hIL1R1. In some embodiments, the CRISPR gene-editing system for the treatment of OA comprises one or more sgRNAs targeting exon 13 of hIL1R1. In some embodiments, the CRISPR gene-editing system for the treatment of OA comprises one or more sgRNAs targeting exon 14 of hIL1R1. In some embodiments, the CRISPR gene-editing system for the treatment of OA comprises one or more sgRNAs targeting exon 15 of hIL1R1. In some embodiments, the CRISPR gene-editing system for the treatment of OA comprises one or more sgRNAs targeting exon 16 of hIL1R1. In some embodiments, the CRISPR gene-editing system for the treatment of OA comprises one or more sgRNAs targeting exon 17 of hIL1R1. In some embodiments, the CRISPR gene-editing system for the treatment of OA comprises one or more sgRNAs targeting exon 18 of hIL1R1. In some embodiments, the CRISPR gene-editing system for the treatment of OA comprises one or more sgRNAs targeting exon 19 of hIL1R1. In some embodiments, the CRISPR gene-editing system for the treatment of OA comprises one or more sgRNAs targeting exon 20 of hIL1R1. In some embodiments, the CRISPR gene-editing system for the treatment of OA comprises one or more sgRNAs targeting exon 21 of hIL1R1.

[00182] In some embodiments, the CRISPR gene-editing system for the treatment of OA comprises one or more sgRNAs targeting exon 1 of cIL1R1. In some embodiments, the CRISPR gene-editing system for the treatment of OA comprises one or more sgRNAs targeting exon 2 of cIL1R1. In some embodiments, the CRISPR gene-editing system for the treatment of OA comprises one or more sgRNAs targeting exon 3 of cIL1R1. In some embodiments, the CRISPR gene-editing system for the treatment of OA comprises one or more sgRNAs targeting exon 4 of cIL1R1. In some embodiments, the CRISPR gene-editing system for the treatment of OA comprises one or more sgRNAs targeting exon 5 of cIL1R1. In some embodiments, the CRISPR gene-editing system for the treatment of OA comprises one or more sgRNAs targeting exon 6 of cIL1R1. In some embodiments, the CRISPR gene-editing system for the treatment of OA comprises one or more sgRNAs targeting exon 7 of

cIL1R1. In some embodiments, the CRISPR gene-editing system for the treatment of OA comprises one or more sgRNAs targeting exon 8 of cIL1R1. In some embodiments, the CRISPR gene-editing system for the treatment of OA comprises one or more sgRNAs targeting exon 9 of cIL1R1. In some embodiments, the CRISPR gene-editing system for the treatment of OA comprises one or more sgRNAs targeting exon 10 of cIL1R1. In some embodiments, the CRISPR gene-editing system for the treatment of OA comprises one or more sgRNAs targeting exon 11 of cIL1R1. In some embodiments, the CRISPR gene-editing system for the treatment of OA comprises one or more sgRNAs targeting exon 12 of cIL1R1. In some embodiments, the CRISPR gene-editing system for the treatment of OA comprises one or more sgRNAs targeting exon 13 of cIL1R1. In some embodiments, the CRISPR gene-editing system for the treatment of OA comprises one or more sgRNAs targeting exon 14 of cIL1R1. In some embodiments, the CRISPR gene-editing system for the treatment of OA comprises one or more sgRNAs targeting exon 15 of cIL1R1. In some embodiments, the CRISPR gene-editing system for the treatment of OA comprises one or more sgRNAs targeting exon 16 of cIL1R1.

[00183] In some embodiments, the CRISPR gene-editing system for the treatment of OA comprises one or more sgRNAs targeting exon 1 of eIL1R1. In some embodiments, the CRISPR gene-editing system for the treatment of OA comprises one or more sgRNAs targeting exon 2 of eIL1R1. In some embodiments, the CRISPR gene-editing system for the treatment of OA comprises one or more sgRNAs targeting exon 3 of eIL1R1. In some embodiments, the CRISPR gene-editing system for the treatment of OA comprises one or more sgRNAs targeting exon 4 of eIL1R1. In some embodiments, the CRISPR gene-editing system for the treatment of OA comprises one or more sgRNAs targeting exon 5 of eIL1R1. In some embodiments, the CRISPR gene-editing system for the treatment of OA comprises one or more sgRNAs targeting exon 6 of eIL1R1. In some embodiments, the CRISPR gene-editing system for the treatment of OA comprises one or more sgRNAs targeting exon 7 of eIL1R1. In some embodiments, the CRISPR gene-editing system for the treatment of OA comprises one or more sgRNAs targeting exon 8 of eIL1R1. In some embodiments, the CRISPR gene-editing system for the treatment of OA comprises one or more sgRNAs targeting exon 9 of eIL1R1. In some embodiments, the CRISPR gene-editing system for the treatment of OA comprises one or more sgRNAs targeting exon 10 of eIL1R1. In some embodiments, the CRISPR gene-editing system for the treatment of OA comprises one or more sgRNAs targeting exon 11 of eIL1R1. In some embodiments, the CRISPR gene-editing

system for the treatment of OA comprises one or more sgRNAs targeting exon 12 of eIL1R1. In some embodiments, the CRISPR gene-editing system for the treatment of OA comprises one or more sgRNAs targeting exon 13 of eIL1R1. In some embodiments, the CRISPR gene-editing system for the treatment of OA comprises one or more sgRNAs targeting exon 14 of eIL1R1. In some embodiments, the CRISPR gene-editing system for the treatment of OA comprises one or more sgRNAs targeting exon 15 of eIL1R1.

[00184] In some embodiments, the CRISPR gene-editing system for the treatment of OA comprises one or more sgRNAs targeting exon 1 of fIL1R1. In some embodiments, the CRISPR gene-editing system for the treatment of OA comprises one or more sgRNAs targeting exon 2 of fIL1R1. In some embodiments, the CRISPR gene-editing system for the treatment of OA comprises one or more sgRNAs targeting exon 3 of fIL1R1. In some embodiments, the CRISPR gene-editing system for the treatment of OA comprises one or more sgRNAs targeting exon 4 of fIL1R1. In some embodiments, the CRISPR gene-editing system for the treatment of OA comprises one or more sgRNAs targeting exon 5 of fIL1R1. In some embodiments, the CRISPR gene-editing system for the treatment of OA comprises one or more sgRNAs targeting exon 6 of fIL1R1. In some embodiments, the CRISPR gene-editing system for the treatment of OA comprises one or more sgRNAs targeting exon 7 of fIL1R1. In some embodiments, the CRISPR gene-editing system for the treatment of OA comprises one or more sgRNAs targeting exon 8 of fIL1R1. In some embodiments, the CRISPR gene-editing system for the treatment of OA comprises one or more sgRNAs targeting exon 9 of fIL1R1. In some embodiments, the CRISPR gene-editing system for the treatment of OA comprises one or more sgRNAs targeting exon 10 of fIL1R1. In some embodiments, the CRISPR gene-editing system for the treatment of OA comprises one or more sgRNAs targeting exon 11 of fIL1R1. In some embodiments, the CRISPR gene-editing system for the treatment of OA comprises one or more sgRNAs targeting exon 12 of fIL1R1. In some embodiments, the CRISPR gene-editing system for the treatment of OA comprises one or more sgRNAs targeting exon 13 of fIL1R1. In some embodiments, the CRISPR gene-editing system for the treatment of OA comprises one or more sgRNAs targeting exon 14 of fIL1R1. In some embodiments, the CRISPR gene-editing system for the treatment of OA comprises one or more sgRNAs targeting exon 15 of fIL1R1. In some embodiments, the CRISPR gene-editing system for the treatment of OA comprises one or more sgRNAs targeting exon 16 of fIL1R1. In some embodiments, the CRISPR gene-editing system for the treatment of OA comprises one or more sgRNAs targeting exon 17 of fIL1R1. In some

embodiments, the CRISPR gene-editing system for the treatment of OA comprises one or more sgRNAs targeting exon 18 of fIL1R1.

[00185] In some embodiments, the CRISPR gene-editing system for the treatment of OA comprises one or more sgRNAs targeting IL1RAP. In some embodiments, the CRISPR gene-editing system for the treatment of OA comprises one or more sgRNAs targeting hIL1RAP. In some embodiments, the CRISPR gene-editing system for the treatment of OA comprises one or more sgRNAs targeting cIL1RAP. In some embodiments, the CRISPR gene-editing system for the treatment of OA comprises one or more sgRNAs targeting eIL1RAP. In some embodiments, the CRISPR gene-editing system for the treatment of OA comprises one or more sgRNAs targeting fIL1RAP.

[00186] In some embodiments, the CRISPR gene-editing system for the treatment of OA comprises one or more sgRNAs targeting exon 1 of hIL1RAP. In some embodiments, the CRISPR gene-editing system for the treatment of OA comprises one or more sgRNAs targeting exon 2 of hIL1RAP. In some embodiments, the CRISPR gene-editing system for the treatment of OA comprises one or more sgRNAs targeting exon 3 of hIL1RAP. In some embodiments, the CRISPR gene-editing system for the treatment of OA comprises one or more sgRNAs targeting exon 4 of hIL1RAP. In some embodiments, the CRISPR gene-editing system for the treatment of OA comprises one or more sgRNAs targeting exon 5 of hIL1RAP. In some embodiments, the CRISPR gene-editing system for the treatment of OA comprises one or more sgRNAs targeting exon 6 of hIL1RAP. In some embodiments, the CRISPR gene-editing system for the treatment of OA comprises one or more sgRNAs targeting exon 7 of hIL1RAP. In some embodiments, the CRISPR gene-editing system for the treatment of OA comprises one or more sgRNAs targeting exon 8 of hIL1RAP. In some embodiments, the CRISPR gene-editing system for the treatment of OA comprises one or more sgRNAs targeting exon 9 of hIL1RAP. In some embodiments, the CRISPR gene-editing system for the treatment of OA comprises one or more sgRNAs targeting exon 10 of hIL1RAP. In some embodiments, the CRISPR gene-editing system for the treatment of OA comprises one or more sgRNAs targeting exon 11 of hIL1RAP. In some embodiments, the CRISPR gene-editing system for the treatment of OA comprises one or more sgRNAs targeting exon 12 of hIL1RAP. In some embodiments, the CRISPR gene-editing system for the treatment of OA comprises one or more sgRNAs targeting exon 13 of hIL1RAP. In some embodiments, the CRISPR gene-editing system for the treatment of OA comprises one or more sgRNAs targeting exon 14 of hIL1RAP. In some embodiments, the CRISPR gene-

editing system for the treatment of OA comprises one or more sgRNAs targeting exon 15 of hIL1RAP. In some embodiments, the CRISPR gene-editing system for the treatment of OA comprises one or more sgRNAs targeting exon 16 of hIL1RAP. In some embodiments, the CRISPR gene-editing system for the treatment of OA comprises one or more sgRNAs targeting exon 17 of hIL1RAP.

[00187] In some embodiments, the CRISPR gene-editing system for the treatment of OA comprises one or more sgRNAs targeting exon 1 of cIL1RAP. In some embodiments, the CRISPR gene-editing system for the treatment of OA comprises one or more sgRNAs targeting exon 2 of cIL1RAP. In some embodiments, the CRISPR gene-editing system for the treatment of OA comprises one or more sgRNAs targeting exon 3 of cIL1RAP. In some embodiments, the CRISPR gene-editing system for the treatment of OA comprises one or more sgRNAs targeting exon 4 of cIL1RAP. In some embodiments, the CRISPR gene-editing system for the treatment of OA comprises one or more sgRNAs targeting exon 5 of cIL1RAP. In some embodiments, the CRISPR gene-editing system for the treatment of OA comprises one or more sgRNAs targeting exon 6 of cIL1RAP. In some embodiments, the CRISPR gene-editing system for the treatment of OA comprises one or more sgRNAs targeting exon 7 of cIL1RAP. In some embodiments, the CRISPR gene-editing system for the treatment of OA comprises one or more sgRNAs targeting exon 8 of cIL1RAP. In some embodiments, the CRISPR gene-editing system for the treatment of OA comprises one or more sgRNAs targeting exon 9 of cIL1RAP. In some embodiments, the CRISPR gene-editing system for the treatment of OA comprises one or more sgRNAs targeting exon 10 of cIL1RAP. In some embodiments, the CRISPR gene-editing system for the treatment of OA comprises one or more sgRNAs targeting exon 11 of cIL1RAP. In some embodiments, the CRISPR gene-editing system for the treatment of OA comprises one or more sgRNAs targeting exon 12 of cIL1RAP. In some embodiments, the CRISPR gene-editing system for the treatment of OA comprises one or more sgRNAs targeting exon 13 of cIL1RAP. In some embodiments, the CRISPR gene-editing system for the treatment of OA comprises one or more sgRNAs targeting exon 14 of cIL1RAP. In some embodiments, the CRISPR gene-editing system for the treatment of OA comprises one or more sgRNAs targeting exon 15 of cIL1RAP. In some embodiments, the CRISPR gene-editing system for the treatment of OA comprises one or more sgRNAs targeting exon 16 of cIL1RAP.

[00188] In some embodiments, the CRISPR gene-editing system for the treatment of OA comprises one or more sgRNAs targeting exon 1 of eIL1RAP. In some embodiments, the

CRISPR gene-editing system for the treatment of OA comprises one or more sgRNAs targeting exon 2 of eIL1RAP. In some embodiments, the CRISPR gene-editing system for the treatment of OA comprises one or more sgRNAs targeting exon 3 of eIL1RAP. In some embodiments, the CRISPR gene-editing system for the treatment of OA comprises one or more sgRNAs targeting exon 4 of eIL1RAP. In some embodiments, the CRISPR gene-editing system for the treatment of OA comprises one or more sgRNAs targeting exon 5 of eIL1RAP. In some embodiments, the CRISPR gene-editing system for the treatment of OA comprises one or more sgRNAs targeting exon 6 of eIL1RAP. In some embodiments, the CRISPR gene-editing system for the treatment of OA comprises one or more sgRNAs targeting exon 7 of eIL1RAP. In some embodiments, the CRISPR gene-editing system for the treatment of OA comprises one or more sgRNAs targeting exon 8 of eIL1RAP. In some embodiments, the CRISPR gene-editing system for the treatment of OA comprises one or more sgRNAs targeting exon 9 of eIL1RAP. In some embodiments, the CRISPR gene-editing system for the treatment of OA comprises one or more sgRNAs targeting exon 10 of eIL1RAP. In some embodiments, the CRISPR gene-editing system for the treatment of OA comprises one or more sgRNAs targeting exon 11 of eIL1RAP. In some embodiments, the CRISPR gene-editing system for the treatment of OA comprises one or more sgRNAs targeting exon 12 of eIL1RAP. In some embodiments, the CRISPR gene-editing system for the treatment of OA comprises one or more sgRNAs targeting exon 13 of eIL1RAP.

[00189] In some embodiments, the CRISPR gene-editing system for the treatment of OA comprises one or more sgRNAs targeting exon 1 of fIL1RAP. In some embodiments, the CRISPR gene-editing system for the treatment of OA comprises one or more sgRNAs targeting exon 2 of fIL1RAP. In some embodiments, the CRISPR gene-editing system for the treatment of OA comprises one or more sgRNAs targeting exon 3 of fIL1RAP. In some embodiments, the CRISPR gene-editing system for the treatment of OA comprises one or more sgRNAs targeting exon 4 of fIL1RAP. In some embodiments, the CRISPR gene-editing system for the treatment of OA comprises one or more sgRNAs targeting exon 5 of fIL1RAP. In some embodiments, the CRISPR gene-editing system for the treatment of OA comprises one or more sgRNAs targeting exon 6 of fIL1RAP. In some embodiments, the CRISPR gene-editing system for the treatment of OA comprises one or more sgRNAs targeting exon 7 of fIL1RAP. In some embodiments, the CRISPR gene-editing system for the treatment of OA comprises one or more sgRNAs targeting exon 8 of fIL1RAP. In some embodiments, the CRISPR gene-editing system for the treatment of OA comprises one or more sgRNAs

targeting exon 9 of flL1RAP. In some embodiments, the CRISPR gene-editing system for the treatment of OA comprises one or more sgRNAs targeting exon 10 of flL1RAP. In some embodiments, the CRISPR gene-editing system for the treatment of OA comprises one or more sgRNAs targeting exon 11 of flL1RAP. In some embodiments, the CRISPR gene-editing system for the treatment of OA comprises one or more sgRNAs targeting exon 12 of flL1RAP. In some embodiments, the CRISPR gene-editing system for the treatment of OA comprises one or more sgRNAs targeting exon 13 of flL1RAP. In some embodiments, the CRISPR gene-editing system for the treatment of OA comprises one or more sgRNAs targeting exon 14 of flL1RAP.

[00190] In some embodiments, the CRISPR gene-editing system for the treatment of OA comprises one or more sgRNAs targeting TGFBR1. In some embodiments, the CRISPR gene-editing system for the treatment of OA comprises one or more sgRNAs targeting hTGFBR1. In some embodiments, the CRISPR gene-editing system for the treatment of OA comprises one or more sgRNAs targeting cTGFBR1. In some embodiments, the CRISPR gene-editing system for the treatment of OA comprises one or more sgRNAs targeting e TGFBR1. In some embodiments, the CRISPR gene-editing system for the treatment of OA comprises one or more sgRNAs targeting fTGFBR1.

[00191] In some embodiments, the CRISPR gene-editing system for the treatment of OA comprises one or more sgRNAs targeting exon 1 of hTGFBR1. In some embodiments, the CRISPR gene-editing system for the treatment of OA comprises one or more sgRNAs targeting exon 2 of hTGFBR1. In some embodiments, the CRISPR gene-editing system for the treatment of OA comprises one or more sgRNAs targeting exon 3 of hTGFBR1. In some embodiments, the CRISPR gene-editing system for the treatment of OA comprises one or more sgRNAs targeting exon 4 of hTGFBR1. In some embodiments, the CRISPR gene-editing system for the treatment of OA comprises one or more sgRNAs targeting exon 5 of hTGFBR1. In some embodiments, the CRISPR gene-editing system for the treatment of OA comprises one or more sgRNAs targeting exon 6 of hTGFBR1. In some embodiments, the CRISPR gene-editing system for the treatment of OA comprises one or more sgRNAs targeting exon 7 of hTGFBR1. In some embodiments, the CRISPR gene-editing system for the treatment of OA comprises one or more sgRNAs targeting exon 8 of hTGFBR1. In some embodiments, the CRISPR gene-editing system for the treatment of OA comprises one or more sgRNAs targeting exon 9 of hTGFBR1. In some embodiments, the CRISPR gene-editing system for the treatment of OA comprises one or more sgRNAs targeting exon 10 of

hTGFBR1. In some embodiments, the CRISPR gene-editing system for the treatment of OA comprises one or more sgRNAs targeting exon 11 of hTGFBR1.

[00192] In some embodiments, the CRISPR gene-editing system for the treatment of OA comprises one or more sgRNAs targeting exon 1 of cTGFBR1. In some embodiments, the CRISPR gene-editing system for the treatment of OA comprises one or more sgRNAs targeting exon 2 of cTGFBR1. In some embodiments, the CRISPR gene-editing system for the treatment of OA comprises one or more sgRNAs targeting exon 3 of cTGFBR1. In some embodiments, the CRISPR gene-editing system for the treatment of OA comprises one or more sgRNAs targeting exon 4 of cTGFBR1. In some embodiments, the CRISPR gene-editing system for the treatment of OA comprises one or more sgRNAs targeting exon 5 of cTGFBR1. In some embodiments, the CRISPR gene-editing system for the treatment of OA comprises one or more sgRNAs targeting exon 6 of cTGFBR1. In some embodiments, the CRISPR gene-editing system for the treatment of OA comprises one or more sgRNAs targeting exon 7 of cTGFBR1. In some embodiments, the CRISPR gene-editing system for the treatment of OA comprises one or more sgRNAs targeting exon 8 of cTGFBR1. In some embodiments, the CRISPR gene-editing system for the treatment of OA comprises one or more sgRNAs targeting exon 9 of cTGFBR1.

[00193] In some embodiments, the CRISPR gene-editing system for the treatment of OA comprises one or more sgRNAs targeting exon 1 of eTGFBR1. In some embodiments, the CRISPR gene-editing system for the treatment of OA comprises one or more sgRNAs targeting exon 2 of eTGFBR1. In some embodiments, the CRISPR gene-editing system for the treatment of OA comprises one or more sgRNAs targeting exon 3 of eTGFBR1. In some embodiments, the CRISPR gene-editing system for the treatment of OA comprises one or more sgRNAs targeting exon 4 of eTGFBR1. In some embodiments, the CRISPR gene-editing system for the treatment of OA comprises one or more sgRNAs targeting exon 5 of eTGFBR1. In some embodiments, the CRISPR gene-editing system for the treatment of OA comprises one or more sgRNAs targeting exon 6 of eTGFBR1. In some embodiments, the CRISPR gene-editing system for the treatment of OA comprises one or more sgRNAs targeting exon 7 of eTGFBR1. In some embodiments, the CRISPR gene-editing system for the treatment of OA comprises one or more sgRNAs targeting exon 8 of eTGFBR1. In some embodiments, the CRISPR gene-editing system for the treatment of OA comprises one or more sgRNAs targeting exon 9 of eTGFBR1. In some embodiments, the CRISPR gene-editing system for the treatment of OA comprises one or more sgRNAs targeting exon 10 of

eTGFBR1. In some embodiments, the CRISPR gene-editing system for the treatment of OA comprises one or more sgRNAs targeting exon 11 of eTGFBR1. In some embodiments, the CRISPR gene-editing system for the treatment of OA comprises one or more sgRNAs targeting exon 12 of eTGFBR1.

[00194] In some embodiments, the CRISPR gene-editing system for the treatment of OA comprises one or more sgRNAs targeting exon 1 of fTGFBR1. In some embodiments, the CRISPR gene-editing system for the treatment of OA comprises one or more sgRNAs targeting exon 2 of fTGFBR1. In some embodiments, the CRISPR gene-editing system for the treatment of OA comprises one or more sgRNAs targeting exon 3 of fTGFBR1. In some embodiments, the CRISPR gene-editing system for the treatment of OA comprises one or more sgRNAs targeting exon 4 of fTGFBR1. In some embodiments, the CRISPR gene-editing system for the treatment of OA comprises one or more sgRNAs targeting exon 5 of fTGFBR1. In some embodiments, the CRISPR gene-editing system for the treatment of OA comprises one or more sgRNAs targeting exon 6 of fTGFBR1. In some embodiments, the CRISPR gene-editing system for the treatment of OA comprises one or more sgRNAs targeting exon 7 of fTGFBR1. In some embodiments, the CRISPR gene-editing system for the treatment of OA comprises one or more sgRNAs targeting exon 8 of fTGFBR1. In some embodiments, the CRISPR gene-editing system for the treatment of OA comprises one or more sgRNAs targeting exon 9 of fTGFBR1. In some embodiments, the CRISPR gene-editing system for the treatment of OA comprises one or more sgRNAs targeting exon 10 of fTGFBR1. In some embodiments, the CRISPR gene-editing system for the treatment of OA comprises one or more sgRNAs targeting exon 11 of fTGFBR1.

[00195] In some embodiments, the CRISPR gene-editing system for the treatment of OA comprises one or more sgRNAs targeting TGFBR2. In some embodiments, the CRISPR gene-editing system for the treatment of OA comprises one or more sgRNAs targeting hTGFBR2. In some embodiments, the CRISPR gene-editing system for the treatment of OA comprises one or more sgRNAs targeting cTGFBR2. In some embodiments, the CRISPR gene-editing system for the treatment of OA comprises one or more sgRNAs targeting eTGFBR2. In some embodiments, the CRISPR gene-editing system for the treatment of OA comprises one or more sgRNAs targeting fTGFBR2.

[00196] In some embodiments, the CRISPR gene-editing system for the treatment of OA comprises one or more sgRNAs targeting exon 1 of hTGFBR2. In some embodiments, the CRISPR gene-editing system for the treatment of OA comprises one or more sgRNAs

targeting exon 2 of hTGFBR2. In some embodiments, the CRISPR gene-editing system for the treatment of OA comprises one or more sgRNAs targeting exon 3 of hTGFBR2. In some embodiments, the CRISPR gene-editing system for the treatment of OA comprises one or more sgRNAs targeting exon 4 of hTGFBR2. In some embodiments, the CRISPR gene-editing system for the treatment of OA comprises one or more sgRNAs targeting exon 5 of hTGFBR2. In some embodiments, the CRISPR gene-editing system for the treatment of OA comprises one or more sgRNAs targeting exon 6 of hTGFBR2. In some embodiments, the CRISPR gene-editing system for the treatment of OA comprises one or more sgRNAs targeting exon 7 of hTGFBR2. In some embodiments, the CRISPR gene-editing system for the treatment of OA comprises one or more sgRNAs targeting exon 8 of hTGFBR2. In some embodiments, the CRISPR gene-editing system for the treatment of OA comprises one or more sgRNAs targeting exon 9 of hTGFBR2.

[00197] In some embodiments, the CRISPR gene-editing system for the treatment of OA comprises one or more sgRNAs targeting exon 1 of cTGFBR2. In some embodiments, the CRISPR gene-editing system for the treatment of OA comprises one or more sgRNAs targeting exon 2 of cTGFBR2. In some embodiments, the CRISPR gene-editing system for the treatment of OA comprises one or more sgRNAs targeting exon 3 of cTGFBR2. In some embodiments, the CRISPR gene-editing system for the treatment of OA comprises one or more sgRNAs targeting exon 4 of cTGFBR2. In some embodiments, the CRISPR gene-editing system for the treatment of OA comprises one or more sgRNAs targeting exon 5 of cTGFBR2. In some embodiments, the CRISPR gene-editing system for the treatment of OA comprises one or more sgRNAs targeting exon 6 of cTGFBR2. In some embodiments, the CRISPR gene-editing system for the treatment of OA comprises one or more sgRNAs targeting exon 7 of cTGFBR2. In some embodiments, the CRISPR gene-editing system for the treatment of OA comprises one or more sgRNAs targeting exon 8 of cTGFBR2.

[00198] In some embodiments, the CRISPR gene-editing system for the treatment of OA comprises one or more sgRNAs targeting exon 1 of eTGFBR2. In some embodiments, the CRISPR gene-editing system for the treatment of OA comprises one or more sgRNAs targeting exon 2 of eTGFBR2. In some embodiments, the CRISPR gene-editing system for the treatment of OA comprises one or more sgRNAs targeting exon 3 of eTGFBR2. In some embodiments, the CRISPR gene-editing system for the treatment of OA comprises one or more sgRNAs targeting exon 4 of eTGFBR2. In some embodiments, the CRISPR gene-editing system for the treatment of OA comprises one or more sgRNAs targeting exon 5 of

eTGFBR2. In some embodiments, the CRISPR gene-editing system for the treatment of OA comprises one or more sgRNAs targeting exon 6 of eTGFBR2. In some embodiments, the CRISPR gene-editing system for the treatment of OA comprises one or more sgRNAs targeting exon 7 of eTGFBR2. In some embodiments, the CRISPR gene-editing system for the treatment of OA comprises one or more sgRNAs targeting exon 8 of eTGFBR2. In some embodiments, the CRISPR gene-editing system for the treatment of OA comprises one or more sgRNAs targeting exon 9 of eTGFBR2. In some embodiments, the CRISPR gene-editing system for the treatment of OA comprises one or more sgRNAs targeting exon 10 of eTGFBR2.

[00199] In some embodiments, the CRISPR gene-editing system for the treatment of OA comprises one or more sgRNAs targeting exon 1 of fTGFBR2. In some embodiments, the CRISPR gene-editing system for the treatment of OA comprises one or more sgRNAs targeting exon 2 of fTGFBR2. In some embodiments, the CRISPR gene-editing system for the treatment of OA comprises one or more sgRNAs targeting exon 3 of fTGFBR2. In some embodiments, the CRISPR gene-editing system for the treatment of OA comprises one or more sgRNAs targeting exon 4 of fTGFBR2. In some embodiments, the CRISPR gene-editing system for the treatment of OA comprises one or more sgRNAs targeting exon 5 of fTGFBR2. In some embodiments, the CRISPR gene-editing system for the treatment of OA comprises one or more sgRNAs targeting exon 6 of fTGFBR2. In some embodiments, the CRISPR gene-editing system for the treatment of OA comprises one or more sgRNAs targeting exon 7 of fTGFBR2. In some embodiments, the CRISPR gene-editing system for the treatment of OA comprises one or more sgRNAs targeting exon 8 of fTGFBR2.

[00200] In some embodiments, the CRISPR gene-editing system for the treatment of OA comprises one or more sgRNAs targeting IL6R. In some embodiments, the CRISPR gene-editing system for the treatment of OA comprises one or more sgRNAs targeting hIL6R. In some embodiments, the CRISPR gene-editing system for the treatment of OA comprises one or more sgRNAs targeting cIL6R. In some embodiments, the CRISPR gene-editing system for the treatment of OA comprises one or more sgRNAs targeting eIL6R. In some embodiments, the CRISPR gene-editing system for the treatment of OA comprises one or more sgRNAs targeting fIL6R.

[00201] In some embodiments, the CRISPR gene-editing system for the treatment of OA comprises one or more sgRNAs targeting exon 1 of hIL6R. In some embodiments, the CRISPR gene-editing system for the treatment of OA comprises one or more sgRNAs

targeting exon 2 of hIL6R. In some embodiments, the CRISPR gene-editing system for the treatment of OA comprises one or more sgRNAs targeting exon 3 of hIL6R. In some embodiments, the CRISPR gene-editing system for the treatment of OA comprises one or more sgRNAs targeting exon 4 of hIL6R. In some embodiments, the CRISPR gene-editing system for the treatment of OA comprises one or more sgRNAs targeting exon 5 of hIL6R. In some embodiments, the CRISPR gene-editing system for the treatment of OA comprises one or more sgRNAs targeting exon 6 of hIL6R. In some embodiments, the CRISPR gene-editing system for the treatment of OA comprises one or more sgRNAs targeting exon 7 of hIL6R. In some embodiments, the CRISPR gene-editing system for the treatment of OA comprises one or more sgRNAs targeting exon 8 of hIL6R. In some embodiments, the CRISPR gene-editing system for the treatment of OA comprises one or more sgRNAs targeting exon 9 of hIL6R. In some embodiments, the CRISPR gene-editing system for the treatment of OA comprises one or more sgRNAs targeting exon 10 of hIL6R. In some embodiments, the CRISPR gene-editing system for the treatment of OA comprises one or more sgRNAs targeting exon 11 of hIL6R In some embodiments, the CRISPR gene-editing system for the treatment of OA comprises one or more sgRNAs targeting exon 12 of hIL6R. In some embodiments, the CRISPR gene-editing system for the treatment of OA comprises one or more sgRNAs targeting exon 13 of hIL6R. In some embodiments, the CRISPR gene-editing system for the treatment of OA comprises one or more sgRNAs targeting exon 14 of hIL6R. In some embodiments, the CRISPR gene-editing system for the treatment of OA comprises one or more sgRNAs targeting exon 15 of hIL6R.

[00202] In some embodiments, the CRISPR gene-editing system for the treatment of OA comprises one or more sgRNAs targeting exon 1 of cIL6R. In some embodiments, the CRISPR gene-editing system for the treatment of OA comprises one or more sgRNAs targeting exon 2 of cIL6R. In some embodiments, the CRISPR gene-editing system for the treatment of OA comprises one or more sgRNAs targeting exon 3 of cIL6R. In some embodiments, the CRISPR gene-editing system for the treatment of OA comprises one or more sgRNAs targeting exon 4 of cIL6R. In some embodiments, the CRISPR gene-editing system for the treatment of OA comprises one or more sgRNAs targeting exon 5 of cIL6R. In some embodiments, the CRISPR gene-editing system for the treatment of OA comprises one or more sgRNAs targeting exon 6 of cIL6R. In some embodiments, the CRISPR gene-editing system for the treatment of OA comprises one or more sgRNAs targeting exon 7 of cIL6R. In some embodiments, the CRISPR gene-editing system for the treatment of OA

comprises one or more sgRNAs targeting exon 8 of cIL6R. In some embodiments, the CRISPR gene-editing system for the treatment of OA comprises one or more sgRNAs targeting exon 9 of cIL6R. In some embodiments, the CRISPR gene-editing system for the treatment of OA comprises one or more sgRNAs targeting exon 10 of cIL6R. In some embodiments, the CRISPR gene-editing system for the treatment of OA comprises one or more sgRNAs targeting exon 11 of cIL6R. In some embodiments, the CRISPR gene-editing system for the treatment of OA comprises one or more sgRNAs targeting exon 12 of cIL6R. In some embodiments, the CRISPR gene-editing system for the treatment of OA comprises one or more sgRNAs targeting exon 13 of cIL6R.

[00203] In some embodiments, the CRISPR gene-editing system for the treatment of OA comprises one or more sgRNAs targeting exon 1 of eIL6R. In some embodiments, the CRISPR gene-editing system for the treatment of OA comprises one or more sgRNAs targeting exon 2 of eIL6R. In some embodiments, the CRISPR gene-editing system for the treatment of OA comprises one or more sgRNAs targeting exon 3 of eIL6R. In some embodiments, the CRISPR gene-editing system for the treatment of OA comprises one or more sgRNAs targeting exon 4 of eIL6R. In some embodiments, the CRISPR gene-editing system for the treatment of OA comprises one or more sgRNAs targeting exon 5 of eIL6R. In some embodiments, the CRISPR gene-editing system for the treatment of OA comprises one or more sgRNAs targeting exon 6 of eIL6R. In some embodiments, the CRISPR gene-editing system for the treatment of OA comprises one or more sgRNAs targeting exon 7 of eIL6R. In some embodiments, the CRISPR gene-editing system for the treatment of OA comprises one or more sgRNAs targeting exon 8 of eIL6R. In some embodiments, the CRISPR gene-editing system for the treatment of OA comprises one or more sgRNAs targeting exon 9 of eIL6R. In some embodiments, the CRISPR gene-editing system for the treatment of OA comprises one or more sgRNAs targeting exon 10 of eIL6R. In some embodiments, the CRISPR gene-editing system for the treatment of OA comprises one or more sgRNAs targeting exon 11 of eIL6R.

[00204] In some embodiments, the CRISPR gene-editing system for the treatment of OA comprises one or more sgRNAs targeting exon 1 of fIL6R. In some embodiments, the CRISPR gene-editing system for the treatment of OA comprises one or more sgRNAs targeting exon 2 of fIL6R. In some embodiments, the CRISPR gene-editing system for the treatment of OA comprises one or more sgRNAs targeting exon 3 of fIL6R. In some embodiments, the CRISPR gene-editing system for the treatment of OA comprises one or

more sgRNAs targeting exon 4 of fIL6R. In some embodiments, the CRISPR gene-editing system for the treatment of OA comprises one or more sgRNAs targeting exon 5 of fIL6R. In some embodiments, the CRISPR gene-editing system for the treatment of OA comprises one or more sgRNAs targeting exon 6 of fIL6R. In some embodiments, the CRISPR gene-editing system for the treatment of OA comprises one or more sgRNAs targeting exon 7 of fIL6R. In some embodiments, the CRISPR gene-editing system for the treatment of OA comprises one or more sgRNAs targeting exon 8 of fIL6R. In some embodiments, the CRISPR gene-editing system for the treatment of OA comprises one or more sgRNAs targeting exon 9 of fIL6R. In some embodiments, the CRISPR gene-editing system for the treatment of OA comprises one or more sgRNAs targeting exon 10 of fIL6R.

[00205] In some embodiments, the CRISPR gene-editing system for the treatment of OA comprises one or more sgRNAs targeting IL6ST. In some embodiments, the CRISPR gene-editing system for the treatment of OA comprises one or more sgRNAs targeting hIL6ST. In some embodiments, the CRISPR gene-editing system for the treatment of OA comprises one or more sgRNAs targeting cIL6ST. In some embodiments, the CRISPR gene-editing system for the treatment of OA comprises one or more sgRNAs targeting eIL6ST. In some embodiments, the CRISPR gene-editing system for the treatment of OA comprises one or more sgRNAs targeting fIL6ST.

[00206] In some embodiments, the CRISPR gene-editing system for the treatment of OA comprises one or more sgRNAs targeting exon 1 of hIL6ST. In some embodiments, the CRISPR gene-editing system for the treatment of OA comprises one or more sgRNAs targeting exon 2 of hIL6ST. In some embodiments, the CRISPR gene-editing system for the treatment of OA comprises one or more sgRNAs targeting exon 3 of hIL6ST. In some embodiments, the CRISPR gene-editing system for the treatment of OA comprises one or more sgRNAs targeting exon 4 of hIL6ST. In some embodiments, the CRISPR gene-editing system for the treatment of OA comprises one or more sgRNAs targeting exon 5 of hIL6ST. In some embodiments, the CRISPR gene-editing system for the treatment of OA comprises one or more sgRNAs targeting exon 6 of hIL6ST. In some embodiments, the CRISPR gene-editing system for the treatment of OA comprises one or more sgRNAs targeting exon 7 of hIL6ST. In some embodiments, the CRISPR gene-editing system for the treatment of OA comprises one or more sgRNAs targeting exon 8 of hIL6ST. In some embodiments, the CRISPR gene-editing system for the treatment of OA comprises one or more sgRNAs targeting exon 9 of hIL6ST. In some embodiments, the CRISPR gene-editing system for the

treatment of OA comprises one or more sgRNAs targeting exon 10 of hIL6ST. In some embodiments, the CRISPR gene-editing system for the treatment of OA comprises one or more sgRNAs targeting exon 11 of hIL6ST. In some embodiments, the CRISPR gene-editing system for the treatment of OA comprises one or more sgRNAs targeting exon 12 of hIL6ST. In some embodiments, the CRISPR gene-editing system for the treatment of OA comprises one or more sgRNAs targeting exon 13 of hIL6ST. In some embodiments, the CRISPR gene-editing system for the treatment of OA comprises one or more sgRNAs targeting exon 14 of hIL6ST. In some embodiments, the CRISPR gene-editing system for the treatment of OA comprises one or more sgRNAs targeting exon 15 of hIL6ST. In some embodiments, the CRISPR gene-editing system for the treatment of OA comprises one or more sgRNAs targeting exon 16 of hIL6ST. In some embodiments, the CRISPR gene-editing system for the treatment of OA comprises one or more sgRNAs targeting exon 17 of hIL6ST. In some embodiments, the CRISPR gene-editing system for the treatment of OA comprises one or more sgRNAs targeting exon 18 of hIL6ST. In some embodiments, the CRISPR gene-editing system for the treatment of OA comprises one or more sgRNAs targeting exon 19 of hIL6ST.

[00207] In some embodiments, the CRISPR gene-editing system for the treatment of OA comprises one or more sgRNAs targeting exon 1 of cIL6ST. In some embodiments, the CRISPR gene-editing system for the treatment of OA comprises one or more sgRNAs targeting exon 2 of cIL6ST. In some embodiments, the CRISPR gene-editing system for the treatment of OA comprises one or more sgRNAs targeting exon 3 of cIL6ST. In some embodiments, the CRISPR gene-editing system for the treatment of OA comprises one or more sgRNAs targeting exon 4 of cIL6ST. In some embodiments, the CRISPR gene-editing system for the treatment of OA comprises one or more sgRNAs targeting exon 5 of cIL6ST. In some embodiments, the CRISPR gene-editing system for the treatment of OA comprises one or more sgRNAs targeting exon 6 of cIL6ST. In some embodiments, the CRISPR gene-editing system for the treatment of OA comprises one or more sgRNAs targeting exon 7 of cIL6ST. In some embodiments, the CRISPR gene-editing system for the treatment of OA comprises one or more sgRNAs targeting exon 8 of cIL6ST. In some embodiments, the CRISPR gene-editing system for the treatment of OA comprises one or more sgRNAs targeting exon 9 of cIL6ST. In some embodiments, the CRISPR gene-editing system for the treatment of OA comprises one or more sgRNAs targeting exon 10 of cIL6ST. In some embodiments, the CRISPR gene-editing system for the treatment of OA comprises one or more sgRNAs targeting exon 11 of cIL6ST In some embodiments, the CRISPR gene-editing

system for the treatment of OA comprises one or more sgRNAs targeting exon 12 of cIL6ST. In some embodiments, the CRISPR gene-editing system for the treatment of OA comprises one or more sgRNAs targeting exon 13 of cIL6ST. In some embodiments, the CRISPR gene-editing system for the treatment of OA comprises one or more sgRNAs targeting exon 14 of cIL6ST. In some embodiments, the CRISPR gene-editing system for the treatment of OA comprises one or more sgRNAs targeting exon 15 of cIL6ST. In some embodiments, the CRISPR gene-editing system for the treatment of OA comprises one or more sgRNAs targeting exon 16 of cIL6ST. In some embodiments, the CRISPR gene-editing system for the treatment of OA comprises one or more sgRNAs targeting exon 17 of cIL6ST. In some embodiments, the CRISPR gene-editing system for the treatment of OA comprises one or more sgRNAs targeting exon 18 of cIL6ST.

[00208] In some embodiments, the CRISPR gene-editing system for the treatment of OA comprises one or more sgRNAs targeting exon 1 of eIL6ST. In some embodiments, the CRISPR gene-editing system for the treatment of OA comprises one or more sgRNAs targeting exon 2 of eIL6ST. In some embodiments, the CRISPR gene-editing system for the treatment of OA comprises one or more sgRNAs targeting exon 3 of eIL6ST. In some embodiments, the CRISPR gene-editing system for the treatment of OA comprises one or more sgRNAs targeting exon 4 of eIL6ST. In some embodiments, the CRISPR gene-editing system for the treatment of OA comprises one or more sgRNAs targeting exon 5 of eIL6ST. In some embodiments, the CRISPR gene-editing system for the treatment of OA comprises one or more sgRNAs targeting exon 6 of eIL6ST. In some embodiments, the CRISPR gene-editing system for the treatment of OA comprises one or more sgRNAs targeting exon 7 of eIL6ST. In some embodiments, the CRISPR gene-editing system for the treatment of OA comprises one or more sgRNAs targeting exon 8 of eIL6ST. In some embodiments, the CRISPR gene-editing system for the treatment of OA comprises one or more sgRNAs targeting exon 9 of eIL6ST. In some embodiments, the CRISPR gene-editing system for the treatment of OA comprises one or more sgRNAs targeting exon 10 of eIL6ST. In some embodiments, the CRISPR gene-editing system for the treatment of OA comprises one or more sgRNAs targeting exon 11 of eIL6ST In some embodiments, the CRISPR gene-editing system for the treatment of OA comprises one or more sgRNAs targeting exon 12 of eIL6ST. In some embodiments, the CRISPR gene-editing system for the treatment of OA comprises one or more sgRNAs targeting exon 13 of eIL6ST. In some embodiments, the CRISPR gene-editing system for the treatment of OA comprises one or more sgRNAs targeting exon 14 of

eIL6ST. In some embodiments, the CRISPR gene-editing system for the treatment of OA comprises one or more sgRNAs targeting exon 15 of eIL6ST. In some embodiments, the CRISPR gene-editing system for the treatment of OA comprises one or more sgRNAs targeting exon 16 of eIL6ST. In some embodiments, the CRISPR gene-editing system for the treatment of OA comprises one or more sgRNAs targeting exon 17 of eIL6ST. In some embodiments, the CRISPR gene-editing system for the treatment of OA comprises one or more sgRNAs targeting exon 18 of eIL6ST.

[00209] In some embodiments, the CRISPR gene-editing system for the treatment of OA comprises one or more sgRNAs targeting exon 1 of fIL6ST. In some embodiments, the CRISPR gene-editing system for the treatment of OA comprises one or more sgRNAs targeting exon 2 of fIL6ST. In some embodiments, the CRISPR gene-editing system for the treatment of OA comprises one or more sgRNAs targeting exon 3 of fIL6ST. In some embodiments, the CRISPR gene-editing system for the treatment of OA comprises one or more sgRNAs targeting exon 4 of fIL6ST. In some embodiments, the CRISPR gene-editing system for the treatment of OA comprises one or more sgRNAs targeting exon 5 of fIL6ST. In some embodiments, the CRISPR gene-editing system for the treatment of OA comprises one or more sgRNAs targeting exon 6 of fIL6ST. In some embodiments, the CRISPR gene-editing system for the treatment of OA comprises one or more sgRNAs targeting exon 7 of fIL6ST. In some embodiments, the CRISPR gene-editing system for the treatment of OA comprises one or more sgRNAs targeting exon 8 of fIL6ST. In some embodiments, the CRISPR gene-editing system for the treatment of OA comprises one or more sgRNAs targeting exon 9 of fIL6ST. In some embodiments, the CRISPR gene-editing system for the treatment of OA comprises one or more sgRNAs targeting exon 10 of fIL6ST. In some embodiments, the CRISPR gene-editing system for the treatment of OA comprises one or more sgRNAs targeting exon 11 of fIL6ST In some embodiments, the CRISPR gene-editing system for the treatment of OA comprises one or more sgRNAs targeting exon 12 of fIL6ST. In some embodiments, the CRISPR gene-editing system for the treatment of OA comprises one or more sgRNAs targeting exon 13 of fIL6ST. In some embodiments, the CRISPR gene-editing system for the treatment of OA comprises one or more sgRNAs targeting exon 14 of fIL6ST. In some embodiments, the CRISPR gene-editing system for the treatment of OA comprises one or more sgRNAs targeting exon 15 of fIL6ST. In some embodiments, the CRISPR gene-editing system for the treatment of OA comprises one or more sgRNAs targeting exon 16 of fIL6ST. In some embodiments, the CRISPR gene-editing system for the

treatment of OA comprises one or more sgRNAs targeting exon 17 of flL6ST. In some embodiments, the CRISPR gene-editing system for the treatment of OA comprises one or more sgRNAs targeting exon 18 of flL6ST. In some embodiments, the CRISPR gene-editing system for the treatment of OA comprises one or more sgRNAs targeting exon 19 of flL6ST. In some embodiments, the CRISPR gene-editing system for the treatment of OA comprises one or more sgRNAs targeting exon 20 of flL6ST.

[00210] In some embodiments, the CRISPR gene-editing system for the treatment of OA comprises one or more sgRNAs targeting TNFRSF1A. In some embodiments, the CRISPR gene-editing system for the treatment of OA comprises one or more sgRNAs targeting hTNFRSF1A. In some embodiments, the CRISPR gene-editing system for the treatment of OA comprises one or more sgRNAs targeting cTNFRSF1A. In some embodiments, the CRISPR gene-editing system for the treatment of OA comprises one or more sgRNAs targeting eTNFRSF1A. In some embodiments, the CRISPR gene-editing system for the treatment of OA comprises one or more sgRNAs targeting fTNFRSF1A.

[00211] In some embodiments, the CRISPR gene-editing system for the treatment of OA comprises one or more sgRNAs targeting exon 1 of hTNFRSF1A. In some embodiments, the CRISPR gene-editing system for the treatment of OA comprises one or more sgRNAs targeting exon 2 of hTNFRSF1A. In some embodiments, the CRISPR gene-editing system for the treatment of OA comprises one or more sgRNAs targeting exon 3 of hTNFRSF1A. In some embodiments, the CRISPR gene-editing system for the treatment of OA comprises one or more sgRNAs targeting exon 4 of hTNFRSF1A. In some embodiments, the CRISPR gene-editing system for the treatment of OA comprises one or more sgRNAs targeting exon 5 of hTNFRSF1A. In some embodiments, the CRISPR gene-editing system for the treatment of OA comprises one or more sgRNAs targeting exon 6 of hTNFRSF1A. In some embodiments, the CRISPR gene-editing system for the treatment of OA comprises one or more sgRNAs targeting exon 7 of hTNFRSF1A. In some embodiments, the CRISPR gene-editing system for the treatment of OA comprises one or more sgRNAs targeting exon 8 of hTNFRSF1A. In some embodiments, the CRISPR gene-editing system for the treatment of OA comprises one or more sgRNAs targeting exon 9 of hTNFRSF1A. In some embodiments, the CRISPR gene-editing system for the treatment of OA comprises one or more sgRNAs targeting exon 10 of hTNFRSF1A. In some embodiments, the CRISPR gene-editing system for the treatment of OA comprises one or more sgRNAs targeting exon 11 of hTNFRSF1A.

[00212] In some embodiments, the CRISPR gene-editing system for the treatment of OA comprises one or more sgRNAs targeting exon 1 of cTNFRSF1A. In some embodiments, the CRISPR gene-editing system for the treatment of OA comprises one or more sgRNAs targeting exon 2 of cTNFRSF1A. In some embodiments, the CRISPR gene-editing system for the treatment of OA comprises one or more sgRNAs targeting exon 3 of cTNFRSF1A. In some embodiments, the CRISPR gene-editing system for the treatment of OA comprises one or more sgRNAs targeting exon 4 of cTNFRSF1A. In some embodiments, the CRISPR gene-editing system for the treatment of OA comprises one or more sgRNAs targeting exon 5 of cTNFRSF1A. In some embodiments, the CRISPR gene-editing system for the treatment of OA comprises one or more sgRNAs targeting exon 6 of cTNFRSF1A. In some embodiments, the CRISPR gene-editing system for the treatment of OA comprises one or more sgRNAs targeting exon 7 of cTNFRSF1A. In some embodiments, the CRISPR gene-editing system for the treatment of OA comprises one or more sgRNAs targeting exon 8 of cTNFRSF1A. In some embodiments, the CRISPR gene-editing system for the treatment of OA comprises one or more sgRNAs targeting exon 9 of cTNFRSF1A. In some embodiments, the CRISPR gene-editing system for the treatment of OA comprises one or more sgRNAs targeting exon 10 of cTNFRSF1A. In some embodiments, the CRISPR gene-editing system for the treatment of OA comprises one or more sgRNAs targeting exon 11 of cTNFRSF1A.

[00213] In some embodiments, the CRISPR gene-editing system for the treatment of OA comprises one or more sgRNAs targeting exon 1 of eTNFRSF1A. In some embodiments, the CRISPR gene-editing system for the treatment of OA comprises one or more sgRNAs targeting exon 2 of eTNFRSF1A. In some embodiments, the CRISPR gene-editing system for the treatment of OA comprises one or more sgRNAs targeting exon 3 of eTNFRSF1A. In some embodiments, the CRISPR gene-editing system for the treatment of OA comprises one or more sgRNAs targeting exon 4 of eTNFRSF1A. In some embodiments, the CRISPR gene-editing system for the treatment of OA comprises one or more sgRNAs targeting exon 5 of eTNFRSF1A. In some embodiments, the CRISPR gene-editing system for the treatment of OA comprises one or more sgRNAs targeting exon 6 of eTNFRSF1A. In some embodiments, the CRISPR gene-editing system for the treatment of OA comprises one or more sgRNAs targeting exon 7 of eTNFRSF1A. In some embodiments, the CRISPR gene-editing system for the treatment of OA comprises one or more sgRNAs targeting exon 8 of eTNFRSF1A. In some embodiments, the CRISPR gene-editing system for the treatment of

OA comprises one or more sgRNAs targeting exon 9 of eTNFRSF1A. In some embodiments, the CRISPR gene-editing system for the treatment of OA comprises one or more sgRNAs targeting exon 10 of eTNFRSF1A.

[00214] In some embodiments, the CRISPR gene-editing system for the treatment of OA comprises one or more sgRNAs targeting exon 1 of fTNFRSF1A. In some embodiments, the CRISPR gene-editing system for the treatment of OA comprises one or more sgRNAs targeting exon 2 of fTNFRSF1A. In some embodiments, the CRISPR gene-editing system for the treatment of OA comprises one or more sgRNAs targeting exon 3 of fTNFRSF1A. In some embodiments, the CRISPR gene-editing system for the treatment of OA comprises one or more sgRNAs targeting exon 4 of fTNFRSF1A. In some embodiments, the CRISPR gene-editing system for the treatment of OA comprises one or more sgRNAs targeting exon 5 of fTNFRSF1A. In some embodiments, the CRISPR gene-editing system for the treatment of OA comprises one or more sgRNAs targeting exon 6 of fTNFRSF1A. In some embodiments, the CRISPR gene-editing system for the treatment of OA comprises one or more sgRNAs targeting exon 7 of fTNFRSF1A. In some embodiments, the CRISPR gene-editing system for the treatment of OA comprises one or more sgRNAs targeting exon 8 of fTNFRSF1A. In some embodiments, the CRISPR gene-editing system for the treatment of OA comprises one or more sgRNAs targeting exon 9 of fTNFRSF1A. In some embodiments, the CRISPR gene-editing system for the treatment of OA comprises one or more sgRNAs targeting exon 10 of fTNFRSF1A.

[00215] In some embodiments, the CRISPR gene-editing system for the treatment of OA comprises one or more sgRNAs targeting TNFRSF1B. In some embodiments, the CRISPR gene-editing system for the treatment of OA comprises one or more sgRNAs targeting hTNFRSF1B. In some embodiments, the CRISPR gene-editing system for the treatment of OA comprises one or more sgRNAs targeting cTNFRSF1B. In some embodiments, the CRISPR gene-editing system for the treatment of OA comprises one or more sgRNAs targeting eTNFRSF1B. In some embodiments, the CRISPR gene-editing system for the treatment of OA comprises one or more sgRNAs targeting fTNFRSF1B.

[00216] In some embodiments, the CRISPR gene-editing system for the treatment of OA comprises one or more sgRNAs targeting exon 1 of hTNFRSF1B. In some embodiments, the CRISPR gene-editing system for the treatment of OA comprises one or more sgRNAs targeting exon 2 of hTNFRSF1B. In some embodiments, the CRISPR gene-editing system for the treatment of OA comprises one or more sgRNAs targeting exon 3 of hTNFRSF1B. In

some embodiments, the CRISPR gene-editing system for the treatment of OA comprises one or more sgRNAs targeting exon 4 of hTNFRSF1B. In some embodiments, the CRISPR gene-editing system for the treatment of OA comprises one or more sgRNAs targeting exon 5 of hTNFRSF1B. In some embodiments, the CRISPR gene-editing system for the treatment of OA comprises one or more sgRNAs targeting exon 6 of hTNFRSF1B. In some embodiments, the CRISPR gene-editing system for the treatment of OA comprises one or more sgRNAs targeting exon 7 of hTNFRSF1B. In some embodiments, the CRISPR gene-editing system for the treatment of OA comprises one or more sgRNAs targeting exon 8 of hTNFRSF1B. In some embodiments, the CRISPR gene-editing system for the treatment of OA comprises one or more sgRNAs targeting exon 9 of hTNFRSF1B. In some embodiments, the CRISPR gene-editing system for the treatment of OA comprises one or more sgRNAs targeting exon 10 of hTNFRSF1B. In some embodiments, the CRISPR gene-editing system for the treatment of OA comprises one or more sgRNAs targeting exon 11 of hTNFRSF1B In some embodiments, the CRISPR gene-editing system for the treatment of OA comprises one or more sgRNAs targeting exon 12 of hTNFRSF1B. In some embodiments, the CRISPR gene-editing system for the treatment of OA comprises one or more sgRNAs targeting exon 13 of hTNFRSF1B.

[00217] In some embodiments, the CRISPR gene-editing system for the treatment of OA comprises one or more sgRNAs targeting exon 1 of cTNFRSF1B. In some embodiments, the CRISPR gene-editing system for the treatment of OA comprises one or more sgRNAs targeting exon 2 of cTNFRSF1B. In some embodiments, the CRISPR gene-editing system for the treatment of OA comprises one or more sgRNAs targeting exon 3 of cTNFRSF1B. In some embodiments, the CRISPR gene-editing system for the treatment of OA comprises one or more sgRNAs targeting exon 4 of cTNFRSF1B. In some embodiments, the CRISPR gene-editing system for the treatment of OA comprises one or more sgRNAs targeting exon 5 of cTNFRSF1B. In some embodiments, the CRISPR gene-editing system for the treatment of OA comprises one or more sgRNAs targeting exon 6 of cTNFRSF1B. In some embodiments, the CRISPR gene-editing system for the treatment of OA comprises one or more sgRNAs targeting exon 7 of cTNFRSF1B. In some embodiments, the CRISPR gene-editing system for the treatment of OA comprises one or more sgRNAs targeting exon 8 of cTNFRSF1B. In some embodiments, the CRISPR gene-editing system for the treatment of OA comprises one or more sgRNAs targeting exon 9 of cTNFRSF1B. In some embodiments, the CRISPR gene-editing system for the treatment of OA comprises one or

more sgRNAs targeting exon 10 of cTNFRSF1B. In some embodiments, the CRISPR gene-editing system for the treatment of OA comprises one or more sgRNAs targeting exon 11 of cTNFRSF1B.

[00218] In some embodiments, the CRISPR gene-editing system for the treatment of OA comprises one or more sgRNAs targeting exon 1 of eTNFRSF1B. In some embodiments, the CRISPR gene-editing system for the treatment of OA comprises one or more sgRNAs targeting exon 2 of eTNFRSF1B. In some embodiments, the CRISPR gene-editing system for the treatment of OA comprises one or more sgRNAs targeting exon 3 of eTNFRSF1B. In some embodiments, the CRISPR gene-editing system for the treatment of OA comprises one or more sgRNAs targeting exon 4 of eTNFRSF1B. In some embodiments, the CRISPR gene-editing system for the treatment of OA comprises one or more sgRNAs targeting exon 5 of eTNFRSF1B. In some embodiments, the CRISPR gene-editing system for the treatment of OA comprises one or more sgRNAs targeting exon 6 of eTNFRSF1B. In some embodiments, the CRISPR gene-editing system for the treatment of OA comprises one or more sgRNAs targeting exon 7 of eTNFRSF1B. In some embodiments, the CRISPR gene-editing system for the treatment of OA comprises one or more sgRNAs targeting exon 8 of eTNFRSF1B. In some embodiments, the CRISPR gene-editing system for the treatment of OA comprises one or more sgRNAs targeting exon 9 of eTNFRSF1B. In some embodiments, the CRISPR gene-editing system for the treatment of OA comprises one or more sgRNAs targeting exon 10 of eTNFRSF1B. In some embodiments, the CRISPR gene-editing system for the treatment of OA comprises one or more sgRNAs targeting exon 11 of eTNFRSF1B.

[00219] In some embodiments, the CRISPR gene-editing system for the treatment of OA comprises one or more sgRNAs targeting exon 1 of fTNFRSF1B. In some embodiments, the CRISPR gene-editing system for the treatment of OA comprises one or more sgRNAs targeting exon 2 of fTNFRSF1B. In some embodiments, the CRISPR gene-editing system for the treatment of OA comprises one or more sgRNAs targeting exon 3 of fTNFRSF1B. In some embodiments, the CRISPR gene-editing system for the treatment of OA comprises one or more sgRNAs targeting exon 4 of fTNFRSF1B. In some embodiments, the CRISPR gene-editing system for the treatment of OA comprises one or more sgRNAs targeting exon 5 of fTNFRSF1B. In some embodiments, the CRISPR gene-editing system for the treatment of OA comprises one or more sgRNAs targeting exon 6 of fTNFRSF1B. In some embodiments, the CRISPR gene-editing system for the treatment of OA comprises one or more sgRNAs

targeting exon 7 of fTNFRSF1B. In some embodiments, the CRISPR gene-editing system for the treatment of OA comprises one or more sgRNAs targeting exon 8 of fTNFRSF1B. In some embodiments, the CRISPR gene-editing system for the treatment of OA comprises one or more sgRNAs targeting exon 9 of fTNFRSF1B. In some embodiments, the CRISPR gene-editing system for the treatment of OA comprises one or more sgRNAs targeting exon 10 of fTNFRSF1B.

[00220] In some embodiments, the CRISPR gene-editing system for the treatment of OA comprises one or more sgRNAs targeting TNFRSF3. In some embodiments, the CRISPR gene-editing system for the treatment of OA comprises one or more sgRNAs targeting hTNFRSF3. In some embodiments, the CRISPR gene-editing system for the treatment of OA comprises one or more sgRNAs targeting cTNFRSF3. In some embodiments, the CRISPR gene-editing system for the treatment of OA comprises one or more sgRNAs targeting eTNFRSF3. In some embodiments, the CRISPR gene-editing system for the treatment of OA comprises one or more sgRNAs targeting fTNFRSF3.

[00221] In some embodiments, the CRISPR gene-editing system for the treatment of OA comprises one or more sgRNAs targeting exon 1 of hTNFRSF3. In some embodiments, the CRISPR gene-editing system for the treatment of OA comprises one or more sgRNAs targeting exon 2 of hTNFRSF3. In some embodiments, the CRISPR gene-editing system for the treatment of OA comprises one or more sgRNAs targeting exon 3 of hTNFRSF3. In some embodiments, the CRISPR gene-editing system for the treatment of OA comprises one or more sgRNAs targeting exon 4 of hTNFRSF3. In some embodiments, the CRISPR gene-editing system for the treatment of OA comprises one or more sgRNAs targeting exon 5 of hTNFRSF3. In some embodiments, the CRISPR gene-editing system for the treatment of OA comprises one or more sgRNAs targeting exon 6 of hTNFRSF3. In some embodiments, the CRISPR gene-editing system for the treatment of OA comprises one or more sgRNAs targeting exon 7 of hTNFRSF3. In some embodiments, the CRISPR gene-editing system for the treatment of OA comprises one or more sgRNAs targeting exon 8 of hTNFRSF3. In some embodiments, the CRISPR gene-editing system for the treatment of OA comprises one or more sgRNAs targeting exon 9 of hTNFRSF3. In some embodiments, the CRISPR gene-editing system for the treatment of OA comprises one or more sgRNAs targeting exon 10 of hTNFRSF3. In some embodiments, the CRISPR gene-editing system for the treatment of OA comprises one or more sgRNAs targeting exon 11 of hTNFRSF3. In some embodiments,

the CRISPR gene-editing system for the treatment of OA comprises one or more sgRNAs targeting exon 12 of hTNFRSF3.

[00222] In some embodiments, the CRISPR gene-editing system for the treatment of OA comprises one or more sgRNAs targeting exon 1 of cTNFRSF3. In some embodiments, the CRISPR gene-editing system for the treatment of OA comprises one or more sgRNAs targeting exon 2 of cTNFRSF3. In some embodiments, the CRISPR gene-editing system for the treatment of OA comprises one or more sgRNAs targeting exon 3 of cTNFRSF3. In some embodiments, the CRISPR gene-editing system for the treatment of OA comprises one or more sgRNAs targeting exon 4 of cTNFRSF3. In some embodiments, the CRISPR gene-editing system for the treatment of OA comprises one or more sgRNAs targeting exon 5 of cTNFRSF3. In some embodiments, the CRISPR gene-editing system for the treatment of OA comprises one or more sgRNAs targeting exon 6 of cTNFRSF3. In some embodiments, the CRISPR gene-editing system for the treatment of OA comprises one or more sgRNAs targeting exon 7 of cTNFRSF3. In some embodiments, the CRISPR gene-editing system for the treatment of OA comprises one or more sgRNAs targeting exon 8 of cTNFRSF3. In some embodiments, the CRISPR gene-editing system for the treatment of OA comprises one or more sgRNAs targeting exon 9 of cTNFRSF3. In some embodiments, the CRISPR gene-editing system for the treatment of OA comprises one or more sgRNAs targeting exon 10 of cTNFRSF3.

[00223] In some embodiments, the CRISPR gene-editing system for the treatment of OA comprises one or more sgRNAs targeting exon 1 of eTNFRSF3. In some embodiments, the CRISPR gene-editing system for the treatment of OA comprises one or more sgRNAs targeting exon 2 of eTNFRSF3. In some embodiments, the CRISPR gene-editing system for the treatment of OA comprises one or more sgRNAs targeting exon 3 of eTNFRSF3. In some embodiments, the CRISPR gene-editing system for the treatment of OA comprises one or more sgRNAs targeting exon 4 of eTNFRSF3. In some embodiments, the CRISPR gene-editing system for the treatment of OA comprises one or more sgRNAs targeting exon 5 of eTNFRSF3. In some embodiments, the CRISPR gene-editing system for the treatment of OA comprises one or more sgRNAs targeting exon 6 of eTNFRSF3. In some embodiments, the CRISPR gene-editing system for the treatment of OA comprises one or more sgRNAs targeting exon 7 of eTNFRSF3. In some embodiments, the CRISPR gene-editing system for the treatment of OA comprises one or more sgRNAs targeting exon 8 of eTNFRSF3. In some embodiments, the CRISPR gene-editing system for the treatment of OA comprises one

or more sgRNAs targeting exon 9 of eTNFRSF3. In some embodiments, the CRISPR gene-editing system for the treatment of OA comprises one or more sgRNAs targeting exon 10 of eTNFRSF3.

[00224] In some embodiments, the CRISPR gene-editing system for the treatment of OA comprises one or more sgRNAs targeting exon 1 of fTNFRSF3. In some embodiments, the CRISPR gene-editing system for the treatment of OA comprises one or more sgRNAs targeting exon 2 of fTNFRSF3. In some embodiments, the CRISPR gene-editing system for the treatment of OA comprises one or more sgRNAs targeting exon 3 of fTNFRSF3. In some embodiments, the CRISPR gene-editing system for the treatment of OA comprises one or more sgRNAs targeting exon 4 of fTNFRSF3. In some embodiments, the CRISPR gene-editing system for the treatment of OA comprises one or more sgRNAs targeting exon 5 of fTNFRSF3. In some embodiments, the CRISPR gene-editing system for the treatment of OA comprises one or more sgRNAs targeting exon 6 of fTNFRSF3. In some embodiments, the CRISPR gene-editing system for the treatment of OA comprises one or more sgRNAs targeting exon 7 of fTNFRSF3. In some embodiments, the CRISPR gene-editing system for the treatment of OA comprises one or more sgRNAs targeting exon 8 of fTNFRSF3. In some embodiments, the CRISPR gene-editing system for the treatment of OA comprises one or more sgRNAs targeting exon 9 of fTNFRSF3. In some embodiments, the CRISPR gene-editing system for the treatment of OA comprises one or more sgRNAs targeting exon 10 of fTNFRSF3.

[00225] In some embodiments, the CRISPR gene-editing system for the treatment of OA comprises one or more sgRNAs targeting TNFRSF4. In some embodiments, the CRISPR gene-editing system for the treatment of OA comprises one or more sgRNAs targeting hTNFRSF4. In some embodiments, the CRISPR gene-editing system for the treatment of OA comprises one or more sgRNAs targeting cTNFRSF4. In some embodiments, the CRISPR gene-editing system for the treatment of OA comprises one or more sgRNAs targeting eTNFRSF4. In some embodiments, the CRISPR gene-editing system for the treatment of OA comprises one or more sgRNAs targeting fTNFRSF4.

[00226] In some embodiments, the CRISPR gene-editing system for the treatment of OA comprises one or more sgRNAs targeting exon 1 of hTNFRSF4. In some embodiments, the CRISPR gene-editing system for the treatment of OA comprises one or more sgRNAs targeting exon 2 of hTNFRSF4. In some embodiments, the CRISPR gene-editing system for the treatment of OA comprises one or more sgRNAs targeting exon 3 of hTNFRSF4. In

some embodiments, the CRISPR gene-editing system for the treatment of OA comprises one or more sgRNAs targeting exon 4 of hTNFRSF4. In some embodiments, the CRISPR gene-editing system for the treatment of OA comprises one or more sgRNAs targeting exon 5 of hTNFRSF4. In some embodiments, the CRISPR gene-editing system for the treatment of OA comprises one or more sgRNAs targeting exon 6 of hTNFRSF4.

[00227] In some embodiments, the CRISPR gene-editing system for the treatment of OA comprises one or more sgRNAs targeting exon 1 of cTNFRSF4. In some embodiments, the CRISPR gene-editing system for the treatment of OA comprises one or more sgRNAs targeting exon 2 of cTNFRSF4. In some embodiments, the CRISPR gene-editing system for the treatment of OA comprises one or more sgRNAs targeting exon 3 of cTNFRSF4. In some embodiments, the CRISPR gene-editing system for the treatment of OA comprises one or more sgRNAs targeting exon 4 of cTNFRSF4. In some embodiments, the CRISPR gene-editing system for the treatment of OA comprises one or more sgRNAs targeting exon 5 of cTNFRSF4. In some embodiments, the CRISPR gene-editing system for the treatment of OA comprises one or more sgRNAs targeting exon 6 of cTNFRSF4. In some embodiments, the CRISPR gene-editing system for the treatment of OA comprises one or more sgRNAs targeting exon 7 of cTNFRSF4.

[00228] In some embodiments, the CRISPR gene-editing system for the treatment of OA comprises one or more sgRNAs targeting exon 1 of eTNFRSF4. In some embodiments, the CRISPR gene-editing system for the treatment of OA comprises one or more sgRNAs targeting exon 2 of eTNFRSF4. In some embodiments, the CRISPR gene-editing system for the treatment of OA comprises one or more sgRNAs targeting exon 3 of eTNFRSF4. In some embodiments, the CRISPR gene-editing system for the treatment of OA comprises one or more sgRNAs targeting exon 4 of eTNFRSF4. In some embodiments, the CRISPR gene-editing system for the treatment of OA comprises one or more sgRNAs targeting exon 5 of eTNFRSF4. In some embodiments, the CRISPR gene-editing system for the treatment of OA comprises one or more sgRNAs targeting exon 6 of eTNFRSF4. In some embodiments, the CRISPR gene-editing system for the treatment of OA comprises one or more sgRNAs targeting exon 7 of eTNFRSF4.

[00229] In some embodiments, the CRISPR gene-editing system for the treatment of OA comprises one or more sgRNAs targeting exon 1 of fTNFRSF4. In some embodiments, the CRISPR gene-editing system for the treatment of OA comprises one or more sgRNAs targeting exon 2 of fTNFRSF4. In some embodiments, the CRISPR gene-editing system for

the treatment of OA comprises one or more sgRNAs targeting exon 3 of fTNFRSF4. In some embodiments, the CRISPR gene-editing system for the treatment of OA comprises one or more sgRNAs targeting exon 4 of fTNFRSF4. In some embodiments, the CRISPR gene-editing system for the treatment of OA comprises one or more sgRNAs targeting exon 5 of fTNFRSF4. In some embodiments, the CRISPR gene-editing system for the treatment of OA comprises one or more sgRNAs targeting exon 6 of fTNFRSF4. In some embodiments, the CRISPR gene-editing system for the treatment of OA comprises one or more sgRNAs targeting exon 7 of fTNFRSF4.

[00230] In some embodiments, the CRISPR gene-editing system for the treatment of OA comprises one or more sgRNAs targeting TNFRSF11A. In some embodiments, the CRISPR gene-editing system for the treatment of OA comprises one or more sgRNAs targeting hTNFRSF11A. In some embodiments, the CRISPR gene-editing system for the treatment of OA comprises one or more sgRNAs targeting cTNFRSF11A. In some embodiments, the CRISPR gene-editing system for the treatment of OA comprises one or more sgRNAs targeting eTNFRSF11A. In some embodiments, the CRISPR gene-editing system for the treatment of OA comprises one or more sgRNAs targeting fTNFRSF11A.

[00231] In some embodiments, the CRISPR gene-editing system for the treatment of OA comprises one or more sgRNAs targeting exon 1 of hTNFRSF11A. In some embodiments, the CRISPR gene-editing system for the treatment of OA comprises one or more sgRNAs targeting exon 2 of hTNFRSF11A. In some embodiments, the CRISPR gene-editing system for the treatment of OA comprises one or more sgRNAs targeting exon 3 of hTNFRSF11A. In some embodiments, the CRISPR gene-editing system for the treatment of OA comprises one or more sgRNAs targeting exon 4 of hTNFRSF11A. In some embodiments, the CRISPR gene-editing system for the treatment of OA comprises one or more sgRNAs targeting exon 5 of hTNFRSF11A. In some embodiments, the CRISPR gene-editing system for the treatment of OA comprises one or more sgRNAs targeting exon 6 of hTNFRSF11A. In some embodiments, the CRISPR gene-editing system for the treatment of OA comprises one or more sgRNAs targeting exon 7 of hTNFRSF11A. In some embodiments, the CRISPR gene-editing system for the treatment of OA comprises one or more sgRNAs targeting exon 8 of hTNFRSF11A. In some embodiments, the CRISPR gene-editing system for the treatment of OA comprises one or more sgRNAs targeting exon 9 of hTNFRSF11A. In some embodiments, the CRISPR gene-editing system for the treatment of OA comprises one or more sgRNAs targeting exon 10 of hTNFRSF11A. In some embodiments, the CRISPR

gene-editing system for the treatment of OA comprises one or more sgRNAs targeting exon 11 of hTNFRSF11A. In some embodiments, the CRISPR gene-editing system for the treatment of OA comprises one or more sgRNAs targeting exon 12 of hTNFRSF11A.

[00232] In some embodiments, the CRISPR gene-editing system for the treatment of OA comprises one or more sgRNAs targeting exon 1 of cTNFRSF11A. In some embodiments, the CRISPR gene-editing system for the treatment of OA comprises one or more sgRNAs targeting exon 2 of cTNFRSF11A. In some embodiments, the CRISPR gene-editing system for the treatment of OA comprises one or more sgRNAs targeting exon 3 of cTNFRSF11A. In some embodiments, the CRISPR gene-editing system for the treatment of OA comprises one or more sgRNAs targeting exon 4 of cTNFRSF11A. In some embodiments, the CRISPR gene-editing system for the treatment of OA comprises one or more sgRNAs targeting exon 5 of cTNFRSF11A. In some embodiments, the CRISPR gene-editing system for the treatment of OA comprises one or more sgRNAs targeting exon 6 of cTNFRSF11A. In some embodiments, the CRISPR gene-editing system for the treatment of OA comprises one or more sgRNAs targeting exon 7 of cTNFRSF11A. In some embodiments, the CRISPR gene-editing system for the treatment of OA comprises one or more sgRNAs targeting exon 8 of cTNFRSF11A. In some embodiments, the CRISPR gene-editing system for the treatment of OA comprises one or more sgRNAs targeting exon 9 of cTNFRSF11A. In some embodiments, the CRISPR gene-editing system for the treatment of OA comprises one or more sgRNAs targeting exon 10 of cTNFRSF11A. In some embodiments, the CRISPR gene-editing system for the treatment of OA comprises one or more sgRNAs targeting exon 11 of cTNFRSF11A.

[00233] In some embodiments, the CRISPR gene-editing system for the treatment of OA comprises one or more sgRNAs targeting exon 1 of eTNFRSF11A. In some embodiments, the CRISPR gene-editing system for the treatment of OA comprises one or more sgRNAs targeting exon 2 of eTNFRSF11A. In some embodiments, the CRISPR gene-editing system for the treatment of OA comprises one or more sgRNAs targeting exon 3 of eTNFRSF11A. In some embodiments, the CRISPR gene-editing system for the treatment of OA comprises one or more sgRNAs targeting exon 4 of eTNFRSF11A. In some embodiments, the CRISPR gene-editing system for the treatment of OA comprises one or more sgRNAs targeting exon 5 of eTNFRSF11A. In some embodiments, the CRISPR gene-editing system for the treatment of OA comprises one or more sgRNAs targeting exon 6 of eTNFRSF11A. In some embodiments, the CRISPR gene-editing system for the treatment of OA comprises one or

more sgRNAs targeting exon 7 of eTNFRSF11A. In some embodiments, the CRISPR gene-editing system for the treatment of OA comprises one or more sgRNAs targeting exon 8 of eTNFRSF11A. In some embodiments, the CRISPR gene-editing system for the treatment of OA comprises one or more sgRNAs targeting exon 9 of eTNFRSF11A. In some embodiments, the CRISPR gene-editing system for the treatment of OA comprises one or more sgRNAs targeting exon 10 of eTNFRSF11A.

[00234] In some embodiments, the CRISPR gene-editing system for the treatment of OA comprises one or more sgRNAs targeting exon 1 of fTNFRSF11A. In some embodiments, the CRISPR gene-editing system for the treatment of OA comprises one or more sgRNAs targeting exon 2 of fTNFRSF11A. In some embodiments, the CRISPR gene-editing system for the treatment of OA comprises one or more sgRNAs targeting exon 3 of fTNFRSF11A. In some embodiments, the CRISPR gene-editing system for the treatment of OA comprises one or more sgRNAs targeting exon 4 of fTNFRSF11A. In some embodiments, the CRISPR gene-editing system for the treatment of OA comprises one or more sgRNAs targeting exon 5 of fTNFRSF11A. In some embodiments, the CRISPR gene-editing system for the treatment of OA comprises one or more sgRNAs targeting exon 6 of fTNFRSF11A. In some embodiments, the CRISPR gene-editing system for the treatment of OA comprises one or more sgRNAs targeting exon 7 of fTNFRSF11A. In some embodiments, the CRISPR gene-editing system for the treatment of OA comprises one or more sgRNAs targeting exon 8 of fTNFRSF11A. In some embodiments, the CRISPR gene-editing system for the treatment of OA comprises one or more sgRNAs targeting exon 9 of fTNFRSF11A. In some embodiments, the CRISPR gene-editing system for the treatment of OA comprises one or more sgRNAs targeting exon 10 of fTNFRSF11A. In some embodiments, the CRISPR gene-editing system for the treatment of OA comprises one or more sgRNAs targeting exon 11 of fTNFRSF11A.

C. Psoriatic arthritis

[00235] In one aspect, the present disclosure encompasses treatments for psoriatic arthritis (PsA). In some embodiments, the psoriatic arthritis treatment comprises a therapeutically effective amount of a Clustered Regularly Interspaced Short Palindromic Repeats (CRISPR) gene-editing system, the system comprising: (i) a CRISPR Associated (Cas) protein; and (ii) at least one guide RNA targeting IL1R1. In some embodiments, the psoriatic arthritis treatment comprises a CRISPR gene-editing system targeting hIL1R1. In some

embodiments, the psoriatic arthritis treatment comprises a CRISPR gene-editing system targeting cIL1R1. In some embodiments, the psoriatic arthritis treatment comprises a CRISP gene-editing system R targeting eIL1R1. In some embodiments, the psoriatic arthritis treatment comprises a CRISPR gene-editing system targeting fIL1R1.

[00236] In some embodiments, the CRISPR gene-editing system for the treatment of psoriatic arthritis comprises one or more sgRNAs targeting exon 1 of hIL1R1. In some embodiments, the CRISPR gene-editing system for the treatment of psoriatic arthritis comprises one or more sgRNAs targeting exon 2 of hIL1R1. In some embodiments, the CRISPR gene-editing system for the treatment of psoriatic arthritis comprises one or more sgRNAs targeting exon 3 of hIL1R1. In some embodiments, the CRISPR gene-editing system for the treatment of psoriatic arthritis comprises one or more sgRNAs targeting exon 4 of hIL1R1. In some embodiments, the CRISPR gene-editing system for the treatment of psoriatic arthritis comprises one or more sgRNAs targeting exon 5 of hIL1R1. In some embodiments, the CRISPR gene-editing system for the treatment of psoriatic arthritis comprises one or more sgRNAs targeting exon 6 of hIL1R1. In some embodiments, the CRISPR gene-editing system for the treatment of psoriatic arthritis comprises one or more sgRNAs targeting exon 7 of hIL1R1. In some embodiments, the CRISPR gene-editing system for the treatment of psoriatic arthritis comprises one or more sgRNAs targeting exon 8 of hIL1R1. In some embodiments, the CRISPR gene-editing system for the treatment of psoriatic arthritis comprises one or more sgRNAs targeting exon 9 of hIL1R1. In some embodiments, the CRISPR gene-editing system for the treatment of psoriatic arthritis comprises one or more sgRNAs targeting exon 10 of hIL1R1. In some embodiments, the CRISPR gene-editing system for the treatment of psoriatic arthritis comprises one or more sgRNAs targeting exon 11 of hIL1R1. In some embodiments, the CRISPR gene-editing system for the treatment of psoriatic arthritis comprises one or more sgRNAs targeting exon 12 of hIL1R1. In some embodiments, the CRISPR gene-editing system for the treatment of psoriatic arthritis comprises one or more sgRNAs targeting exon 13 of hIL1R1. In some embodiments, the CRISPR gene-editing system for the treatment of psoriatic arthritis comprises one or more sgRNAs targeting exon 14 of hIL1R1. In some embodiments, the CRISPR gene-editing system for the treatment of psoriatic arthritis comprises one or more sgRNAs targeting exon 15 of hIL1R1. In some embodiments, the CRISPR gene-editing system for the treatment of psoriatic arthritis comprises one or more sgRNAs targeting exon 16 of hIL1R1. In some embodiments, the CRISPR gene-editing system for the treatment of

psoriatic arthritis comprises one or more sgRNAs targeting exon 17 of hIL1R1. In some embodiments, the CRISPR gene-editing system for the treatment of psoriatic arthritis comprises one or more sgRNAs targeting exon 18 of hIL1R1. In some embodiments, the CRISPR gene-editing system for the treatment of psoriatic arthritis comprises one or more sgRNAs targeting exon 19 of hIL1R1. In some embodiments, the CRISPR gene-editing system for the treatment of psoriatic arthritis comprises one or more sgRNAs targeting exon 20 of hIL1R1. In some embodiments, the CRISPR gene-editing system for the treatment of psoriatic arthritis comprises one or more sgRNAs targeting exon 21 of hIL1R1.

[00237] In some embodiments, the CRISPR gene-editing system for the treatment of psoriatic arthritis comprises one or more sgRNAs targeting exon 1 of cIL1R1. In some embodiments, the CRISPR gene-editing system for the treatment of psoriatic arthritis comprises one or more sgRNAs targeting exon 2 of cIL1R1. In some embodiments, the CRISPR gene-editing system for the treatment of psoriatic arthritis comprises one or more sgRNAs targeting exon 3 of cIL1R1. In some embodiments, the CRISPR gene-editing system for the treatment of psoriatic arthritis comprises one or more sgRNAs targeting exon 4 of cIL1R1. In some embodiments, the CRISPR gene-editing system for the treatment of psoriatic arthritis comprises one or more sgRNAs targeting exon 5 of cIL1R1. In some embodiments, the CRISPR gene-editing system for the treatment of psoriatic arthritis comprises one or more sgRNAs targeting exon 6 of cIL1R1. In some embodiments, the CRISPR gene-editing system for the treatment of psoriatic arthritis comprises one or more sgRNAs targeting exon 7 of cIL1R1. In some embodiments, the CRISPR gene-editing system for the treatment of psoriatic arthritis comprises one or more sgRNAs targeting exon 8 of cIL1R1. In some embodiments, the CRISPR gene-editing system for the treatment of psoriatic arthritis comprises one or more sgRNAs targeting exon 9 of cIL1R1. In some embodiments, the CRISPR gene-editing system for the treatment of psoriatic arthritis comprises one or more sgRNAs targeting exon 10 of cIL1R1. In some embodiments, the CRISPR gene-editing system for the treatment of psoriatic arthritis comprises one or more sgRNAs targeting exon 11 of cIL1R1. In some embodiments, the CRISPR gene-editing system for the treatment of psoriatic arthritis comprises one or more sgRNAs targeting exon 12 of cIL1R1. In some embodiments, the CRISPR gene-editing system for the treatment of psoriatic arthritis comprises one or more sgRNAs targeting exon 13 of cIL1R1. In some embodiments, the CRISPR gene-editing system for the treatment of psoriatic arthritis comprises one or more sgRNAs targeting exon 14 of cIL1R1. In some embodiments, the

CRISPR gene-editing system for the treatment of psoriatic arthritis comprises one or more sgRNAs targeting exon 15 of cIL1R1. In some embodiments, the CRISPR gene-editing system for the treatment of psoriatic arthritis comprises one or more sgRNAs targeting exon 16 of cIL1R1.

[00238] In some embodiments, the CRISPR gene-editing system for the treatment of psoriatic arthritis comprises one or more sgRNAs targeting exon 1 of eIL1R1. In some embodiments, the CRISPR gene-editing system for the treatment of psoriatic arthritis comprises one or more sgRNAs targeting exon 2 of eIL1R1. In some embodiments, the CRISPR gene-editing system for the treatment of psoriatic arthritis comprises one or more sgRNAs targeting exon 3 of eIL1R1. In some embodiments, the CRISPR gene-editing system for the treatment of psoriatic arthritis comprises one or more sgRNAs targeting exon 4 of eIL1R1. In some embodiments, the CRISPR gene-editing system for the treatment of psoriatic arthritis comprises one or more sgRNAs targeting exon 5 of eIL1R1. In some embodiments, the CRISPR gene-editing system for the treatment of psoriatic arthritis comprises one or more sgRNAs targeting exon 6 of eIL1R1. In some embodiments, the CRISPR gene-editing system for the treatment of psoriatic arthritis comprises one or more sgRNAs targeting exon 7 of eIL1R1. In some embodiments, the CRISPR gene-editing system for the treatment of psoriatic arthritis comprises one or more sgRNAs targeting exon 8 of eIL1R1. In some embodiments, the CRISPR gene-editing system for the treatment of psoriatic arthritis comprises one or more sgRNAs targeting exon 9 of eIL1R1. In some embodiments, the CRISPR gene-editing system for the treatment of psoriatic arthritis comprises one or more sgRNAs targeting exon 10 of eIL1R1. In some embodiments, the CRISPR gene-editing system for the treatment of psoriatic arthritis comprises one or more sgRNAs targeting exon 11 of eIL1R1. In some embodiments, the CRISPR gene-editing system for the treatment of psoriatic arthritis comprises one or more sgRNAs targeting exon 12 of eIL1R1. In some embodiments, the CRISPR gene-editing system for the treatment of psoriatic arthritis comprises one or more sgRNAs targeting exon 13 of eIL1R1. In some embodiments, the CRISPR gene-editing system for the treatment of psoriatic arthritis comprises one or more sgRNAs targeting exon 14 of eIL1R1. In some embodiments, the CRISPR gene-editing system for the treatment of psoriatic arthritis comprises one or more sgRNAs targeting exon 15 of eIL1R1.

[00239] In some embodiments, the CRISPR gene-editing system for the treatment of psoriatic arthritis comprises one or more sgRNAs targeting exon 1 of fIL1R1. In some

embodiments, the CRISPR gene-editing system for the treatment of psoriatic arthritis comprises one or more sgRNAs targeting exon 2 of fIL1R1. In some embodiments, the CRISPR gene-editing system for the treatment of psoriatic arthritis comprises one or more sgRNAs targeting exon 3 of fIL1R1. In some embodiments, the CRISPR gene-editing system for the treatment of psoriatic arthritis comprises one or more sgRNAs targeting exon 4 of fIL1R1. In some embodiments, the CRISPR gene-editing system for the treatment of psoriatic arthritis comprises one or more sgRNAs targeting exon 5 of fIL1R1. In some embodiments, the CRISPR gene-editing system for the treatment of psoriatic arthritis comprises one or more sgRNAs targeting exon 6 of fIL1R1. In some embodiments, the CRISPR gene-editing system for the treatment of psoriatic arthritis comprises one or more sgRNAs targeting exon 7 of fIL1R1. In some embodiments, the CRISPR gene-editing system for the treatment of psoriatic arthritis comprises one or more sgRNAs targeting exon 8 of fIL1R1. In some embodiments, the CRISPR gene-editing system for the treatment of psoriatic arthritis comprises one or more sgRNAs targeting exon 9 of fIL1R1. In some embodiments, the CRISPR gene-editing system for the treatment of psoriatic arthritis comprises one or more sgRNAs targeting exon 10 of fIL1R1. In some embodiments, the CRISPR gene-editing system for the treatment of psoriatic arthritis comprises one or more sgRNAs targeting exon 11 of fIL1R1. In some embodiments, the CRISPR gene-editing system for the treatment of psoriatic arthritis comprises one or more sgRNAs targeting exon 12 of fIL1R1. In some embodiments, the CRISPR gene-editing system for the treatment of psoriatic arthritis comprises one or more sgRNAs targeting exon 13 of fIL1R1. In some embodiments, the CRISPR gene-editing system for the treatment of psoriatic arthritis comprises one or more sgRNAs targeting exon 14 of fIL1R1. In some embodiments, the CRISPR gene-editing system for the treatment of psoriatic arthritis comprises one or more sgRNAs targeting exon 15 of fIL1R1. In some embodiments, the CRISPR gene-editing system for the treatment of psoriatic arthritis comprises one or more sgRNAs targeting exon 16 of fIL1R1. In some embodiments, the CRISPR gene-editing system for the treatment of psoriatic arthritis comprises one or more sgRNAs targeting exon 17 of fIL1R1. In some embodiments, the CRISPR gene-editing system for the treatment of psoriatic arthritis comprises one or more sgRNAs targeting exon 18 of fIL1R1.

[00240] In some embodiments, the CRISPR gene-editing system for the treatment of psoriatic arthritis comprises one or more sgRNAs targeting IL1RAP. In some embodiments, the CRISPR gene-editing system for the treatment of psoriatic arthritis comprises one or

more sgRNAs targeting hIL1RAP. In some embodiments, the CRISPR gene-editing system for the treatment of psoriatic arthritis comprises one or more sgRNAs targeting cIL1RAP. In some embodiments, the CRISPR gene-editing system for the treatment of psoriatic arthritis comprises one or more sgRNAs targeting eIL1RAP. In some embodiments, the CRISPR gene-editing system for the treatment of psoriatic arthritis comprises one or more sgRNAs targeting fIL1RAP.

[00241] In some embodiments, the CRISPR gene-editing system for the treatment of psoriatic arthritis comprises one or more sgRNAs targeting exon 1 of hIL1RAP. In some embodiments, the CRISPR gene-editing system for the treatment of psoriatic arthritis comprises one or more sgRNAs targeting exon 2 of hIL1RAP. In some embodiments, the CRISPR gene-editing system for the treatment of psoriatic arthritis comprises one or more sgRNAs targeting exon 3 of hIL1RAP. In some embodiments, the CRISPR gene-editing system for the treatment of psoriatic arthritis comprises one or more sgRNAs targeting exon 4 of hIL1RAP. In some embodiments, the CRISPR gene-editing system for the treatment of psoriatic arthritis comprises one or more sgRNAs targeting exon 5 of hIL1RAP. In some embodiments, the CRISPR gene-editing system for the treatment of psoriatic arthritis comprises one or more sgRNAs targeting exon 6 of hIL1RAP. In some embodiments, the CRISPR gene-editing system for the treatment of psoriatic arthritis comprises one or more sgRNAs targeting exon 7 of hIL1RAP. In some embodiments, the CRISPR gene-editing system for the treatment of psoriatic arthritis comprises one or more sgRNAs targeting exon 8 of hIL1RAP. In some embodiments, the CRISPR gene-editing system for the treatment of psoriatic arthritis comprises one or more sgRNAs targeting exon 9 of hIL1RAP. In some embodiments, the CRISPR gene-editing system for the treatment of psoriatic arthritis comprises one or more sgRNAs targeting exon 10 of hIL1RAP. In some embodiments, the CRISPR gene-editing system for the treatment of psoriatic arthritis comprises one or more sgRNAs targeting exon 11 of hIL1RAP. In some embodiments, the CRISPR gene-editing system for the treatment of psoriatic arthritis comprises one or more sgRNAs targeting exon 12 of hIL1RAP. In some embodiments, the CRISPR gene-editing system for the treatment of psoriatic arthritis comprises one or more sgRNAs targeting exon 13 of hIL1RAP. In some embodiments, the CRISPR gene-editing system for the treatment of psoriatic arthritis comprises one or more sgRNAs targeting exon 14 of hIL1RAP. In some embodiments, the CRISPR gene-editing system for the treatment of psoriatic arthritis comprises one or more sgRNAs targeting exon 15 of hIL1RAP. In some embodiments, the CRISPR gene-editing

system for the treatment of psoriatic arthritis comprises one or more sgRNAs targeting exon 16 of hIL1RAP. In some embodiments, the CRISPR gene-editing system for the treatment of psoriatic arthritis comprises one or more sgRNAs targeting exon 17 of hIL1RAP.

[00242] In some embodiments, the CRISPR gene-editing system for the treatment of psoriatic arthritis comprises one or more sgRNAs targeting exon 1 of cIL1RAP. In some embodiments, the CRISPR gene-editing system for the treatment of psoriatic arthritis comprises one or more sgRNAs targeting exon 2 of cIL1RAP. In some embodiments, the CRISPR gene-editing system for the treatment of psoriatic arthritis comprises one or more sgRNAs targeting exon 3 of cIL1RAP. In some embodiments, the CRISPR gene-editing system for the treatment of psoriatic arthritis comprises one or more sgRNAs targeting exon 4 of cIL1RAP. In some embodiments, the CRISPR gene-editing system for the treatment of psoriatic arthritis comprises one or more sgRNAs targeting exon 5 of cIL1RAP. In some embodiments, the CRISPR gene-editing system for the treatment of psoriatic arthritis comprises one or more sgRNAs targeting exon 6 of cIL1RAP. In some embodiments, the CRISPR gene-editing system for the treatment of psoriatic arthritis comprises one or more sgRNAs targeting exon 7 of cIL1RAP. In some embodiments, the CRISPR gene-editing system for the treatment of psoriatic arthritis comprises one or more sgRNAs targeting exon 8 of cIL1RAP. In some embodiments, the CRISPR gene-editing system for the treatment of psoriatic arthritis comprises one or more sgRNAs targeting exon 9 of cIL1RAP. In some embodiments, the CRISPR gene-editing system for the treatment of psoriatic arthritis comprises one or more sgRNAs targeting exon 10 of cIL1RAP. In some embodiments, the CRISPR gene-editing system for the treatment of psoriatic arthritis comprises one or more sgRNAs targeting exon 11 of cIL1RAP. In some embodiments, the CRISPR gene-editing system for the treatment of psoriatic arthritis comprises one or more sgRNAs targeting exon 12 of cIL1RAP. In some embodiments, the CRISPR gene-editing system for the treatment of psoriatic arthritis comprises one or more sgRNAs targeting exon 13 of cIL1RAP. In some embodiments, the CRISPR gene-editing system for the treatment of psoriatic arthritis comprises one or more sgRNAs targeting exon 14 of cIL1RAP. In some embodiments, the CRISPR gene-editing system for the treatment of psoriatic arthritis comprises one or more sgRNAs targeting exon 15 of cIL1RAP. In some embodiments, the CRISPR gene-editing system for the treatment of psoriatic arthritis comprises one or more sgRNAs targeting exon 16 of cIL1RAP.

[00243] In some embodiments, the CRISPR gene-editing system for the treatment of psoriatic arthritis comprises one or more sgRNAs targeting exon 1 of eIL1RAP. In some embodiments, the CRISPR gene-editing system for the treatment of psoriatic arthritis comprises one or more sgRNAs targeting exon 2 of eIL1RAP. In some embodiments, the CRISPR gene-editing system for the treatment of psoriatic arthritis comprises one or more sgRNAs targeting exon 3 of eIL1RAP. In some embodiments, the CRISPR gene-editing system for the treatment of psoriatic arthritis comprises one or more sgRNAs targeting exon 4 of eIL1RAP. In some embodiments, the CRISPR gene-editing system for the treatment of psoriatic arthritis comprises one or more sgRNAs targeting exon 5 of eIL1RAP. In some embodiments, the CRISPR gene-editing system for the treatment of psoriatic arthritis comprises one or more sgRNAs targeting exon 6 of eIL1RAP. In some embodiments, the CRISPR gene-editing system for the treatment of psoriatic arthritis comprises one or more sgRNAs targeting exon 7 of eIL1RAP. In some embodiments, the CRISPR gene-editing system for the treatment of psoriatic arthritis comprises one or more sgRNAs targeting exon 8 of eIL1RAP. In some embodiments, the CRISPR gene-editing system for the treatment of psoriatic arthritis comprises one or more sgRNAs targeting exon 9 of eIL1RAP. In some embodiments, the CRISPR gene-editing system for the treatment of psoriatic arthritis comprises one or more sgRNAs targeting exon 10 of eIL1RAP. In some embodiments, the CRISPR gene-editing system for the treatment of psoriatic arthritis comprises one or more sgRNAs targeting exon 11 of eIL1RAP. In some embodiments, the CRISPR gene-editing system for the treatment of psoriatic arthritis comprises one or more sgRNAs targeting exon 12 of eIL1RAP. In some embodiments, the CRISPR gene-editing system for the treatment of psoriatic arthritis comprises one or more sgRNAs targeting exon 13 of eIL1RAP.

[00244] In some embodiments, the CRISPR gene-editing system for the treatment of psoriatic arthritis comprises one or more sgRNAs targeting exon 1 of fIL1RAP. In some embodiments, the CRISPR gene-editing system for the treatment of psoriatic arthritis comprises one or more sgRNAs targeting exon 2 of fIL1RAP. In some embodiments, the CRISPR gene-editing system for the treatment of psoriatic arthritis comprises one or more sgRNAs targeting exon 3 of fIL1RAP. In some embodiments, the CRISPR gene-editing system for the treatment of psoriatic arthritis comprises one or more sgRNAs targeting exon 4 of fIL1RAP. In some embodiments, the CRISPR gene-editing system for the treatment of psoriatic arthritis comprises one or more sgRNAs targeting exon 5 of fIL1RAP. In some embodiments, the CRISPR gene-editing system for the treatment of psoriatic arthritis

comprises one or more sgRNAs targeting exon 6 of flL1RAP. In some embodiments, the CRISPR gene-editing system for the treatment of psoriatic arthritis comprises one or more sgRNAs targeting exon 7 of flL1RAP. In some embodiments, the CRISPR gene-editing system for the treatment of psoriatic arthritis comprises one or more sgRNAs targeting exon 8 of flL1RAP. In some embodiments, the CRISPR gene-editing system for the treatment of psoriatic arthritis comprises one or more sgRNAs targeting exon 9 of flL1RAP. In some embodiments, the CRISPR gene-editing system for the treatment of psoriatic arthritis comprises one or more sgRNAs targeting exon 10 of flL1RAP. In some embodiments, the CRISPR gene-editing system for the treatment of psoriatic arthritis comprises one or more sgRNAs targeting exon 11 of flL1RAP. In some embodiments, the CRISPR gene-editing system for the treatment of psoriatic arthritis comprises one or more sgRNAs targeting exon 12 of flL1RAP. In some embodiments, the CRISPR gene-editing system for the treatment of psoriatic arthritis comprises one or more sgRNAs targeting exon 13 of flL1RAP. In some embodiments, the CRISPR gene-editing system for the treatment of psoriatic arthritis comprises one or more sgRNAs targeting exon 14 of flL1RAP.

[00245] In some embodiments, the CRISPR gene-editing system for the treatment of psoriatic arthritis comprises one or more sgRNAs targeting TGFBR1. In some embodiments, the CRISPR gene-editing system for the treatment of psoriatic arthritis comprises one or more sgRNAs targeting hTGFBR1. In some embodiments, the CRISPR gene-editing system for the treatment of psoriatic arthritis comprises one or more sgRNAs targeting cTGFBR1. In some embodiments, the CRISPR gene-editing system for the treatment of psoriatic arthritis comprises one or more sgRNAs targeting e TGFBR1. In some embodiments, the CRISPR gene-editing system for the treatment of psoriatic arthritis comprises one or more sgRNAs targeting fTGFBR1.

[00246] In some embodiments, the CRISPR gene-editing system for the treatment of psoriatic arthritis comprises one or more sgRNAs targeting exon 1 of hTGFBR1. In some embodiments, the CRISPR gene-editing system for the treatment of psoriatic arthritis comprises one or more sgRNAs targeting exon 2 of hTGFBR1. In some embodiments, the CRISPR gene-editing system for the treatment of psoriatic arthritis comprises one or more sgRNAs targeting exon 3 of hTGFBR1. In some embodiments, the CRISPR gene-editing system for the treatment of psoriatic arthritis comprises one or more sgRNAs targeting exon 4 of hTGFBR1. In some embodiments, the CRISPR gene-editing system for the treatment of psoriatic arthritis comprises one or more sgRNAs targeting exon 5 of hTGFBR1. In some

embodiments, the CRISPR gene-editing system for the treatment of psoriatic arthritis comprises one or more sgRNAs targeting exon 6 of hTGFBR1. In some embodiments, the CRISPR gene-editing system for the treatment of psoriatic arthritis comprises one or more sgRNAs targeting exon 7 of hTGFBR1. In some embodiments, the CRISPR gene-editing system for the treatment of psoriatic arthritis comprises one or more sgRNAs targeting exon 8 of hTGFBR1. In some embodiments, the CRISPR gene-editing system for the treatment of psoriatic arthritis comprises one or more sgRNAs targeting exon 9 of hTGFBR1. In some embodiments, the CRISPR gene-editing system for the treatment of psoriatic arthritis comprises one or more sgRNAs targeting exon 10 of hTGFBR1. In some embodiments, the CRISPR gene-editing system for the treatment of psoriatic arthritis comprises one or more sgRNAs targeting exon 11 of hTGFBR1.

[00247] In some embodiments, the CRISPR gene-editing system for the treatment of psoriatic arthritis comprises one or more sgRNAs targeting exon 1 of cTGFBR1. In some embodiments, the CRISPR gene-editing system for the treatment of psoriatic arthritis comprises one or more sgRNAs targeting exon 2 of cTGFBR1. In some embodiments, the CRISPR gene-editing system for the treatment of psoriatic arthritis comprises one or more sgRNAs targeting exon 3 of cTGFBR1. In some embodiments, the CRISPR gene-editing system for the treatment of psoriatic arthritis comprises one or more sgRNAs targeting exon 4 of cTGFBR1. In some embodiments, the CRISPR gene-editing system for the treatment of psoriatic arthritis comprises one or more sgRNAs targeting exon 5 of cTGFBR1. In some embodiments, the CRISPR gene-editing system for the treatment of psoriatic arthritis comprises one or more sgRNAs targeting exon 6 of cTGFBR1. In some embodiments, the CRISPR gene-editing system for the treatment of psoriatic arthritis comprises one or more sgRNAs targeting exon 7 of cTGFBR1. In some embodiments, the CRISPR gene-editing system for the treatment of psoriatic arthritis comprises one or more sgRNAs targeting exon 8 of cTGFBR1. In some embodiments, the CRISPR gene-editing system for the treatment of psoriatic arthritis comprises one or more sgRNAs targeting exon 9 of cTGFBR1.

[00248] In some embodiments, the CRISPR gene-editing system for the treatment of psoriatic arthritis comprises one or more sgRNAs targeting exon 1 of eTGFBR1. In some embodiments, the CRISPR gene-editing system for the treatment of psoriatic arthritis comprises one or more sgRNAs targeting exon 2 of eTGFBR1. In some embodiments, the CRISPR gene-editing system for the treatment of psoriatic arthritis comprises one or more sgRNAs targeting exon 3 of eTGFBR1. In some embodiments, the CRISPR gene-editing

system for the treatment of psoriatic arthritis comprises one or more sgRNAs targeting exon 4 of eTGFBR1. In some embodiments, the CRISPR gene-editing system for the treatment of psoriatic arthritis comprises one or more sgRNAs targeting exon 5 of eTGFBR1. In some embodiments, the CRISPR gene-editing system for the treatment of psoriatic arthritis comprises one or more sgRNAs targeting exon 6 of eTGFBR1. In some embodiments, the CRISPR gene-editing system for the treatment of psoriatic arthritis comprises one or more sgRNAs targeting exon 7 of eTGFBR1. In some embodiments, the CRISPR gene-editing system for the treatment of psoriatic arthritis comprises one or more sgRNAs targeting exon 8 of eTGFBR1. In some embodiments, the CRISPR gene-editing system for the treatment of psoriatic arthritis comprises one or more sgRNAs targeting exon 9 of eTGFBR1. In some embodiments, the CRISPR gene-editing system for the treatment of psoriatic arthritis comprises one or more sgRNAs targeting exon 10 of eTGFBR1. In some embodiments, the CRISPR gene-editing system for the treatment of psoriatic arthritis comprises one or more sgRNAs targeting exon 11 of eTGFBR1. In some embodiments, the CRISPR gene-editing system for the treatment of psoriatic arthritis comprises one or more sgRNAs targeting exon 12 of eTGFBR1.

[00249] In some embodiments, the CRISPR gene-editing system for the treatment of psoriatic arthritis comprises one or more sgRNAs targeting exon 1 of fTGFBR1. In some embodiments, the CRISPR gene-editing system for the treatment of psoriatic arthritis comprises one or more sgRNAs targeting exon 2 of fTGFBR1. In some embodiments, the CRISPR gene-editing system for the treatment of psoriatic arthritis comprises one or more sgRNAs targeting exon 3 of fTGFBR1. In some embodiments, the CRISPR gene-editing system for the treatment of psoriatic arthritis comprises one or more sgRNAs targeting exon 4 of fTGFBR1. In some embodiments, the CRISPR gene-editing system for the treatment of psoriatic arthritis comprises one or more sgRNAs targeting exon 5 of fTGFBR1. In some embodiments, the CRISPR gene-editing system for the treatment of psoriatic arthritis comprises one or more sgRNAs targeting exon 6 of fTGFBR1. In some embodiments, the CRISPR gene-editing system for the treatment of psoriatic arthritis comprises one or more sgRNAs targeting exon 7 of fTGFBR1. In some embodiments, the CRISPR gene-editing system for the treatment of psoriatic arthritis comprises one or more sgRNAs targeting exon 8 of fTGFBR1. In some embodiments, the CRISPR gene-editing system for the treatment of psoriatic arthritis comprises one or more sgRNAs targeting exon 9 of fTGFBR1. In some embodiments, the CRISPR gene-editing system for the treatment of psoriatic arthritis

comprises one or more sgRNAs targeting exon 10 of fTGFBR1. In some embodiments, the CRISPR gene-editing system for the treatment of psoriatic arthritis comprises one or more sgRNAs targeting exon 11 of fTGFBR1.

[00250] In some embodiments, the CRISPR gene-editing system for the treatment of psoriatic arthritis comprises one or more sgRNAs targeting TGFBR2. In some embodiments, the CRISPR gene-editing system for the treatment of psoriatic arthritis comprises one or more sgRNAs targeting hTGFBR2. In some embodiments, the CRISPR gene-editing system for the treatment of psoriatic arthritis comprises one or more sgRNAs targeting cTGFBR2. In some embodiments, the CRISPR gene-editing system for the treatment of psoriatic arthritis comprises one or more sgRNAs targeting eTGFBR2. In some embodiments, the CRISPR gene-editing system for the treatment of psoriatic arthritis comprises one or more sgRNAs targeting fTGFBR2.

[00251] In some embodiments, the CRISPR gene-editing system for the treatment of psoriatic arthritis comprises one or more sgRNAs targeting exon 1 of hTGFBR2. In some embodiments, the CRISPR gene-editing system for the treatment of psoriatic arthritis comprises one or more sgRNAs targeting exon 2 of hTGFBR2. In some embodiments, the CRISPR gene-editing system for the treatment of psoriatic arthritis comprises one or more sgRNAs targeting exon 3 of hTGFBR2. In some embodiments, the CRISPR gene-editing system for the treatment of psoriatic arthritis comprises one or more sgRNAs targeting exon 4 of hTGFBR2. In some embodiments, the CRISPR gene-editing system for the treatment of psoriatic arthritis comprises one or more sgRNAs targeting exon 5 of hTGFBR2. In some embodiments, the CRISPR gene-editing system for the treatment of psoriatic arthritis comprises one or more sgRNAs targeting exon 6 of hTGFBR2. In some embodiments, the CRISPR gene-editing system for the treatment of psoriatic arthritis comprises one or more sgRNAs targeting exon 7 of hTGFBR2. In some embodiments, the CRISPR gene-editing system for the treatment of psoriatic arthritis comprises one or more sgRNAs targeting exon 8 of hTGFBR2. In some embodiments, the CRISPR gene-editing system for the treatment of psoriatic arthritis comprises one or more sgRNAs targeting exon 9 of hTGFBR2.

[00252] In some embodiments, the CRISPR gene-editing system for the treatment of psoriatic arthritis comprises one or more sgRNAs targeting exon 1 of cTGFBR2. In some embodiments, the CRISPR gene-editing system for the treatment of psoriatic arthritis comprises one or more sgRNAs targeting exon 2 of cTGFBR2. In some embodiments, the CRISPR gene-editing system for the treatment of psoriatic arthritis comprises one or more

sgRNAs targeting exon 3 of cTGFBR2. In some embodiments, the CRISPR gene-editing system for the treatment of psoriatic arthritis comprises one or more sgRNAs targeting exon 4 of cTGFBR2. In some embodiments, the CRISPR gene-editing system for the treatment of psoriatic arthritis comprises one or more sgRNAs targeting exon 5 of cTGFBR2. In some embodiments, the CRISPR gene-editing system for the treatment of psoriatic arthritis comprises one or more sgRNAs targeting exon 6 of cTGFBR2. In some embodiments, the CRISPR gene-editing system for the treatment of psoriatic arthritis comprises one or more sgRNAs targeting exon 7 of cTGFBR2. In some embodiments, the CRISPR gene-editing system for the treatment of psoriatic arthritis comprises one or more sgRNAs targeting exon 8 of cTGFBR2.

[00253] In some embodiments, the CRISPR gene-editing system for the treatment of psoriatic arthritis comprises one or more sgRNAs targeting exon 1 of eTGFBR2. In some embodiments, the CRISPR gene-editing system for the treatment of psoriatic arthritis comprises one or more sgRNAs targeting exon 2 of eTGFBR2. In some embodiments, the CRISPR gene-editing system for the treatment of psoriatic arthritis comprises one or more sgRNAs targeting exon 3 of eTGFBR2. In some embodiments, the CRISPR gene-editing system for the treatment of psoriatic arthritis comprises one or more sgRNAs targeting exon 4 of eTGFBR2. In some embodiments, the CRISPR gene-editing system for the treatment of psoriatic arthritis comprises one or more sgRNAs targeting exon 5 of eTGFBR2. In some embodiments, the CRISPR gene-editing system for the treatment of psoriatic arthritis comprises one or more sgRNAs targeting exon 6 of eTGFBR2. In some embodiments, the CRISPR gene-editing system for the treatment of psoriatic arthritis comprises one or more sgRNAs targeting exon 7 of eTGFBR2. In some embodiments, the CRISPR gene-editing system for the treatment of psoriatic arthritis comprises one or more sgRNAs targeting exon 8 of eTGFBR2. In some embodiments, the CRISPR gene-editing system for the treatment of psoriatic arthritis comprises one or more sgRNAs targeting exon 9 of eTGFBR2. In some embodiments, the CRISPR gene-editing system for the treatment of psoriatic arthritis comprises one or more sgRNAs targeting exon 10 of eTGFBR2.

[00254] In some embodiments, the CRISPR gene-editing system for the treatment of psoriatic arthritis comprises one or more sgRNAs targeting exon 1 of fTGFBR2. In some embodiments, the CRISPR gene-editing system for the treatment of psoriatic arthritis comprises one or more sgRNAs targeting exon 2 of fTGFBR2. In some embodiments, the CRISPR gene-editing system for the treatment of psoriatic arthritis comprises one or more

sgRNAs targeting exon 3 of fTGFBR2. In some embodiments, the CRISPR gene-editing system for the treatment of psoriatic arthritis comprises one or more sgRNAs targeting exon 4 of fTGFBR2. In some embodiments, the CRISPR gene-editing system for the treatment of psoriatic arthritis comprises one or more sgRNAs targeting exon 5 of fTGFBR2. In some embodiments, the CRISPR gene-editing system for the treatment of psoriatic arthritis comprises one or more sgRNAs targeting exon 6 of fTGFBR2. In some embodiments, the CRISPR gene-editing system for the treatment of psoriatic arthritis comprises one or more sgRNAs targeting exon 7 of fTGFBR2. In some embodiments, the CRISPR gene-editing system for the treatment of psoriatic arthritis comprises one or more sgRNAs targeting exon 8 of fTGFBR2.

[00255] In some embodiments, the CRISPR gene-editing system for the treatment of psoriatic arthritis comprises one or more sgRNAs targeting IL6R. In some embodiments, the CRISPR gene-editing system for the treatment of psoriatic arthritis comprises one or more sgRNAs targeting hIL6R. In some embodiments, the CRISPR gene-editing system for the treatment of psoriatic arthritis comprises one or more sgRNAs targeting cIL6R. In some embodiments, the CRISPR gene-editing system for the treatment of psoriatic arthritis comprises one or more sgRNAs targeting eIL6R. In some embodiments, the CRISPR gene-editing system for the treatment of psoriatic arthritis comprises one or more sgRNAs targeting fIL6R.

[00256] In some embodiments, the CRISPR gene-editing system for the treatment of psoriatic arthritis comprises one or more sgRNAs targeting exon 1 of hIL6R. In some embodiments, the CRISPR gene-editing system for the treatment of psoriatic arthritis comprises one or more sgRNAs targeting exon 2 of hIL6R. In some embodiments, the CRISPR gene-editing system for the treatment of psoriatic arthritis comprises one or more sgRNAs targeting exon 3 of hIL6R. In some embodiments, the CRISPR gene-editing system for the treatment of psoriatic arthritis comprises one or more sgRNAs targeting exon 4 of hIL6R. In some embodiments, the CRISPR gene-editing system for the treatment of psoriatic arthritis comprises one or more sgRNAs targeting exon 5 of hIL6R. In some embodiments, the CRISPR gene-editing system for the treatment of psoriatic arthritis comprises one or more sgRNAs targeting exon 6 of hIL6R. In some embodiments, the CRISPR gene-editing system for the treatment of psoriatic arthritis comprises one or more sgRNAs targeting exon 7 of hIL6R. In some embodiments, the CRISPR gene-editing system for the treatment of psoriatic arthritis comprises one or more sgRNAs targeting exon 8 of hIL6R. In some

embodiments, the CRISPR gene-editing system for the treatment of psoriatic arthritis comprises one or more sgRNAs targeting exon 9 of hIL6R. In some embodiments, the CRISPR gene-editing system for the treatment of psoriatic arthritis comprises one or more sgRNAs targeting exon 10 of hIL6R. In some embodiments, the CRISPR gene-editing system for the treatment of psoriatic arthritis comprises one or more sgRNAs targeting exon 11 of hIL6R In some embodiments, the CRISPR gene-editing system for the treatment of psoriatic arthritis comprises one or more sgRNAs targeting exon 12 of hIL6R. In some embodiments, the CRISPR gene-editing system for the treatment of psoriatic arthritis comprises one or more sgRNAs targeting exon 13 of hIL6R. In some embodiments, the CRISPR gene-editing system for the treatment of psoriatic arthritis comprises one or more sgRNAs targeting exon 14 of hIL6R. In some embodiments, the CRISPR gene-editing system for the treatment of psoriatic arthritis comprises one or more sgRNAs targeting exon 15 of hIL6R.

[00257] In some embodiments, the CRISPR gene-editing system for the treatment of psoriatic arthritis comprises one or more sgRNAs targeting exon 1 of cIL6R. In some embodiments, the CRISPR gene-editing system for the treatment of psoriatic arthritis comprises one or more sgRNAs targeting exon 2 of cIL6R. In some embodiments, the CRISPR gene-editing system for the treatment of psoriatic arthritis comprises one or more sgRNAs targeting exon 3 of cIL6R. In some embodiments, the CRISPR gene-editing system for the treatment of psoriatic arthritis comprises one or more sgRNAs targeting exon 4 of cIL6R. In some embodiments, the CRISPR gene-editing system for the treatment of psoriatic arthritis comprises one or more sgRNAs targeting exon 5 of cIL6R. In some embodiments, the CRISPR gene-editing system for the treatment of psoriatic arthritis comprises one or more sgRNAs targeting exon 6 of cIL6R. In some embodiments, the CRISPR gene-editing system for the treatment of psoriatic arthritis comprises one or more sgRNAs targeting exon 7 of cIL6R. In some embodiments, the CRISPR gene-editing system for the treatment of psoriatic arthritis comprises one or more sgRNAs targeting exon 8 of cIL6R. In some embodiments, the CRISPR gene-editing system for the treatment of psoriatic arthritis comprises one or more sgRNAs targeting exon 9 of cIL6R. In some embodiments, the CRISPR gene-editing system for the treatment of psoriatic arthritis comprises one or more sgRNAs targeting exon 10 of cIL6R. In some embodiments, the CRISPR gene-editing system for the treatment of psoriatic arthritis comprises one or more sgRNAs targeting exon 11 of cIL6R. In some embodiments, the CRISPR gene-editing system for the treatment of

psoriatic arthritis comprises one or more sgRNAs targeting exon 12 of cIL6R. In some embodiments, the CRISPR gene-editing system for the treatment of psoriatic arthritis comprises one or more sgRNAs targeting exon 13 of cIL6R.

[00258] In some embodiments, the CRISPR gene-editing system for the treatment of psoriatic arthritis comprises one or more sgRNAs targeting exon 1 of eIL6R. In some embodiments, the CRISPR gene-editing system for the treatment of psoriatic arthritis comprises one or more sgRNAs targeting exon 2 of eIL6R. In some embodiments, the CRISPR gene-editing system for the treatment of psoriatic arthritis comprises one or more sgRNAs targeting exon 3 of eIL6R. In some embodiments, the CRISPR gene-editing system for the treatment of psoriatic arthritis comprises one or more sgRNAs targeting exon 4 of eIL6R. In some embodiments, the CRISPR gene-editing system for the treatment of psoriatic arthritis comprises one or more sgRNAs targeting exon 5 of eIL6R. In some embodiments, the CRISPR gene-editing system for the treatment of psoriatic arthritis comprises one or more sgRNAs targeting exon 6 of eIL6R. In some embodiments, the CRISPR gene-editing system for the treatment of psoriatic arthritis comprises one or more sgRNAs targeting exon 7 of eIL6R. In some embodiments, the CRISPR gene-editing system for the treatment of psoriatic arthritis comprises one or more sgRNAs targeting exon 8 of eIL6R. In some embodiments, the CRISPR gene-editing system for the treatment of psoriatic arthritis comprises one or more sgRNAs targeting exon 9 of eIL6R. In some embodiments, the CRISPR gene-editing system for the treatment of psoriatic arthritis comprises one or more sgRNAs targeting exon 10 of eIL6R. In some embodiments, the CRISPR gene-editing system for the treatment of psoriatic arthritis comprises one or more sgRNAs targeting exon 11 of eIL6R.

[00259] In some embodiments, the CRISPR gene-editing system for the treatment of psoriatic arthritis comprises one or more sgRNAs targeting exon 1 of fIL6R. In some embodiments, the CRISPR gene-editing system for the treatment of psoriatic arthritis comprises one or more sgRNAs targeting exon 2 of fIL6R. In some embodiments, the CRISPR gene-editing system for the treatment of psoriatic arthritis comprises one or more sgRNAs targeting exon 3 of fIL6R. In some embodiments, the CRISPR gene-editing system for the treatment of psoriatic arthritis comprises one or more sgRNAs targeting exon 4 of fIL6R. In some embodiments, the CRISPR gene-editing system for the treatment of psoriatic arthritis comprises one or more sgRNAs targeting exon 5 of fIL6R. In some embodiments, the CRISPR gene-editing system for the treatment of psoriatic arthritis comprises one or

more sgRNAs targeting exon 6 of fIL6R. In some embodiments, the CRISPR gene-editing system for the treatment of psoriatic arthritis comprises one or more sgRNAs targeting exon 7 of fIL6R. In some embodiments, the CRISPR gene-editing system for the treatment of psoriatic arthritis comprises one or more sgRNAs targeting exon 8 of fIL6R. In some embodiments, the CRISPR gene-editing system for the treatment of psoriatic arthritis comprises one or more sgRNAs targeting exon 9 of fIL6R. In some embodiments, the CRISPR gene-editing system for the treatment of psoriatic arthritis comprises one or more sgRNAs targeting exon 10 of fIL6R.

[00260] In some embodiments, the CRISPR gene-editing system for the treatment of psoriatic arthritis comprises one or more sgRNAs targeting IL6ST. In some embodiments, the CRISPR gene-editing system for the treatment of psoriatic arthritis comprises one or more sgRNAs targeting hIL6ST. In some embodiments, the CRISPR gene-editing system for the treatment of psoriatic arthritis comprises one or more sgRNAs targeting cIL6ST. In some embodiments, the CRISPR gene-editing system for the treatment of psoriatic arthritis comprises one or more sgRNAs targeting eIL6ST. In some embodiments, the CRISPR gene-editing system for the treatment of psoriatic arthritis comprises one or more sgRNAs targeting fIL6ST.

[00261] In some embodiments, the CRISPR gene-editing system for the treatment of psoriatic arthritis comprises one or more sgRNAs targeting exon 1 of hIL6ST. In some embodiments, the CRISPR gene-editing system for the treatment of psoriatic arthritis comprises one or more sgRNAs targeting exon 2 of hIL6ST. In some embodiments, the CRISPR gene-editing system for the treatment of psoriatic arthritis comprises one or more sgRNAs targeting exon 3 of hIL6ST. In some embodiments, the CRISPR gene-editing system for the treatment of psoriatic arthritis comprises one or more sgRNAs targeting exon 4 of hIL6ST. In some embodiments, the CRISPR gene-editing system for the treatment of psoriatic arthritis comprises one or more sgRNAs targeting exon 5 of hIL6ST. In some embodiments, the CRISPR gene-editing system for the treatment of psoriatic arthritis comprises one or more sgRNAs targeting exon 6 of hIL6ST. In some embodiments, the CRISPR gene-editing system for the treatment of psoriatic arthritis comprises one or more sgRNAs targeting exon 7 of hIL6ST. In some embodiments, the CRISPR gene-editing system for the treatment of psoriatic arthritis comprises one or more sgRNAs targeting exon 8 of hIL6ST. In some embodiments, the CRISPR gene-editing system for the treatment of psoriatic arthritis comprises one or more sgRNAs targeting exon 9 of hIL6ST. In some

embodiments, the CRISPR gene-editing system for the treatment of psoriatic arthritis comprises one or more sgRNAs targeting exon 10 of hIL6ST. In some embodiments, the CRISPR gene-editing system for the treatment of psoriatic arthritis comprises one or more sgRNAs targeting exon 11 of hIL6ST. In some embodiments, the CRISPR gene-editing system for the treatment of psoriatic arthritis comprises one or more sgRNAs targeting exon 12 of hIL6ST. In some embodiments, the CRISPR gene-editing system for the treatment of psoriatic arthritis comprises one or more sgRNAs targeting exon 13 of hIL6ST. In some embodiments, the CRISPR gene-editing system for the treatment of psoriatic arthritis comprises one or more sgRNAs targeting exon 14 of hIL6ST. In some embodiments, the CRISPR gene-editing system for the treatment of psoriatic arthritis comprises one or more sgRNAs targeting exon 15 of hIL6ST. In some embodiments, the CRISPR gene-editing system for the treatment of psoriatic arthritis comprises one or more sgRNAs targeting exon 16 of hIL6ST. In some embodiments, the CRISPR gene-editing system for the treatment of psoriatic arthritis comprises one or more sgRNAs targeting exon 17 of hIL6ST. In some embodiments, the CRISPR gene-editing system for the treatment of psoriatic arthritis comprises one or more sgRNAs targeting exon 18 of hIL6ST. In some embodiments, the CRISPR gene-editing system for the treatment of psoriatic arthritis comprises one or more sgRNAs targeting exon 19 of hIL6ST.

[00262] In some embodiments, the CRISPR gene-editing system for the treatment of psoriatic arthritis comprises one or more sgRNAs targeting exon 1 of cIL6ST. In some embodiments, the CRISPR gene-editing system for the treatment of psoriatic arthritis comprises one or more sgRNAs targeting exon 2 of cIL6ST. In some embodiments, the CRISPR gene-editing system for the treatment of psoriatic arthritis comprises one or more sgRNAs targeting exon 3 of cIL6ST. In some embodiments, the CRISPR gene-editing system for the treatment of psoriatic arthritis comprises one or more sgRNAs targeting exon 4 of cIL6ST. In some embodiments, the CRISPR gene-editing system for the treatment of psoriatic arthritis comprises one or more sgRNAs targeting exon 5 of cIL6ST. In some embodiments, the CRISPR gene-editing system for the treatment of psoriatic arthritis comprises one or more sgRNAs targeting exon 6 of cIL6ST. In some embodiments, the CRISPR gene-editing system for the treatment of psoriatic arthritis comprises one or more sgRNAs targeting exon 7 of cIL6ST. In some embodiments, the CRISPR gene-editing system for the treatment of psoriatic arthritis comprises one or more sgRNAs targeting exon 8 of cIL6ST. In some embodiments, the CRISPR gene-editing system for the treatment of

psoriatic arthritis comprises one or more sgRNAs targeting exon 9 of cIL6ST. In some embodiments, the CRISPR gene-editing system for the treatment of psoriatic arthritis comprises one or more sgRNAs targeting exon 10 of cIL6ST. In some embodiments, the CRISPR gene-editing system for the treatment of psoriatic arthritis comprises one or more sgRNAs targeting exon 11 of cIL6ST In some embodiments, the CRISPR gene-editing system for the treatment of psoriatic arthritis comprises one or more sgRNAs targeting exon 12 of cIL6ST. In some embodiments, the CRISPR gene-editing system for the treatment of psoriatic arthritis comprises one or more sgRNAs targeting exon 13 of cIL6ST. In some embodiments, the CRISPR gene-editing system for the treatment of psoriatic arthritis comprises one or more sgRNAs targeting exon 14 of cIL6ST. In some embodiments, the CRISPR gene-editing system for the treatment of psoriatic arthritis comprises one or more sgRNAs targeting exon 15 of cIL6ST. In some embodiments, the CRISPR gene-editing system for the treatment of psoriatic arthritis comprises one or more sgRNAs targeting exon 16 of cIL6ST. In some embodiments, the CRISPR gene-editing system for the treatment of psoriatic arthritis comprises one or more sgRNAs targeting exon 17 of cIL6ST. In some embodiments, the CRISPR gene-editing system for the treatment of psoriatic arthritis comprises one or more sgRNAs targeting exon 18 of cIL6ST.

[00263] In some embodiments, the CRISPR gene-editing system for the treatment of psoriatic arthritis comprises one or more sgRNAs targeting exon 1 of eIL6ST. In some embodiments, the CRISPR gene-editing system for the treatment of psoriatic arthritis comprises one or more sgRNAs targeting exon 2 of eIL6ST. In some embodiments, the CRISPR gene-editing system for the treatment of psoriatic arthritis comprises one or more sgRNAs targeting exon 3 of eIL6ST. In some embodiments, the CRISPR gene-editing system for the treatment of psoriatic arthritis comprises one or more sgRNAs targeting exon 4 of eIL6ST. In some embodiments, the CRISPR gene-editing system for the treatment of psoriatic arthritis comprises one or more sgRNAs targeting exon 5 of eIL6ST. In some embodiments, the CRISPR gene-editing system for the treatment of psoriatic arthritis comprises one or more sgRNAs targeting exon 6 of eIL6ST. In some embodiments, the CRISPR gene-editing system for the treatment of psoriatic arthritis comprises one or more sgRNAs targeting exon 7 of eIL6ST. In some embodiments, the CRISPR gene-editing system for the treatment of psoriatic arthritis comprises one or more sgRNAs targeting exon 8 of eIL6ST. In some embodiments, the CRISPR gene-editing system for the treatment of psoriatic arthritis comprises one or more sgRNAs targeting exon 9 of eIL6ST. In some

embodiments, the CRISPR gene-editing system for the treatment of psoriatic arthritis comprises one or more sgRNAs targeting exon 10 of eIL6ST. In some embodiments, the CRISPR gene-editing system for the treatment of psoriatic arthritis comprises one or more sgRNAs targeting exon 11 of eIL6ST In some embodiments, the CRISPR gene-editing system for the treatment of psoriatic arthritis comprises one or more sgRNAs targeting exon 12 of eIL6ST. In some embodiments, the CRISPR gene-editing system for the treatment of psoriatic arthritis comprises one or more sgRNAs targeting exon 13 of eIL6ST. In some embodiments, the CRISPR gene-editing system for the treatment of psoriatic arthritis comprises one or more sgRNAs targeting exon 14 of eIL6ST. In some embodiments, the CRISPR gene-editing system for the treatment of psoriatic arthritis comprises one or more sgRNAs targeting exon 15 of eIL6ST. In some embodiments, the CRISPR gene-editing system for the treatment of psoriatic arthritis comprises one or more sgRNAs targeting exon 16 of eIL6ST. In some embodiments, the CRISPR gene-editing system for the treatment of psoriatic arthritis comprises one or more sgRNAs targeting exon 17 of eIL6ST. In some embodiments, the CRISPR gene-editing system for the treatment of psoriatic arthritis comprises one or more sgRNAs targeting exon 18 of eIL6ST.

[00264] In some embodiments, the CRISPR gene-editing system for the treatment of psoriatic arthritis comprises one or more sgRNAs targeting exon 1 of fIL6ST. In some embodiments, the CRISPR gene-editing system for the treatment of psoriatic arthritis comprises one or more sgRNAs targeting exon 2 of fIL6ST. In some embodiments, the CRISPR gene-editing system for the treatment of psoriatic arthritis comprises one or more sgRNAs targeting exon 3 of fIL6ST. In some embodiments, the CRISPR gene-editing system for the treatment of psoriatic arthritis comprises one or more sgRNAs targeting exon 4 of fIL6ST. In some embodiments, the CRISPR gene-editing system for the treatment of psoriatic arthritis comprises one or more sgRNAs targeting exon 5 of fIL6ST. In some embodiments, the CRISPR gene-editing system for the treatment of psoriatic arthritis comprises one or more sgRNAs targeting exon 6 of fIL6ST. In some embodiments, the CRISPR gene-editing system for the treatment of psoriatic arthritis comprises one or more sgRNAs targeting exon 7 of fIL6ST. In some embodiments, the CRISPR gene-editing system for the treatment of psoriatic arthritis comprises one or more sgRNAs targeting exon 8 of fIL6ST. In some embodiments, the CRISPR gene-editing system for the treatment of psoriatic arthritis comprises one or more sgRNAs targeting exon 9 of fIL6ST. In some embodiments, the CRISPR gene-editing system for the treatment of psoriatic arthritis

comprises one or more sgRNAs targeting exon 10 of fIL6ST. In some embodiments, the CRISPR gene-editing system for the treatment of psoriatic arthritis comprises one or more sgRNAs targeting exon 11 of fIL6ST In some embodiments, the CRISPR gene-editing system for the treatment of psoriatic arthritis comprises one or more sgRNAs targeting exon 12 of fIL6ST. In some embodiments, the CRISPR gene-editing system for the treatment of psoriatic arthritis comprises one or more sgRNAs targeting exon 13 of fIL6ST. In some embodiments, the CRISPR gene-editing system for the treatment of psoriatic arthritis comprises one or more sgRNAs targeting exon 14 of fIL6ST. In some embodiments, the CRISPR gene-editing system for the treatment of psoriatic arthritis comprises one or more sgRNAs targeting exon 15 of fIL6ST. In some embodiments, the CRISPR gene-editing system for the treatment of psoriatic arthritis comprises one or more sgRNAs targeting exon 16 of fIL6ST. In some embodiments, the CRISPR gene-editing system for the treatment of psoriatic arthritis comprises one or more sgRNAs targeting exon 17 of fIL6ST. In some embodiments, the CRISPR gene-editing system for the treatment of psoriatic arthritis comprises one or more sgRNAs targeting exon 18 of fIL6ST. In some embodiments, the CRISPR gene-editing system for the treatment of psoriatic arthritis comprises one or more sgRNAs targeting exon 19 of fIL6ST. In some embodiments, the CRISPR gene-editing system for the treatment of psoriatic arthritis comprises one or more sgRNAs targeting exon 20 of fIL6ST.

[00265] In some embodiments, the CRISPR gene-editing system for the treatment of psoriatic arthritis comprises one or more sgRNAs targeting TNFRSF1A. In some embodiments, the CRISPR gene-editing system for the treatment of psoriatic arthritis comprises one or more sgRNAs targeting hTNFRSF1A. In some embodiments, the CRISPR gene-editing system for the treatment of psoriatic arthritis comprises one or more sgRNAs targeting cTNFRSF1A. In some embodiments, the CRISPR gene-editing system for the treatment of psoriatic arthritis comprises one or more sgRNAs targeting eTNFRSF1A. In some embodiments, the CRISPR gene-editing system for the treatment of psoriatic arthritis comprises one or more sgRNAs targeting fTNFRSF1A.

[00266] In some embodiments, the CRISPR gene-editing system for the treatment of psoriatic arthritis comprises one or more sgRNAs targeting exon 1 of hTNFRSF1A. In some embodiments, the CRISPR gene-editing system for the treatment of psoriatic arthritis comprises one or more sgRNAs targeting exon 2 of hTNFRSF1A. In some embodiments, the CRISPR gene-editing system for the treatment of psoriatic arthritis comprises one or more

sgRNAs targeting exon 3 of hTNFRSF1A. In some embodiments, the CRISPR gene-editing system for the treatment of psoriatic arthritis comprises one or more sgRNAs targeting exon 4 of hTNFRSF1A. In some embodiments, the CRISPR gene-editing system for the treatment of psoriatic arthritis comprises one or more sgRNAs targeting exon 5 of hTNFRSF1A. In some embodiments, the CRISPR gene-editing system for the treatment of psoriatic arthritis comprises one or more sgRNAs targeting exon 6 of hTNFRSF1A. In some embodiments, the CRISPR gene-editing system for the treatment of psoriatic arthritis comprises one or more sgRNAs targeting exon 7 of hTNFRSF1A. In some embodiments, the CRISPR gene-editing system for the treatment of psoriatic arthritis comprises one or more sgRNAs targeting exon 8 of hTNFRSF1A. In some embodiments, the CRISPR gene-editing system for the treatment of psoriatic arthritis comprises one or more sgRNAs targeting exon 9 of hTNFRSF1A. In some embodiments, the CRISPR gene-editing system for the treatment of psoriatic arthritis comprises one or more sgRNAs targeting exon 10 of hTNFRSF1A. In some embodiments, the CRISPR gene-editing system for the treatment of psoriatic arthritis comprises one or more sgRNAs targeting exon 11 of hTNFRSF1A.

[00267] In some embodiments, the CRISPR gene-editing system for the treatment of psoriatic arthritis comprises one or more sgRNAs targeting exon 1 of cTNFRSF1A. In some embodiments, the CRISPR gene-editing system for the treatment of psoriatic arthritis comprises one or more sgRNAs targeting exon 2 of cTNFRSF1A. In some embodiments, the CRISPR gene-editing system for the treatment of psoriatic arthritis comprises one or more sgRNAs targeting exon 3 of cTNFRSF1A. In some embodiments, the CRISPR gene-editing system for the treatment of psoriatic arthritis comprises one or more sgRNAs targeting exon 4 of cTNFRSF1A. In some embodiments, the CRISPR gene-editing system for the treatment of psoriatic arthritis comprises one or more sgRNAs targeting exon 5 of cTNFRSF1A. In some embodiments, the CRISPR gene-editing system for the treatment of psoriatic arthritis comprises one or more sgRNAs targeting exon 6 of cTNFRSF1A. In some embodiments, the CRISPR gene-editing system for the treatment of psoriatic arthritis comprises one or more sgRNAs targeting exon 7 of cTNFRSF1A. In some embodiments, the CRISPR gene-editing system for the treatment of psoriatic arthritis comprises one or more sgRNAs targeting exon 8 of cTNFRSF1A. In some embodiments, the CRISPR gene-editing system for the treatment of psoriatic arthritis comprises one or more sgRNAs targeting exon 9 of cTNFRSF1A. In some embodiments, the CRISPR gene-editing system for the treatment of psoriatic arthritis comprises one or more sgRNAs targeting exon 10 of cTNFRSF1A. In some embodiments,

the CRISPR gene-editing system for the treatment of psoriatic arthritis comprises one or more sgRNAs targeting exon 11 of cTNFRSF1A.

[00268] In some embodiments, the CRISPR gene-editing system for the treatment of psoriatic arthritis comprises one or more sgRNAs targeting exon 1 of eTNFRSF1A. In some embodiments, the CRISPR gene-editing system for the treatment of psoriatic arthritis comprises one or more sgRNAs targeting exon 2 of eTNFRSF1A. In some embodiments, the CRISPR gene-editing system for the treatment of psoriatic arthritis comprises one or more sgRNAs targeting exon 3 of eTNFRSF1A. In some embodiments, the CRISPR gene-editing system for the treatment of psoriatic arthritis comprises one or more sgRNAs targeting exon 4 of eTNFRSF1A. In some embodiments, the CRISPR gene-editing system for the treatment of psoriatic arthritis comprises one or more sgRNAs targeting exon 5 of eTNFRSF1A. In some embodiments, the CRISPR gene-editing system for the treatment of psoriatic arthritis comprises one or more sgRNAs targeting exon 6 of eTNFRSF1A. In some embodiments, the CRISPR gene-editing system for the treatment of psoriatic arthritis comprises one or more sgRNAs targeting exon 7 of eTNFRSF1A. In some embodiments, the CRISPR gene-editing system for the treatment of psoriatic arthritis comprises one or more sgRNAs targeting exon 8 of eTNFRSF1A. In some embodiments, the CRISPR gene-editing system for the treatment of psoriatic arthritis comprises one or more sgRNAs targeting exon 9 of eTNFRSF1A. In some embodiments, the CRISPR gene-editing system for the treatment of psoriatic arthritis comprises one or more sgRNAs targeting exon 10 of eTNFRSF1A.

[00269] In some embodiments, the CRISPR gene-editing system for the treatment of psoriatic arthritis comprises one or more sgRNAs targeting exon 1 of fTNFRSF1A. In some embodiments, the CRISPR gene-editing system for the treatment of psoriatic arthritis comprises one or more sgRNAs targeting exon 2 of fTNFRSF1A. In some embodiments, the CRISPR gene-editing system for the treatment of psoriatic arthritis comprises one or more sgRNAs targeting exon 3 of fTNFRSF1A. In some embodiments, the CRISPR gene-editing system for the treatment of psoriatic arthritis comprises one or more sgRNAs targeting exon 4 of fTNFRSF1A. In some embodiments, the CRISPR gene-editing system for the treatment of psoriatic arthritis comprises one or more sgRNAs targeting exon 5 of fTNFRSF1A. In some embodiments, the CRISPR gene-editing system for the treatment of psoriatic arthritis comprises one or more sgRNAs targeting exon 6 of fTNFRSF1A. In some embodiments, the CRISPR gene-editing system for the treatment of psoriatic arthritis comprises one or more sgRNAs targeting exon 7 of fTNFRSF1A. In some embodiments, the CRISPR gene-editing

system for the treatment of psoriatic arthritis comprises one or more sgRNAs targeting exon 8 of fTNFRSF1A. In some embodiments, the CRISPR gene-editing system for the treatment of psoriatic arthritis comprises one or more sgRNAs targeting exon 9 of fTNFRSF1A. In some embodiments, the CRISPR gene-editing system for the treatment of psoriatic arthritis comprises one or more sgRNAs targeting exon 10 of fTNFRSF1A.

[00270] In some embodiments, the CRISPR gene-editing system for the treatment of psoriatic arthritis comprises one or more sgRNAs targeting TNFRSF1B. In some embodiments, the CRISPR gene-editing system for the treatment of psoriatic arthritis comprises one or more sgRNAs targeting hTNFRSF1B. In some embodiments, the CRISPR gene-editing system for the treatment of psoriatic arthritis comprises one or more sgRNAs targeting cTNFRSF1B. In some embodiments, the CRISPR gene-editing system for the treatment of psoriatic arthritis comprises one or more sgRNAs targeting eTNFRSF1B. In some embodiments, the CRISPR gene-editing system for the treatment of psoriatic arthritis comprises one or more sgRNAs targeting fTNFRSF1B.

[00271] In some embodiments, the CRISPR gene-editing system for the treatment of psoriatic arthritis comprises one or more sgRNAs targeting exon 1 of hTNFRSF1B. In some embodiments, the CRISPR gene-editing system for the treatment of psoriatic arthritis comprises one or more sgRNAs targeting exon 2 of hTNFRSF1B. In some embodiments, the CRISPR gene-editing system for the treatment of psoriatic arthritis comprises one or more sgRNAs targeting exon 3 of hTNFRSF1B. In some embodiments, the CRISPR gene-editing system for the treatment of psoriatic arthritis comprises one or more sgRNAs targeting exon 4 of hTNFRSF1B. In some embodiments, the CRISPR gene-editing system for the treatment of psoriatic arthritis comprises one or more sgRNAs targeting exon 5 of hTNFRSF1B. In some embodiments, the CRISPR gene-editing system for the treatment of psoriatic arthritis comprises one or more sgRNAs targeting exon 6 of hTNFRSF1B. In some embodiments, the CRISPR gene-editing system for the treatment of psoriatic arthritis comprises one or more sgRNAs targeting exon 7 of hTNFRSF1B. In some embodiments, the CRISPR gene-editing system for the treatment of psoriatic arthritis comprises one or more sgRNAs targeting exon 8 of hTNFRSF1B. In some embodiments, the CRISPR gene-editing system for the treatment of psoriatic arthritis comprises one or more sgRNAs targeting exon 9 of hTNFRSF1B. In some embodiments, the CRISPR gene-editing system for the treatment of psoriatic arthritis comprises one or more sgRNAs targeting exon 10 of hTNFRSF1B. In some embodiments, the CRISPR gene-editing system for the treatment of psoriatic arthritis comprises one or

more sgRNAs targeting exon 11 of hTNFRSF1B In some embodiments, the CRISPR gene-editing system for the treatment of psoriatic arthritis comprises one or more sgRNAs targeting exon 12 of hTNFRSF1B. In some embodiments, the CRISPR gene-editing system for the treatment of psoriatic arthritis comprises one or more sgRNAs targeting exon 13 of hTNFRSF1B.

[00272] In some embodiments, the CRISPR gene-editing system for the treatment of psoriatic arthritis comprises one or more sgRNAs targeting exon 1 of cTNFRSF1B. In some embodiments, the CRISPR gene-editing system for the treatment of psoriatic arthritis comprises one or more sgRNAs targeting exon 2 of cTNFRSF1B. In some embodiments, the CRISPR gene-editing system for the treatment of psoriatic arthritis comprises one or more sgRNAs targeting exon 3 of cTNFRSF1B. In some embodiments, the CRISPR gene-editing system for the treatment of psoriatic arthritis comprises one or more sgRNAs targeting exon 4 of cTNFRSF1B. In some embodiments, the CRISPR gene-editing system for the treatment of psoriatic arthritis comprises one or more sgRNAs targeting exon 5 of cTNFRSF1B. In some embodiments, the CRISPR gene-editing system for the treatment of psoriatic arthritis comprises one or more sgRNAs targeting exon 6 of cTNFRSF1B. In some embodiments, the CRISPR gene-editing system for the treatment of psoriatic arthritis comprises one or more sgRNAs targeting exon 7 of cTNFRSF1B. In some embodiments, the CRISPR gene-editing system for the treatment of psoriatic arthritis comprises one or more sgRNAs targeting exon 8 of cTNFRSF1B. In some embodiments, the CRISPR gene-editing system for the treatment of psoriatic arthritis comprises one or more sgRNAs targeting exon 9 of cTNFRSF1B. In some embodiments, the CRISPR gene-editing system for the treatment of psoriatic arthritis comprises one or more sgRNAs targeting exon 10 of cTNFRSF1B. In some embodiments, the CRISPR gene-editing system for the treatment of psoriatic arthritis comprises one or more sgRNAs targeting exon 11 of cTNFRSF1B.

[00273] In some embodiments, the CRISPR gene-editing system for the treatment of psoriatic arthritis comprises one or more sgRNAs targeting exon 1 of eTNFRSF1B. In some embodiments, the CRISPR gene-editing system for the treatment of psoriatic arthritis comprises one or more sgRNAs targeting exon 2 of eTNFRSF1B. In some embodiments, the CRISPR gene-editing system for the treatment of psoriatic arthritis comprises one or more sgRNAs targeting exon 3 of eTNFRSF1B. In some embodiments, the CRISPR gene-editing system for the treatment of psoriatic arthritis comprises one or more sgRNAs targeting exon 4 of eTNFRSF1B. In some embodiments, the CRISPR gene-editing system for the treatment of

psoriatic arthritis comprises one or more sgRNAs targeting exon 5 of eTNFRSF1B. In some embodiments, the CRISPR gene-editing system for the treatment of psoriatic arthritis comprises one or more sgRNAs targeting exon 6 of eTNFRSF1B. In some embodiments, the CRISPR gene-editing system for the treatment of psoriatic arthritis comprises one or more sgRNAs targeting exon 7 of eTNFRSF1B. In some embodiments, the CRISPR gene-editing system for the treatment of psoriatic arthritis comprises one or more sgRNAs targeting exon 8 of eTNFRSF1B. In some embodiments, the CRISPR gene-editing system for the treatment of psoriatic arthritis comprises one or more sgRNAs targeting exon 9 of eTNFRSF1B. In some embodiments, the CRISPR gene-editing system for the treatment of psoriatic arthritis comprises one or more sgRNAs targeting exon 10 of eTNFRSF1B. In some embodiments, the CRISPR gene-editing system for the treatment of psoriatic arthritis comprises one or more sgRNAs targeting exon 11 of eTNFRSF1B.

[00274] In some embodiments, the CRISPR gene-editing system for the treatment of psoriatic arthritis comprises one or more sgRNAs targeting exon 1 of fTNFRSF1B. In some embodiments, the CRISPR gene-editing system for the treatment of psoriatic arthritis comprises one or more sgRNAs targeting exon 2 of fTNFRSF1B. In some embodiments, the CRISPR gene-editing system for the treatment of psoriatic arthritis comprises one or more sgRNAs targeting exon 3 of fTNFRSF1B. In some embodiments, the CRISPR gene-editing system for the treatment of psoriatic arthritis comprises one or more sgRNAs targeting exon 4 of fTNFRSF1B. In some embodiments, the CRISPR gene-editing system for the treatment of psoriatic arthritis comprises one or more sgRNAs targeting exon 5 of fTNFRSF1B. In some embodiments, the CRISPR gene-editing system for the treatment of psoriatic arthritis comprises one or more sgRNAs targeting exon 6 of fTNFRSF1B. In some embodiments, the CRISPR gene-editing system for the treatment of psoriatic arthritis comprises one or more sgRNAs targeting exon 7 of fTNFRSF1B. In some embodiments, the CRISPR gene-editing system for the treatment of psoriatic arthritis comprises one or more sgRNAs targeting exon 8 of fTNFRSF1B. In some embodiments, the CRISPR gene-editing system for the treatment of psoriatic arthritis comprises one or more sgRNAs targeting exon 9 of fTNFRSF1B. In some embodiments, the CRISPR gene-editing system for the treatment of psoriatic arthritis comprises one or more sgRNAs targeting exon 10 of fTNFRSF1B.

[00275] In some embodiments, the CRISPR gene-editing system for the treatment of psoriatic arthritis comprises one or more sgRNAs targeting TNFRSF3. In some embodiments, the CRISPR gene-editing system for the treatment of psoriatic arthritis

comprises one or more sgRNAs targeting hTNFRSF3. In some embodiments, the CRISPR gene-editing system for the treatment of psoriatic arthritis comprises one or more sgRNAs targeting cTNFRSF3. In some embodiments, the CRISPR gene-editing system for the treatment of psoriatic arthritis comprises one or more sgRNAs targeting eTNFRSF3. In some embodiments, the CRISPR gene-editing system for the treatment of psoriatic arthritis comprises one or more sgRNAs targeting fTNFRSF3.

[00276] In some embodiments, the CRISPR gene-editing system for the treatment of psoriatic arthritis comprises one or more sgRNAs targeting exon 1 of hTNFRSF3. In some embodiments, the CRISPR gene-editing system for the treatment of psoriatic arthritis comprises one or more sgRNAs targeting exon 2 of hTNFRSF3. In some embodiments, the CRISPR gene-editing system for the treatment of psoriatic arthritis comprises one or more sgRNAs targeting exon 3 of hTNFRSF3. In some embodiments, the CRISPR gene-editing system for the treatment of psoriatic arthritis comprises one or more sgRNAs targeting exon 4 of hTNFRSF3. In some embodiments, the CRISPR gene-editing system for the treatment of psoriatic arthritis comprises one or more sgRNAs targeting exon 5 of hTNFRSF3. In some embodiments, the CRISPR gene-editing system for the treatment of psoriatic arthritis comprises one or more sgRNAs targeting exon 6 of hTNFRSF3. In some embodiments, the CRISPR gene-editing system for the treatment of psoriatic arthritis comprises one or more sgRNAs targeting exon 7 of hTNFRSF3. In some embodiments, the CRISPR gene-editing system for the treatment of psoriatic arthritis comprises one or more sgRNAs targeting exon 8 of hTNFRSF3. In some embodiments, the CRISPR gene-editing system for the treatment of psoriatic arthritis comprises one or more sgRNAs targeting exon 9 of hTNFRSF3. In some embodiments, the CRISPR gene-editing system for the treatment of psoriatic arthritis comprises one or more sgRNAs targeting exon 10 of hTNFRSF3. In some embodiments, the CRISPR gene-editing system for the treatment of psoriatic arthritis comprises one or more sgRNAs targeting exon 11 of hTNFRSF3. In some embodiments, the CRISPR gene-editing system for the treatment of psoriatic arthritis comprises one or more sgRNAs targeting exon 12 of hTNFRSF3.

[00277] In some embodiments, the CRISPR gene-editing system for the treatment of psoriatic arthritis comprises one or more sgRNAs targeting exon 1 of cTNFRSF3. In some embodiments, the CRISPR gene-editing system for the treatment of psoriatic arthritis comprises one or more sgRNAs targeting exon 2 of cTNFRSF3. In some embodiments, the CRISPR gene-editing system for the treatment of psoriatic arthritis comprises one or more

sgRNAs targeting exon 3 of cTNFRSF3. In some embodiments, the CRISPR gene-editing system for the treatment of psoriatic arthritis comprises one or more sgRNAs targeting exon 4 of cTNFRSF3. In some embodiments, the CRISPR gene-editing system for the treatment of psoriatic arthritis comprises one or more sgRNAs targeting exon 5 of cTNFRSF3. In some embodiments, the CRISPR gene-editing system for the treatment of psoriatic arthritis comprises one or more sgRNAs targeting exon 6 of cTNFRSF3. In some embodiments, the CRISPR gene-editing system for the treatment of psoriatic arthritis comprises one or more sgRNAs targeting exon 7 of cTNFRSF3. In some embodiments, the CRISPR gene-editing system for the treatment of psoriatic arthritis comprises one or more sgRNAs targeting exon 8 of cTNFRSF3. In some embodiments, the CRISPR gene-editing system for the treatment of psoriatic arthritis comprises one or more sgRNAs targeting exon 9 of cTNFRSF3. In some embodiments, the CRISPR gene-editing system for the treatment of psoriatic arthritis comprises one or more sgRNAs targeting exon 10 of cTNFRSF3.

[00278] In some embodiments, the CRISPR gene-editing system for the treatment of psoriatic arthritis comprises one or more sgRNAs targeting exon 1 of eTNFRSF3. In some embodiments, the CRISPR gene-editing system for the treatment of psoriatic arthritis comprises one or more sgRNAs targeting exon 2 of eTNFRSF3. In some embodiments, the CRISPR gene-editing system for the treatment of psoriatic arthritis comprises one or more sgRNAs targeting exon 3 of eTNFRSF3. In some embodiments, the CRISPR gene-editing system for the treatment of psoriatic arthritis comprises one or more sgRNAs targeting exon 4 of eTNFRSF3. In some embodiments, the CRISPR gene-editing system for the treatment of psoriatic arthritis comprises one or more sgRNAs targeting exon 5 of eTNFRSF3. In some embodiments, the CRISPR gene-editing system for the treatment of psoriatic arthritis comprises one or more sgRNAs targeting exon 6 of eTNFRSF3. In some embodiments, the CRISPR gene-editing system for the treatment of psoriatic arthritis comprises one or more sgRNAs targeting exon 7 of eTNFRSF3. In some embodiments, the CRISPR gene-editing system for the treatment of psoriatic arthritis comprises one or more sgRNAs targeting exon 8 of eTNFRSF3. In some embodiments, the CRISPR gene-editing system for the treatment of psoriatic arthritis comprises one or more sgRNAs targeting exon 9 of eTNFRSF3. In some embodiments, the CRISPR gene-editing system for the treatment of psoriatic arthritis comprises one or more sgRNAs targeting exon 10 of eTNFRSF3.

[00279] In some embodiments, the CRISPR gene-editing system for the treatment of psoriatic arthritis comprises one or more sgRNAs targeting exon 1 of fTNFRSF3. In some

embodiments, the CRISPR gene-editing system for the treatment of psoriatic arthritis comprises one or more sgRNAs targeting exon 2 of fTNFRSF3. In some embodiments, the CRISPR gene-editing system for the treatment of psoriatic arthritis comprises one or more sgRNAs targeting exon 3 of fTNFRSF3. In some embodiments, the CRISPR gene-editing system for the treatment of psoriatic arthritis comprises one or more sgRNAs targeting exon 4 of fTNFRSF3. In some embodiments, the CRISPR gene-editing system for the treatment of psoriatic arthritis comprises one or more sgRNAs targeting exon 5 of fTNFRSF3. In some embodiments, the CRISPR gene-editing system for the treatment of psoriatic arthritis comprises one or more sgRNAs targeting exon 6 of fTNFRSF3. In some embodiments, the CRISPR gene-editing system for the treatment of psoriatic arthritis comprises one or more sgRNAs targeting exon 7 of fTNFRSF3. In some embodiments, the CRISPR gene-editing system for the treatment of psoriatic arthritis comprises one or more sgRNAs targeting exon 8 of fTNFRSF3. In some embodiments, the CRISPR gene-editing system for the treatment of psoriatic arthritis comprises one or more sgRNAs targeting exon 9 of fTNFRSF3. In some embodiments, the CRISPR gene-editing system for the treatment of psoriatic arthritis comprises one or more sgRNAs targeting exon 10 of fTNFRSF3.

[00280] In some embodiments, the CRISPR gene-editing system for the treatment of psoriatic arthritis comprises one or more sgRNAs targeting TNFRSF4. In some embodiments, the CRISPR gene-editing system for the treatment of psoriatic arthritis comprises one or more sgRNAs targeting hTNFRSF4. In some embodiments, the CRISPR gene-editing system for the treatment of psoriatic arthritis comprises one or more sgRNAs targeting cTNFRSF4. In some embodiments, the CRISPR gene-editing system for the treatment of psoriatic arthritis comprises one or more sgRNAs targeting eTNFRSF4. In some embodiments, the CRISPR gene-editing system for the treatment of psoriatic arthritis comprises one or more sgRNAs targeting fTNFRSF4.

[00281] In some embodiments, the CRISPR gene-editing system for the treatment of psoriatic arthritis comprises one or more sgRNAs targeting exon 1 of hTNFRSF4. In some embodiments, the CRISPR gene-editing system for the treatment of psoriatic arthritis comprises one or more sgRNAs targeting exon 2 of hTNFRSF4. In some embodiments, the CRISPR gene-editing system for the treatment of psoriatic arthritis comprises one or more sgRNAs targeting exon 3 of hTNFRSF4. In some embodiments, the CRISPR gene-editing system for the treatment of psoriatic arthritis comprises one or more sgRNAs targeting exon 4 of hTNFRSF4. In some embodiments, the CRISPR gene-editing system for the treatment of

psoriatic arthritis comprises one or more sgRNAs targeting exon 5 of hTNFRSF4. In some embodiments, the CRISPR gene-editing system for the treatment of psoriatic arthritis comprises one or more sgRNAs targeting exon 6 of hTNFRSF4.

[00282] In some embodiments, the CRISPR gene-editing system for the treatment of psoriatic arthritis comprises one or more sgRNAs targeting exon 1 of cTNFRSF4. In some embodiments, the CRISPR gene-editing system for the treatment of psoriatic arthritis comprises one or more sgRNAs targeting exon 2 of cTNFRSF4. In some embodiments, the CRISPR gene-editing system for the treatment of psoriatic arthritis comprises one or more sgRNAs targeting exon 3 of cTNFRSF4. In some embodiments, the CRISPR gene-editing system for the treatment of psoriatic arthritis comprises one or more sgRNAs targeting exon 4 of cTNFRSF4. In some embodiments, the CRISPR gene-editing system for the treatment of psoriatic arthritis comprises one or more sgRNAs targeting exon 5 of cTNFRSF4. In some embodiments, the CRISPR gene-editing system for the treatment of psoriatic arthritis comprises one or more sgRNAs targeting exon 6 of cTNFRSF4. In some embodiments, the CRISPR gene-editing system for the treatment of psoriatic arthritis comprises one or more sgRNAs targeting exon 7 of cTNFRSF4.

[00283] In some embodiments, the CRISPR gene-editing system for the treatment of psoriatic arthritis comprises one or more sgRNAs targeting exon 1 of eTNFRSF4. In some embodiments, the CRISPR gene-editing system for the treatment of psoriatic arthritis comprises one or more sgRNAs targeting exon 2 of eTNFRSF4. In some embodiments, the CRISPR gene-editing system for the treatment of psoriatic arthritis comprises one or more sgRNAs targeting exon 3 of eTNFRSF4. In some embodiments, the CRISPR gene-editing system for the treatment of psoriatic arthritis comprises one or more sgRNAs targeting exon 4 of eTNFRSF4. In some embodiments, the CRISPR gene-editing system for the treatment of psoriatic arthritis comprises one or more sgRNAs targeting exon 5 of eTNFRSF4. In some embodiments, the CRISPR gene-editing system for the treatment of psoriatic arthritis comprises one or more sgRNAs targeting exon 6 of eTNFRSF4. In some embodiments, the CRISPR gene-editing system for the treatment of psoriatic arthritis comprises one or more sgRNAs targeting exon 7 of eTNFRSF4.

[00284] In some embodiments, the CRISPR gene-editing system for the treatment of psoriatic arthritis comprises one or more sgRNAs targeting exon 1 of fTNFRSF4. In some embodiments, the CRISPR gene-editing system for the treatment of psoriatic arthritis comprises one or more sgRNAs targeting exon 2 of fTNFRSF4. In some embodiments, the

CRISPR gene-editing system for the treatment of psoriatic arthritis comprises one or more sgRNAs targeting exon 3 of fTNFRSF4. In some embodiments, the CRISPR gene-editing system for the treatment of psoriatic arthritis comprises one or more sgRNAs targeting exon 4 of fTNFRSF4. In some embodiments, the CRISPR gene-editing system for the treatment of psoriatic arthritis comprises one or more sgRNAs targeting exon 5 of fTNFRSF4. In some embodiments, the CRISPR gene-editing system for the treatment of psoriatic arthritis comprises one or more sgRNAs targeting exon 6 of fTNFRSF4. In some embodiments, the CRISPR gene-editing system for the treatment of psoriatic arthritis comprises one or more sgRNAs targeting exon 7 of fTNFRSF4.

[00285] In some embodiments, the CRISPR gene-editing system for the treatment of psoriatic arthritis comprises one or more sgRNAs targeting TNFRSF11A. In some embodiments, the CRISPR gene-editing system for the treatment of psoriatic arthritis comprises one or more sgRNAs targeting hTNFRSF11A. In some embodiments, the CRISPR gene-editing system for the treatment of psoriatic arthritis comprises one or more sgRNAs targeting cTNFRSF11A. In some embodiments, the CRISPR gene-editing system for the treatment of psoriatic arthritis comprises one or more sgRNAs targeting eTNFRSF11A. In some embodiments, the CRISPR gene-editing system for the treatment of psoriatic arthritis comprises one or more sgRNAs targeting fTNFRSF11A.

[00286] In some embodiments, the CRISPR gene-editing system for the treatment of psoriatic arthritis comprises one or more sgRNAs targeting exon 1 of hTNFRSF11A. In some embodiments, the CRISPR gene-editing system for the treatment of psoriatic arthritis comprises one or more sgRNAs targeting exon 2 of hTNFRSF11A. In some embodiments, the CRISPR gene-editing system for the treatment of psoriatic arthritis comprises one or more sgRNAs targeting exon 3 of hTNFRSF11A. In some embodiments, the CRISPR gene-editing system for the treatment of psoriatic arthritis comprises one or more sgRNAs targeting exon 4 of hTNFRSF11A. In some embodiments, the CRISPR gene-editing system for the treatment of psoriatic arthritis comprises one or more sgRNAs targeting exon 5 of hTNFRSF11A. In some embodiments, the CRISPR gene-editing system for the treatment of psoriatic arthritis comprises one or more sgRNAs targeting exon 6 of hTNFRSF11A. In some embodiments, the CRISPR gene-editing system for the treatment of psoriatic arthritis comprises one or more sgRNAs targeting exon 7 of hTNFRSF11A. In some embodiments, the CRISPR gene-editing system for the treatment of psoriatic arthritis comprises one or more sgRNAs targeting exon 8 of hTNFRSF11A. In some embodiments, the CRISPR gene-

editing system for the treatment of psoriatic arthritis comprises one or more sgRNAs targeting exon 9 of hTNFRSF11A. In some embodiments, the CRISPR gene-editing system for the treatment of psoriatic arthritis comprises one or more sgRNAs targeting exon 10 of hTNFRSF11A. In some embodiments, the CRISPR gene-editing system for the treatment of psoriatic arthritis comprises one or more sgRNAs targeting exon 11 of hTNFRSF11A. In some embodiments, the CRISPR gene-editing system for the treatment of psoriatic arthritis comprises one or more sgRNAs targeting exon 12 of hTNFRSF11A.

[00287] In some embodiments, the CRISPR gene-editing system for the treatment of psoriatic arthritis comprises one or more sgRNAs targeting exon 1 of cTNFRSF11A. In some embodiments, the CRISPR gene-editing system for the treatment of psoriatic arthritis comprises one or more sgRNAs targeting exon 2 of cTNFRSF11A. In some embodiments, the CRISPR gene-editing system for the treatment of psoriatic arthritis comprises one or more sgRNAs targeting exon 3 of cTNFRSF11A. In some embodiments, the CRISPR gene-editing system for the treatment of psoriatic arthritis comprises one or more sgRNAs targeting exon 4 of cTNFRSF11A. In some embodiments, the CRISPR gene-editing system for the treatment of psoriatic arthritis comprises one or more sgRNAs targeting exon 5 of cTNFRSF11A. In some embodiments, the CRISPR gene-editing system for the treatment of psoriatic arthritis comprises one or more sgRNAs targeting exon 6 of cTNFRSF11A. In some embodiments, the CRISPR gene-editing system for the treatment of psoriatic arthritis comprises one or more sgRNAs targeting exon 7 of cTNFRSF11A. In some embodiments, the CRISPR gene-editing system for the treatment of psoriatic arthritis comprises one or more sgRNAs targeting exon 8 of cTNFRSF11A. In some embodiments, the CRISPR gene-editing system for the treatment of psoriatic arthritis comprises one or more sgRNAs targeting exon 9 of cTNFRSF11A. In some embodiments, the CRISPR gene-editing system for the treatment of psoriatic arthritis comprises one or more sgRNAs targeting exon 10 of cTNFRSF11A. In some embodiments, the CRISPR gene-editing system for the treatment of psoriatic arthritis comprises one or more sgRNAs targeting exon 11 of cTNFRSF11A.

[00288] In some embodiments, the CRISPR gene-editing system for the treatment of psoriatic arthritis comprises one or more sgRNAs targeting exon 1 of eTNFRSF11A. In some embodiments, the CRISPR gene-editing system for the treatment of psoriatic arthritis comprises one or more sgRNAs targeting exon 2 of eTNFRSF11A. In some embodiments, the CRISPR gene-editing system for the treatment of psoriatic arthritis comprises one or more sgRNAs targeting exon 3 of eTNFRSF11A. In some embodiments, the CRISPR gene-

editing system for the treatment of psoriatic arthritis comprises one or more sgRNAs targeting exon 4 of eTNFRSF11A. In some embodiments, the CRISPR gene-editing system for the treatment of psoriatic arthritis comprises one or more sgRNAs targeting exon 5 of eTNFRSF11A. In some embodiments, the CRISPR gene-editing system for the treatment of psoriatic arthritis comprises one or more sgRNAs targeting exon 6 of eTNFRSF11A. In some embodiments, the CRISPR gene-editing system for the treatment of psoriatic arthritis comprises one or more sgRNAs targeting exon 7 of eTNFRSF11A. In some embodiments, the CRISPR gene-editing system for the treatment of psoriatic arthritis comprises one or more sgRNAs targeting exon 8 of eTNFRSF11A. In some embodiments, the CRISPR gene-editing system for the treatment of psoriatic arthritis comprises one or more sgRNAs targeting exon 9 of eTNFRSF11A. In some embodiments, the CRISPR gene-editing system for the treatment of psoriatic arthritis comprises one or more sgRNAs targeting exon 10 of eTNFRSF11A.

[00289] In some embodiments, the CRISPR gene-editing system for the treatment of psoriatic arthritis comprises one or more sgRNAs targeting exon 1 of fTNFRSF11A. In some embodiments, the CRISPR gene-editing system for the treatment of psoriatic arthritis comprises one or more sgRNAs targeting exon 2 of fTNFRSF11A. In some embodiments, the CRISPR gene-editing system for the treatment of psoriatic arthritis comprises one or more sgRNAs targeting exon 3 of fTNFRSF11A. In some embodiments, the CRISPR gene-editing system for the treatment of psoriatic arthritis comprises one or more sgRNAs targeting exon 4 of fTNFRSF11A. In some embodiments, the CRISPR gene-editing system for the treatment of psoriatic arthritis comprises one or more sgRNAs targeting exon 5 of fTNFRSF11A. In some embodiments, the CRISPR gene-editing system for the treatment of psoriatic arthritis comprises one or more sgRNAs targeting exon 6 of fTNFRSF11A. In some embodiments, the CRISPR gene-editing system for the treatment of psoriatic arthritis comprises one or more sgRNAs targeting exon 7 of fTNFRSF11A. In some embodiments, the CRISPR gene-editing system for the treatment of psoriatic arthritis comprises one or more sgRNAs targeting exon 8 of fTNFRSF11A. In some embodiments, the CRISPR gene-editing system for the treatment of psoriatic arthritis comprises one or more sgRNAs targeting exon 9 of fTNFRSF11A. In some embodiments, the CRISPR gene-editing system for the treatment of psoriatic arthritis comprises one or more sgRNAs targeting exon 10 of fTNFRSF11A. In some embodiments, the CRISPR gene-editing system for the treatment of psoriatic arthritis comprises one or more sgRNAs targeting exon 11 of fTNFRSF11A.

D. Gout

[00290] In one aspect, the present disclosure encompasses treatments for gout and other crystallopathies affecting the joint, e.g., octacalcium phosphate and calcium pyrophosphate dihydrate in horses. In some embodiments, the gout treatment comprises a therapeutically effective amount of a Clustered Regularly Interspaced Short Palindromic Repeats (CRISPR) gene-editing system, the system comprising: (i) a CRISPR Associated (Cas) protein; and (ii) at least one guide RNA targeting IL1R1. In some embodiments, the gout treatment comprises a CRISPR gene-editing system targeting hIL1R1. In some embodiments, the gout treatment comprises a CRISPR gene-editing system targeting cIL1R1. In some embodiments, the gout treatment comprises a CRISP gene-editing system R targeting eIL1R1. In some embodiments, the gout treatment comprises a CRISPR gene-editing system targeting fIL1R1.

[00291] In some embodiments, the CRISPR gene-editing system for the treatment of gout comprises one or more sgRNAs targeting exon 1 of hIL1R1. In some embodiments, the CRISPR gene-editing system for the treatment of gout comprises one or more sgRNAs targeting exon 2 of hIL1R1. In some embodiments, the CRISPR gene-editing system for the treatment of gout comprises one or more sgRNAs targeting exon 3 of hIL1R1. In some embodiments, the CRISPR gene-editing system for the treatment of gout comprises one or more sgRNAs targeting exon 4 of hIL1R1. In some embodiments, the CRISPR gene-editing system for the treatment of gout comprises one or more sgRNAs targeting exon 5 of hIL1R1. In some embodiments, the CRISPR gene-editing system for the treatment of gout comprises one or more sgRNAs targeting exon 6 of hIL1R1. In some embodiments, the CRISPR gene-editing system for the treatment of gout comprises one or more sgRNAs targeting exon 7 of hIL1R1. In some embodiments, the CRISPR gene-editing system for the treatment of gout comprises one or more sgRNAs targeting exon 8 of hIL1R1. In some embodiments, the CRISPR gene-editing system for the treatment of gout comprises one or more sgRNAs targeting exon 9 of hIL1R1. In some embodiments, the CRISPR gene-editing system for the treatment of gout comprises one or more sgRNAs targeting exon 10 of hIL1R1. In some embodiments, the CRISPR gene-editing system for the treatment of gout comprises one or more sgRNAs targeting exon 11 of hIL1R1. In some embodiments, the CRISPR gene-editing system for the treatment of gout comprises one or more sgRNAs targeting exon 12 of hIL1R1. In some embodiments, the CRISPR gene-editing system for the treatment of gout comprises one or more sgRNAs targeting exon 13 of hIL1R1. In some embodiments, the

CRISPR gene-editing system for the treatment of gout comprises one or more sgRNAs targeting exon 14 of hIL1R1. In some embodiments, the CRISPR gene-editing system for the treatment of gout comprises one or more sgRNAs targeting exon 15 of hIL1R1. In some embodiments, the CRISPR gene-editing system for the treatment of gout comprises one or more sgRNAs targeting exon 16 of hIL1R1. In some embodiments, the CRISPR gene-editing system for the treatment of gout comprises one or more sgRNAs targeting exon 17 of hIL1R1. In some embodiments, the CRISPR gene-editing system for the treatment of gout comprises one or more sgRNAs targeting exon 18 of hIL1R1. In some embodiments, the CRISPR gene-editing system for the treatment of gout comprises one or more sgRNAs targeting exon 19 of hIL1R1. In some embodiments, the CRISPR gene-editing system for the treatment of gout comprises one or more sgRNAs targeting exon 20 of hIL1R1. In some embodiments, the CRISPR gene-editing system for the treatment of gout comprises one or more sgRNAs targeting exon 21 of hIL1R1.

[00292] In some embodiments, the CRISPR gene-editing system for the treatment of gout comprises one or more sgRNAs targeting exon 1 of cIL1R1. In some embodiments, the CRISPR gene-editing system for the treatment of gout comprises one or more sgRNAs targeting exon 2 of cIL1R1. In some embodiments, the CRISPR gene-editing system for the treatment of gout comprises one or more sgRNAs targeting exon 3 of cIL1R1. In some embodiments, the CRISPR gene-editing system for the treatment of gout comprises one or more sgRNAs targeting exon 4 of cIL1R1. In some embodiments, the CRISPR gene-editing system for the treatment of gout comprises one or more sgRNAs targeting exon 5 of cIL1R1. In some embodiments, the CRISPR gene-editing system for the treatment of gout comprises one or more sgRNAs targeting exon 6 of cIL1R1. In some embodiments, the CRISPR gene-editing system for the treatment of gout comprises one or more sgRNAs targeting exon 7 of cIL1R1. In some embodiments, the CRISPR gene-editing system for the treatment of gout comprises one or more sgRNAs targeting exon 8 of cIL1R1. In some embodiments, the CRISPR gene-editing system for the treatment of gout comprises one or more sgRNAs targeting exon 9 of cIL1R1. In some embodiments, the CRISPR gene-editing system for the treatment of gout comprises one or more sgRNAs targeting exon 10 of cIL1R1. In some embodiments, the CRISPR gene-editing system for the treatment of gout comprises one or more sgRNAs targeting exon 11 of cIL1R1. In some embodiments, the CRISPR gene-editing system for the treatment of gout comprises one or more sgRNAs targeting exon 12 of cIL1R1. In some embodiments, the CRISPR gene-editing system for the treatment of gout

comprises one or more sgRNAs targeting exon 13 of cIL1R1. In some embodiments, the CRISPR gene-editing system for the treatment of gout comprises one or more sgRNAs targeting exon 14 of cIL1R1. In some embodiments, the CRISPR gene-editing system for the treatment of gout comprises one or more sgRNAs targeting exon 15 of cIL1R1. In some embodiments, the CRISPR gene-editing system for the treatment of gout comprises one or more sgRNAs targeting exon 16 of cIL1R1.

[00293] In some embodiments, the CRISPR gene-editing system for the treatment of gout comprises one or more sgRNAs targeting exon 1 of eIL1R1. In some embodiments, the CRISPR gene-editing system for the treatment of gout comprises one or more sgRNAs targeting exon 2 of eIL1R1. In some embodiments, the CRISPR gene-editing system for the treatment of gout comprises one or more sgRNAs targeting exon 3 of eIL1R1. In some embodiments, the CRISPR gene-editing system for the treatment of gout comprises one or more sgRNAs targeting exon 4 of eIL1R1. In some embodiments, the CRISPR gene-editing system for the treatment of gout comprises one or more sgRNAs targeting exon 5 of eIL1R1. In some embodiments, the CRISPR gene-editing system for the treatment of gout comprises one or more sgRNAs targeting exon 6 of eIL1R1. In some embodiments, the CRISPR gene-editing system for the treatment of gout comprises one or more sgRNAs targeting exon 7 of eIL1R1. In some embodiments, the CRISPR gene-editing system for the treatment of gout comprises one or more sgRNAs targeting exon 8 of eIL1R1. In some embodiments, the CRISPR gene-editing system for the treatment of gout comprises one or more sgRNAs targeting exon 9 of eIL1R1. In some embodiments, the CRISPR gene-editing system for the treatment of gout comprises one or more sgRNAs targeting exon 10 of eIL1R1. In some embodiments, the CRISPR gene-editing system for the treatment of gout comprises one or more sgRNAs targeting exon 11 of eIL1R1. In some embodiments, the CRISPR gene-editing system for the treatment of gout comprises one or more sgRNAs targeting exon 12 of eIL1R1. In some embodiments, the CRISPR gene-editing system for the treatment of gout comprises one or more sgRNAs targeting exon 13 of eIL1R1. In some embodiments, the CRISPR gene-editing system for the treatment of gout comprises one or more sgRNAs targeting exon 14 of eIL1R1. In some embodiments, the CRISPR gene-editing system for the treatment of gout comprises one or more sgRNAs targeting exon 15 of eIL1R1.

[00294] In some embodiments, the CRISPR gene-editing system for the treatment of gout comprises one or more sgRNAs targeting exon 1 of fIL1R1. In some embodiments, the CRISPR gene-editing system for the treatment of gout comprises one or more sgRNAs

targeting exon 2 of fIL1R1. In some embodiments, the CRISPR gene-editing system for the treatment of gout comprises one or more sgRNAs targeting exon 3 of fIL1R1. In some embodiments, the CRISPR gene-editing system for the treatment of gout comprises one or more sgRNAs targeting exon 4 of fIL1R1. In some embodiments, the CRISPR gene-editing system for the treatment of gout comprises one or more sgRNAs targeting exon 5 of fIL1R1. In some embodiments, the CRISPR gene-editing system for the treatment of gout comprises one or more sgRNAs targeting exon 6 of fIL1R1. In some embodiments, the CRISPR gene-editing system for the treatment of gout comprises one or more sgRNAs targeting exon 7 of fIL1R1. In some embodiments, the CRISPR gene-editing system for the treatment of gout comprises one or more sgRNAs targeting exon 8 of fIL1R1. In some embodiments, the CRISPR gene-editing system for the treatment of gout comprises one or more sgRNAs targeting exon 9 of fIL1R1. In some embodiments, the CRISPR gene-editing system for the treatment of gout comprises one or more sgRNAs targeting exon 10 of fIL1R1. In some embodiments, the CRISPR gene-editing system for the treatment of gout comprises one or more sgRNAs targeting exon 11 of fIL1R1. In some embodiments, the CRISPR gene-editing system for the treatment of gout comprises one or more sgRNAs targeting exon 12 of fIL1R1. In some embodiments, the CRISPR gene-editing system for the treatment of gout comprises one or more sgRNAs targeting exon 13 of fIL1R1. In some embodiments, the CRISPR gene-editing system for the treatment of gout comprises one or more sgRNAs targeting exon 14 of fIL1R1. In some embodiments, the CRISPR gene-editing system for the treatment of gout comprises one or more sgRNAs targeting exon 15 of fIL1R1. In some embodiments, the CRISPR gene-editing system for the treatment of gout comprises one or more sgRNAs targeting exon 16 of fIL1R1. In some embodiments, the CRISPR gene-editing system for the treatment of gout comprises one or more sgRNAs targeting exon 17 of fIL1R1. In some embodiments, the CRISPR gene-editing system for the treatment of gout comprises one or more sgRNAs targeting exon 18 of fIL1R1.

[00295] In some embodiments, the CRISPR gene-editing system for the treatment of gout comprises one or more sgRNAs targeting IL1RAP. In some embodiments, the CRISPR gene-editing system for the treatment of gout comprises one or more sgRNAs targeting hIL1RAP. In some embodiments, the CRISPR gene-editing system for the treatment of gout comprises one or more sgRNAs targeting cIL1RAP. In some embodiments, the CRISPR gene-editing system for the treatment of gout comprises one or more sgRNAs targeting

eIL1RAP. In some embodiments, the CRISPR gene-editing system for the treatment of gout comprises one or more sgRNAs targeting fIL1RAP.

[00296] In some embodiments, the CRISPR gene-editing system for the treatment of gout comprises one or more sgRNAs targeting exon 1 of hIL1RAP. In some embodiments, the CRISPR gene-editing system for the treatment of gout comprises one or more sgRNAs targeting exon 2 of hIL1RAP. In some embodiments, the CRISPR gene-editing system for the treatment of gout comprises one or more sgRNAs targeting exon 3 of hIL1RAP. In some embodiments, the CRISPR gene-editing system for the treatment of gout comprises one or more sgRNAs targeting exon 4 of hIL1RAP. In some embodiments, the CRISPR gene-editing system for the treatment of gout comprises one or more sgRNAs targeting exon 5 of hIL1RAP. In some embodiments, the CRISPR gene-editing system for the treatment of gout comprises one or more sgRNAs targeting exon 6 of hIL1RAP. In some embodiments, the CRISPR gene-editing system for the treatment of gout comprises one or more sgRNAs targeting exon 7 of hIL1RAP. In some embodiments, the CRISPR gene-editing system for the treatment of gout comprises one or more sgRNAs targeting exon 8 of hIL1RAP. In some embodiments, the CRISPR gene-editing system for the treatment of gout comprises one or more sgRNAs targeting exon 9 of hIL1RAP. In some embodiments, the CRISPR gene-editing system for the treatment of gout comprises one or more sgRNAs targeting exon 10 of hIL1RAP. In some embodiments, the CRISPR gene-editing system for the treatment of gout comprises one or more sgRNAs targeting exon 11 of hIL1RAP. In some embodiments, the CRISPR gene-editing system for the treatment of gout comprises one or more sgRNAs targeting exon 12 of hIL1RAP. In some embodiments, the CRISPR gene-editing system for the treatment of gout comprises one or more sgRNAs targeting exon 13 of hIL1RAP. In some embodiments, the CRISPR gene-editing system for the treatment of gout comprises one or more sgRNAs targeting exon 14 of hIL1RAP. In some embodiments, the CRISPR gene-editing system for the treatment of gout comprises one or more sgRNAs targeting exon 15 of hIL1RAP. In some embodiments, the CRISPR gene-editing system for the treatment of gout comprises one or more sgRNAs targeting exon 16 of hIL1RAP. In some embodiments, the CRISPR gene-editing system for the treatment of gout comprises one or more sgRNAs targeting exon 17 of hIL1RAP.

[00297] In some embodiments, the CRISPR gene-editing system for the treatment of gout comprises one or more sgRNAs targeting exon 1 of cIL1RAP. In some embodiments, the CRISPR gene-editing system for the treatment of gout comprises one or more sgRNAs

targeting exon 2 of cIL1RAP. In some embodiments, the CRISPR gene-editing system for the treatment of gout comprises one or more sgRNAs targeting exon 3 of cIL1RAP. In some embodiments, the CRISPR gene-editing system for the treatment of gout comprises one or more sgRNAs targeting exon 4 of cIL1RAP. In some embodiments, the CRISPR gene-editing system for the treatment of gout comprises one or more sgRNAs targeting exon 5 of cIL1RAP. In some embodiments, the CRISPR gene-editing system for the treatment of gout comprises one or more sgRNAs targeting exon 6 of cIL1RAP. In some embodiments, the CRISPR gene-editing system for the treatment of gout comprises one or more sgRNAs targeting exon 7 of cIL1RAP. In some embodiments, the CRISPR gene-editing system for the treatment of gout comprises one or more sgRNAs targeting exon 8 of cIL1RAP. In some embodiments, the CRISPR gene-editing system for the treatment of gout comprises one or more sgRNAs targeting exon 9 of cIL1RAP. In some embodiments, the CRISPR gene-editing system for the treatment of gout comprises one or more sgRNAs targeting exon 10 of cIL1RAP. In some embodiments, the CRISPR gene-editing system for the treatment of gout comprises one or more sgRNAs targeting exon 11 of cIL1RAP. In some embodiments, the CRISPR gene-editing system for the treatment of gout comprises one or more sgRNAs targeting exon 12 of cIL1RAP. In some embodiments, the CRISPR gene-editing system for the treatment of gout comprises one or more sgRNAs targeting exon 13 of cIL1RAP. In some embodiments, the CRISPR gene-editing system for the treatment of gout comprises one or more sgRNAs targeting exon 14 of cIL1RAP. In some embodiments, the CRISPR gene-editing system for the treatment of gout comprises one or more sgRNAs targeting exon 15 of cIL1RAP. In some embodiments, the CRISPR gene-editing system for the treatment of gout comprises one or more sgRNAs targeting exon 16 of cIL1RAP.

[00298] In some embodiments, the CRISPR gene-editing system for the treatment of gout comprises one or more sgRNAs targeting exon 1 of eIL1RAP. In some embodiments, the CRISPR gene-editing system for the treatment of gout comprises one or more sgRNAs targeting exon 2 of eIL1RAP. In some embodiments, the CRISPR gene-editing system for the treatment of gout comprises one or more sgRNAs targeting exon 3 of eIL1RAP. In some embodiments, the CRISPR gene-editing system for the treatment of gout comprises one or more sgRNAs targeting exon 4 of eIL1RAP. In some embodiments, the CRISPR gene-editing system for the treatment of gout comprises one or more sgRNAs targeting exon 5 of eIL1RAP. In some embodiments, the CRISPR gene-editing system for the treatment of gout comprises one or more sgRNAs targeting exon 6 of eIL1RAP. In some embodiments, the

CRISPR gene-editing system for the treatment of gout comprises one or more sgRNAs targeting exon 7 of eIL1RAP. In some embodiments, the CRISPR gene-editing system for the treatment of gout comprises one or more sgRNAs targeting exon 8 of eIL1RAP. In some embodiments, the CRISPR gene-editing system for the treatment of gout comprises one or more sgRNAs targeting exon 9 of eIL1RAP. In some embodiments, the CRISPR gene-editing system for the treatment of gout comprises one or more sgRNAs targeting exon 10 of eIL1RAP. In some embodiments, the CRISPR gene-editing system for the treatment of gout comprises one or more sgRNAs targeting exon 11 of eIL1RAP. In some embodiments, the CRISPR gene-editing system for the treatment of gout comprises one or more sgRNAs targeting exon 12 of eIL1RAP. In some embodiments, the CRISPR gene-editing system for the treatment of gout comprises one or more sgRNAs targeting exon 13 of eIL1RAP.

[00299] In some embodiments, the CRISPR gene-editing system for the treatment of gout comprises one or more sgRNAs targeting exon 1 of fIL1RAP. In some embodiments, the CRISPR gene-editing system for the treatment of gout comprises one or more sgRNAs targeting exon 2 of fIL1RAP. In some embodiments, the CRISPR gene-editing system for the treatment of gout comprises one or more sgRNAs targeting exon 3 of fIL1RAP. In some embodiments, the CRISPR gene-editing system for the treatment of gout comprises one or more sgRNAs targeting exon 4 of fIL1RAP. In some embodiments, the CRISPR gene-editing system for the treatment of gout comprises one or more sgRNAs targeting exon 5 of fIL1RAP. In some embodiments, the CRISPR gene-editing system for the treatment of gout comprises one or more sgRNAs targeting exon 6 of fIL1RAP. In some embodiments, the CRISPR gene-editing system for the treatment of gout comprises one or more sgRNAs targeting exon 7 of fIL1RAP. In some embodiments, the CRISPR gene-editing system for the treatment of gout comprises one or more sgRNAs targeting exon 8 of fIL1RAP. In some embodiments, the CRISPR gene-editing system for the treatment of gout comprises one or more sgRNAs targeting exon 9 of fIL1RAP. In some embodiments, the CRISPR gene-editing system for the treatment of gout comprises one or more sgRNAs targeting exon 10 of fIL1RAP. In some embodiments, the CRISPR gene-editing system for the treatment of gout comprises one or more sgRNAs targeting exon 11 of fIL1RAP. In some embodiments, the CRISPR gene-editing system for the treatment of gout comprises one or more sgRNAs targeting exon 12 of fIL1RAP. In some embodiments, the CRISPR gene-editing system for the treatment of gout comprises one or more sgRNAs targeting exon 13 of fIL1RAP. In

some embodiments, the CRISPR gene-editing system for the treatment of gout comprises one or more sgRNAs targeting exon 14 of fIL1RAP.

[00300] In some embodiments, the CRISPR gene-editing system for the treatment of gout comprises one or more sgRNAs targeting TGFBR1. In some embodiments, the CRISPR gene-editing system for the treatment of gout comprises one or more sgRNAs targeting hTGFBR1. In some embodiments, the CRISPR gene-editing system for the treatment of gout comprises one or more sgRNAs targeting cTGFBR1. In some embodiments, the CRISPR gene-editing system for the treatment of gout comprises one or more sgRNAs targeting e TGFBR1. In some embodiments, the CRISPR gene-editing system for the treatment of gout comprises one or more sgRNAs targeting fTGFBR1.

[00301] In some embodiments, the CRISPR gene-editing system for the treatment of gout comprises one or more sgRNAs targeting exon 1 of hTGFBR1. In some embodiments, the CRISPR gene-editing system for the treatment of gout comprises one or more sgRNAs targeting exon 2 of hTGFBR1. In some embodiments, the CRISPR gene-editing system for the treatment of gout comprises one or more sgRNAs targeting exon 3 of hTGFBR1. In some embodiments, the CRISPR gene-editing system for the treatment of gout comprises one or more sgRNAs targeting exon 4 of hTGFBR1. In some embodiments, the CRISPR gene-editing system for the treatment of gout comprises one or more sgRNAs targeting exon 5 of hTGFBR1. In some embodiments, the CRISPR gene-editing system for the treatment of gout comprises one or more sgRNAs targeting exon 6 of hTGFBR1. In some embodiments, the CRISPR gene-editing system for the treatment of gout comprises one or more sgRNAs targeting exon 7 of hTGFBR1. In some embodiments, the CRISPR gene-editing system for the treatment of gout comprises one or more sgRNAs targeting exon 8 of hTGFBR1. In some embodiments, the CRISPR gene-editing system for the treatment of gout comprises one or more sgRNAs targeting exon 9 of hTGFBR1. In some embodiments, the CRISPR gene-editing system for the treatment of gout comprises one or more sgRNAs targeting exon 10 of hTGFBR1. In some embodiments, the CRISPR gene-editing system for the treatment of gout comprises one or more sgRNAs targeting exon 11 of hTGFBR1.

[00302] In some embodiments, the CRISPR gene-editing system for the treatment of gout comprises one or more sgRNAs targeting exon 1 of cTGFBR1. In some embodiments, the CRISPR gene-editing system for the treatment of gout comprises one or more sgRNAs targeting exon 2 of cTGFBR1. In some embodiments, the CRISPR gene-editing system for the treatment of gout comprises one or more sgRNAs targeting exon 3 of cTGFBR1. In some

embodiments, the CRISPR gene-editing system for the treatment of gout comprises one or more sgRNAs targeting exon 4 of cTGFBR1. In some embodiments, the CRISPR gene-editing system for the treatment of gout comprises one or more sgRNAs targeting exon 5 of cTGFBR1. In some embodiments, the CRISPR gene-editing system for the treatment of gout comprises one or more sgRNAs targeting exon 6 of cTGFBR1. In some embodiments, the CRISPR gene-editing system for the treatment of gout comprises one or more sgRNAs targeting exon 7 of cTGFBR1. In some embodiments, the CRISPR gene-editing system for the treatment of gout comprises one or more sgRNAs targeting exon 8 of cTGFBR1. In some embodiments, the CRISPR gene-editing system for the treatment of gout comprises one or more sgRNAs targeting exon 9 of cTGFBR1.

[00303] In some embodiments, the CRISPR gene-editing system for the treatment of gout comprises one or more sgRNAs targeting exon 1 of eTGFBR1. In some embodiments, the CRISPR gene-editing system for the treatment of gout comprises one or more sgRNAs targeting exon 2 of eTGFBR1. In some embodiments, the CRISPR gene-editing system for the treatment of gout comprises one or more sgRNAs targeting exon 3 of eTGFBR1. In some embodiments, the CRISPR gene-editing system for the treatment of gout comprises one or more sgRNAs targeting exon 4 of eTGFBR1. In some embodiments, the CRISPR gene-editing system for the treatment of gout comprises one or more sgRNAs targeting exon 5 of eTGFBR1. In some embodiments, the CRISPR gene-editing system for the treatment of gout comprises one or more sgRNAs targeting exon 6 of eTGFBR1. In some embodiments, the CRISPR gene-editing system for the treatment of gout comprises one or more sgRNAs targeting exon 7 of eTGFBR1. In some embodiments, the CRISPR gene-editing system for the treatment of gout comprises one or more sgRNAs targeting exon 8 of eTGFBR1. In some embodiments, the CRISPR gene-editing system for the treatment of gout comprises one or more sgRNAs targeting exon 9 of eTGFBR1. In some embodiments, the CRISPR gene-editing system for the treatment of gout comprises one or more sgRNAs targeting exon 10 of eTGFBR1. In some embodiments, the CRISPR gene-editing system for the treatment of gout comprises one or more sgRNAs targeting exon 11 of eTGFBR1. In some embodiments, the CRISPR gene-editing system for the treatment of gout comprises one or more sgRNAs targeting exon 12 of eTGFBR1.

[00304] In some embodiments, the CRISPR gene-editing system for the treatment of gout comprises one or more sgRNAs targeting exon 1 of fTGFBR1. In some embodiments, the CRISPR gene-editing system for the treatment of gout comprises one or more sgRNAs

targeting exon 2 of fTGFBR1. In some embodiments, the CRISPR gene-editing system for the treatment of gout comprises one or more sgRNAs targeting exon 3 of fTGFBR1. In some embodiments, the CRISPR gene-editing system for the treatment of gout comprises one or more sgRNAs targeting exon 4 of fTGFBR1. In some embodiments, the CRISPR gene-editing system for the treatment of gout comprises one or more sgRNAs targeting exon 5 of fTGFBR1. In some embodiments, the CRISPR gene-editing system for the treatment of gout comprises one or more sgRNAs targeting exon 6 of fTGFBR1. In some embodiments, the CRISPR gene-editing system for the treatment of gout comprises one or more sgRNAs targeting exon 7 of fTGFBR1. In some embodiments, the CRISPR gene-editing system for the treatment of gout comprises one or more sgRNAs targeting exon 8 of fTGFBR1. In some embodiments, the CRISPR gene-editing system for the treatment of gout comprises one or more sgRNAs targeting exon 9 of fTGFBR1. In some embodiments, the CRISPR gene-editing system for the treatment of gout comprises one or more sgRNAs targeting exon 10 of fTGFBR1. In some embodiments, the CRISPR gene-editing system for the treatment of gout comprises one or more sgRNAs targeting exon 11 of fTGFBR1.

[00305] In some embodiments, the CRISPR gene-editing system for the treatment of gout comprises one or more sgRNAs targeting TGFBR2. In some embodiments, the CRISPR gene-editing system for the treatment of gout comprises one or more sgRNAs targeting hTGFBR2. In some embodiments, the CRISPR gene-editing system for the treatment of gout comprises one or more sgRNAs targeting cTGFBR2. In some embodiments, the CRISPR gene-editing system for the treatment of gout comprises one or more sgRNAs targeting eTGFBR2. In some embodiments, the CRISPR gene-editing system for the treatment of gout comprises one or more sgRNAs targeting fTGFBR2.

[00306] In some embodiments, the CRISPR gene-editing system for the treatment of gout comprises one or more sgRNAs targeting exon 1 of hTGFBR2. In some embodiments, the CRISPR gene-editing system for the treatment of gout comprises one or more sgRNAs targeting exon 2 of hTGFBR2. In some embodiments, the CRISPR gene-editing system for the treatment of gout comprises one or more sgRNAs targeting exon 3 of hTGFBR2. In some embodiments, the CRISPR gene-editing system for the treatment of gout comprises one or more sgRNAs targeting exon 4 of hTGFBR2. In some embodiments, the CRISPR gene-editing system for the treatment of gout comprises one or more sgRNAs targeting exon 5 of hTGFBR2. In some embodiments, the CRISPR gene-editing system for the treatment of gout comprises one or more sgRNAs targeting exon 6 of hTGFBR2. In some embodiments, the

CRISPR gene-editing system for the treatment of gout comprises one or more sgRNAs targeting exon 7 of hTGFBR2. In some embodiments, the CRISPR gene-editing system for the treatment of gout comprises one or more sgRNAs targeting exon 8 of hTGFBR2. In some embodiments, the CRISPR gene-editing system for the treatment of gout comprises one or more sgRNAs targeting exon 9 of hTGFBR2.

[00307] In some embodiments, the CRISPR gene-editing system for the treatment of gout comprises one or more sgRNAs targeting exon 1 of cTGFBR2. In some embodiments, the CRISPR gene-editing system for the treatment of gout comprises one or more sgRNAs targeting exon 2 of cTGFBR2. In some embodiments, the CRISPR gene-editing system for the treatment of gout comprises one or more sgRNAs targeting exon 3 of cTGFBR2. In some embodiments, the CRISPR gene-editing system for the treatment of gout comprises one or more sgRNAs targeting exon 4 of cTGFBR2. In some embodiments, the CRISPR gene-editing system for the treatment of gout comprises one or more sgRNAs targeting exon 5 of cTGFBR2. In some embodiments, the CRISPR gene-editing system for the treatment of gout comprises one or more sgRNAs targeting exon 6 of cTGFBR2. In some embodiments, the CRISPR gene-editing system for the treatment of gout comprises one or more sgRNAs targeting exon 7 of cTGFBR2. In some embodiments, the CRISPR gene-editing system for the treatment of gout comprises one or more sgRNAs targeting exon 8 of cTGFBR2.

[00308] In some embodiments, the CRISPR gene-editing system for the treatment of gout comprises one or more sgRNAs targeting exon 1 of eTGFBR2. In some embodiments, the CRISPR gene-editing system for the treatment of gout comprises one or more sgRNAs targeting exon 2 of eTGFBR2. In some embodiments, the CRISPR gene-editing system for the treatment of gout comprises one or more sgRNAs targeting exon 3 of eTGFBR2. In some embodiments, the CRISPR gene-editing system for the treatment of gout comprises one or more sgRNAs targeting exon 4 of eTGFBR2. In some embodiments, the CRISPR gene-editing system for the treatment of gout comprises one or more sgRNAs targeting exon 5 of eTGFBR2. In some embodiments, the CRISPR gene-editing system for the treatment of gout comprises one or more sgRNAs targeting exon 6 of eTGFBR2. In some embodiments, the CRISPR gene-editing system for the treatment of gout comprises one or more sgRNAs targeting exon 7 of eTGFBR2. In some embodiments, the CRISPR gene-editing system for the treatment of gout comprises one or more sgRNAs targeting exon 8 of eTGFBR2. In some embodiments, the CRISPR gene-editing system for the treatment of gout comprises one or more sgRNAs targeting exon 9 of eTGFBR2. In some embodiments, the CRISPR gene-

editing system for the treatment of gout comprises one or more sgRNAs targeting exon 10 of eTGFBR2.

[00309] In some embodiments, the CRISPR gene-editing system for the treatment of gout comprises one or more sgRNAs targeting exon 1 of fTGFBR2. In some embodiments, the CRISPR gene-editing system for the treatment of gout comprises one or more sgRNAs targeting exon 2 of fTGFBR2. In some embodiments, the CRISPR gene-editing system for the treatment of gout comprises one or more sgRNAs targeting exon 3 of fTGFBR2. In some embodiments, the CRISPR gene-editing system for the treatment of gout comprises one or more sgRNAs targeting exon 4 of fTGFBR2. In some embodiments, the CRISPR gene-editing system for the treatment of gout comprises one or more sgRNAs targeting exon 5 of fTGFBR2. In some embodiments, the CRISPR gene-editing system for the treatment of gout comprises one or more sgRNAs targeting exon 6 of fTGFBR2. In some embodiments, the CRISPR gene-editing system for the treatment of gout comprises one or more sgRNAs targeting exon 7 of fTGFBR2. In some embodiments, the CRISPR gene-editing system for the treatment of gout comprises one or more sgRNAs targeting exon 8 of fTGFBR2.

[00310] In some embodiments, the CRISPR gene-editing system for the treatment of gout comprises one or more sgRNAs targeting IL6R. In some embodiments, the CRISPR gene-editing system for the treatment of gout comprises one or more sgRNAs targeting hIL6R. In some embodiments, the CRISPR gene-editing system for the treatment of gout comprises one or more sgRNAs targeting cIL6R. In some embodiments, the CRISPR gene-editing system for the treatment of gout comprises one or more sgRNAs targeting eIL6R. In some embodiments, the CRISPR gene-editing system for the treatment of gout comprises one or more sgRNAs targeting fIL6R.

[00311] In some embodiments, the CRISPR gene-editing system for the treatment of gout comprises one or more sgRNAs targeting exon 1 of hIL6R. In some embodiments, the CRISPR gene-editing system for the treatment of gout comprises one or more sgRNAs targeting exon 2 of hIL6R. In some embodiments, the CRISPR gene-editing system for the treatment of gout comprises one or more sgRNAs targeting exon 3 of hIL6R. In some embodiments, the CRISPR gene-editing system for the treatment of gout comprises one or more sgRNAs targeting exon 4 of hIL6R. In some embodiments, the CRISPR gene-editing system for the treatment of gout comprises one or more sgRNAs targeting exon 5 of hIL6R. In some embodiments, the CRISPR gene-editing system for the treatment of gout comprises one or more sgRNAs targeting exon 6 of hIL6R. In some embodiments, the CRISPR gene-

editing system for the treatment of gout comprises one or more sgRNAs targeting exon 7 of hIL6R. In some embodiments, the CRISPR gene-editing system for the treatment of gout comprises one or more sgRNAs targeting exon 8 of hIL6R. In some embodiments, the CRISPR gene-editing system for the treatment of gout comprises one or more sgRNAs targeting exon 9 of hIL6R. In some embodiments, the CRISPR gene-editing system for the treatment of gout comprises one or more sgRNAs targeting exon 10 of hIL6R. In some embodiments, the CRISPR gene-editing system for the treatment of gout comprises one or more sgRNAs targeting exon 11 of hIL6R In some embodiments, the CRISPR gene-editing system for the treatment of gout comprises one or more sgRNAs targeting exon 12 of hIL6R. In some embodiments, the CRISPR gene-editing system for the treatment of gout comprises one or more sgRNAs targeting exon 13 of hIL6R. In some embodiments, the CRISPR gene-editing system for the treatment of gout comprises one or more sgRNAs targeting exon 14 of hIL6R. In some embodiments, the CRISPR gene-editing system for the treatment of gout comprises one or more sgRNAs targeting exon 15 of hIL6R.

[00312] In some embodiments, the CRISPR gene-editing system for the treatment of gout comprises one or more sgRNAs targeting exon 1 of cIL6R. In some embodiments, the CRISPR gene-editing system for the treatment of gout comprises one or more sgRNAs targeting exon 2 of cIL6R. In some embodiments, the CRISPR gene-editing system for the treatment of gout comprises one or more sgRNAs targeting exon 3 of cIL6R. In some embodiments, the CRISPR gene-editing system for the treatment of gout comprises one or more sgRNAs targeting exon 4 of cIL6R. In some embodiments, the CRISPR gene-editing system for the treatment of gout comprises one or more sgRNAs targeting exon 5 of cIL6R. In some embodiments, the CRISPR gene-editing system for the treatment of gout comprises one or more sgRNAs targeting exon 6 of cIL6R. In some embodiments, the CRISPR gene-editing system for the treatment of gout comprises one or more sgRNAs targeting exon 7 of cIL6R. In some embodiments, the CRISPR gene-editing system for the treatment of gout comprises one or more sgRNAs targeting exon 8 of cIL6R. In some embodiments, the CRISPR gene-editing system for the treatment of gout comprises one or more sgRNAs targeting exon 9 of cIL6R. In some embodiments, the CRISPR gene-editing system for the treatment of gout comprises one or more sgRNAs targeting exon 10 of cIL6R. In some embodiments, the CRISPR gene-editing system for the treatment of gout comprises one or more sgRNAs targeting exon 11 of cIL6R. In some embodiments, the CRISPR gene-editing system for the treatment of gout comprises one or more sgRNAs targeting exon 12 of cIL6R.

In some embodiments, the CRISPR gene-editing system for the treatment of gout comprises one or more sgRNAs targeting exon 13 of cIL6R.

[00313] In some embodiments, the CRISPR gene-editing system for the treatment of gout comprises one or more sgRNAs targeting exon 1 of eIL6R. In some embodiments, the CRISPR gene-editing system for the treatment of gout comprises one or more sgRNAs targeting exon 2 of eIL6R. In some embodiments, the CRISPR gene-editing system for the treatment of gout comprises one or more sgRNAs targeting exon 3 of eIL6R. In some embodiments, the CRISPR gene-editing system for the treatment of gout comprises one or more sgRNAs targeting exon 4 of eIL6R. In some embodiments, the CRISPR gene-editing system for the treatment of gout comprises one or more sgRNAs targeting exon 5 of eIL6R. In some embodiments, the CRISPR gene-editing system for the treatment of gout comprises one or more sgRNAs targeting exon 6 of eIL6R. In some embodiments, the CRISPR gene-editing system for the treatment of gout comprises one or more sgRNAs targeting exon 7 of eIL6R. In some embodiments, the CRISPR gene-editing system for the treatment of gout comprises one or more sgRNAs targeting exon 8 of eIL6R. In some embodiments, the CRISPR gene-editing system for the treatment of gout comprises one or more sgRNAs targeting exon 9 of eIL6R. In some embodiments, the CRISPR gene-editing system for the treatment of gout comprises one or more sgRNAs targeting exon 10 of eIL6R. In some embodiments, the CRISPR gene-editing system for the treatment of gout comprises one or more sgRNAs targeting exon 11 of eIL6R.

[00314] In some embodiments, the CRISPR gene-editing system for the treatment of gout comprises one or more sgRNAs targeting exon 1 of fIL6R. In some embodiments, the CRISPR gene-editing system for the treatment of gout comprises one or more sgRNAs targeting exon 2 of fIL6R. In some embodiments, the CRISPR gene-editing system for the treatment of gout comprises one or more sgRNAs targeting exon 3 of fIL6R. In some embodiments, the CRISPR gene-editing system for the treatment of gout comprises one or more sgRNAs targeting exon 4 of fIL6R. In some embodiments, the CRISPR gene-editing system for the treatment of gout comprises one or more sgRNAs targeting exon 5 of fIL6R. In some embodiments, the CRISPR gene-editing system for the treatment of gout comprises one or more sgRNAs targeting exon 6 of fIL6R. In some embodiments, the CRISPR gene-editing system for the treatment of gout comprises one or more sgRNAs targeting exon 7 of fIL6R. In some embodiments, the CRISPR gene-editing system for the treatment of gout comprises one or more sgRNAs targeting exon 8 of fIL6R. In some embodiments, the

CRISPR gene-editing system for the treatment of gout comprises one or more sgRNAs targeting exon 9 of fIL6R. In some embodiments, the CRISPR gene-editing system for the treatment of gout comprises one or more sgRNAs targeting exon 10 of fIL6R.

[00315] In some embodiments, the CRISPR gene-editing system for the treatment of gout comprises one or more sgRNAs targeting IL6ST. In some embodiments, the CRISPR gene-editing system for the treatment of gout comprises one or more sgRNAs targeting hIL6ST. In some embodiments, the CRISPR gene-editing system for the treatment of gout comprises one or more sgRNAs targeting cIL6ST. In some embodiments, the CRISPR gene-editing system for the treatment of gout comprises one or more sgRNAs targeting eIL6ST. In some embodiments, the CRISPR gene-editing system for the treatment of gout comprises one or more sgRNAs targeting fIL6ST.

[00316] In some embodiments, the CRISPR gene-editing system for the treatment of gout comprises one or more sgRNAs targeting exon 1 of hIL6ST. In some embodiments, the CRISPR gene-editing system for the treatment of gout comprises one or more sgRNAs targeting exon 2 of hIL6ST. In some embodiments, the CRISPR gene-editing system for the treatment of gout comprises one or more sgRNAs targeting exon 3 of hIL6ST. In some embodiments, the CRISPR gene-editing system for the treatment of gout comprises one or more sgRNAs targeting exon 4 of hIL6ST. In some embodiments, the CRISPR gene-editing system for the treatment of gout comprises one or more sgRNAs targeting exon 5 of hIL6ST. In some embodiments, the CRISPR gene-editing system for the treatment of gout comprises one or more sgRNAs targeting exon 6 of hIL6ST. In some embodiments, the CRISPR gene-editing system for the treatment of gout comprises one or more sgRNAs targeting exon 7 of hIL6ST. In some embodiments, the CRISPR gene-editing system for the treatment of gout comprises one or more sgRNAs targeting exon 8 of hIL6ST. In some embodiments, the CRISPR gene-editing system for the treatment of gout comprises one or more sgRNAs targeting exon 9 of hIL6ST. In some embodiments, the CRISPR gene-editing system for the treatment of gout comprises one or more sgRNAs targeting exon 10 of hIL6ST. In some embodiments, the CRISPR gene-editing system for the treatment of gout comprises one or more sgRNAs targeting exon 11 of hIL6ST. In some embodiments, the CRISPR gene-editing system for the treatment of gout comprises one or more sgRNAs targeting exon 12 of hIL6ST. In some embodiments, the CRISPR gene-editing system for the treatment of gout comprises one or more sgRNAs targeting exon 13 of hIL6ST. In some embodiments, the CRISPR gene-editing system for the treatment of gout comprises one or more sgRNAs

targeting exon 14 of hIL6ST. In some embodiments, the CRISPR gene-editing system for the treatment of gout comprises one or more sgRNAs targeting exon 15 of hIL6ST. In some embodiments, the CRISPR gene-editing system for the treatment of gout comprises one or more sgRNAs targeting exon 16 of hIL6ST. In some embodiments, the CRISPR gene-editing system for the treatment of gout comprises one or more sgRNAs targeting exon 17 of hIL6ST. In some embodiments, the CRISPR gene-editing system for the treatment of gout comprises one or more sgRNAs targeting exon 18 of hIL6ST. In some embodiments, the CRISPR gene-editing system for the treatment of gout comprises one or more sgRNAs targeting exon 19 of hIL6ST.

[00317] In some embodiments, the CRISPR gene-editing system for the treatment of gout comprises one or more sgRNAs targeting exon 1 of cIL6ST. In some embodiments, the CRISPR gene-editing system for the treatment of gout comprises one or more sgRNAs targeting exon 2 of cIL6ST. In some embodiments, the CRISPR gene-editing system for the treatment of gout comprises one or more sgRNAs targeting exon 3 of cIL6ST. In some embodiments, the CRISPR gene-editing system for the treatment of gout comprises one or more sgRNAs targeting exon 4 of cIL6ST. In some embodiments, the CRISPR gene-editing system for the treatment of gout comprises one or more sgRNAs targeting exon 5 of cIL6ST. In some embodiments, the CRISPR gene-editing system for the treatment of gout comprises one or more sgRNAs targeting exon 6 of cIL6ST. In some embodiments, the CRISPR gene-editing system for the treatment of gout comprises one or more sgRNAs targeting exon 7 of cIL6ST. In some embodiments, the CRISPR gene-editing system for the treatment of gout comprises one or more sgRNAs targeting exon 8 of cIL6ST. In some embodiments, the CRISPR gene-editing system for the treatment of gout comprises one or more sgRNAs targeting exon 9 of cIL6ST. In some embodiments, the CRISPR gene-editing system for the treatment of gout comprises one or more sgRNAs targeting exon 10 of cIL6ST. In some embodiments, the CRISPR gene-editing system for the treatment of gout comprises one or more sgRNAs targeting exon 11 of cIL6ST In some embodiments, the CRISPR gene-editing system for the treatment of gout comprises one or more sgRNAs targeting exon 12 of cIL6ST. In some embodiments, the CRISPR gene-editing system for the treatment of gout comprises one or more sgRNAs targeting exon 13 of cIL6ST. In some embodiments, the CRISPR gene-editing system for the treatment of gout comprises one or more sgRNAs targeting exon 14 of cIL6ST. In some embodiments, the CRISPR gene-editing system for the treatment of gout comprises one or more sgRNAs targeting exon 15 of cIL6ST. In some

embodiments, the CRISPR gene-editing system for the treatment of gout comprises one or more sgRNAs targeting exon 16 of cIL6ST. In some embodiments, the CRISPR gene-editing system for the treatment of gout comprises one or more sgRNAs targeting exon 17 of cIL6ST. In some embodiments, the CRISPR gene-editing system for the treatment of gout comprises one or more sgRNAs targeting exon 18 of cIL6ST.

[00318] In some embodiments, the CRISPR gene-editing system for the treatment of gout comprises one or more sgRNAs targeting exon 1 of eIL6ST. In some embodiments, the CRISPR gene-editing system for the treatment of gout comprises one or more sgRNAs targeting exon 2 of eIL6ST. In some embodiments, the CRISPR gene-editing system for the treatment of gout comprises one or more sgRNAs targeting exon 3 of eIL6ST. In some embodiments, the CRISPR gene-editing system for the treatment of gout comprises one or more sgRNAs targeting exon 4 of eIL6ST. In some embodiments, the CRISPR gene-editing system for the treatment of gout comprises one or more sgRNAs targeting exon 5 of eIL6ST. In some embodiments, the CRISPR gene-editing system for the treatment of gout comprises one or more sgRNAs targeting exon 6 of eIL6ST. In some embodiments, the CRISPR gene-editing system for the treatment of gout comprises one or more sgRNAs targeting exon 7 of eIL6ST. In some embodiments, the CRISPR gene-editing system for the treatment of gout comprises one or more sgRNAs targeting exon 8 of eIL6ST. In some embodiments, the CRISPR gene-editing system for the treatment of gout comprises one or more sgRNAs targeting exon 9 of eIL6ST. In some embodiments, the CRISPR gene-editing system for the treatment of gout comprises one or more sgRNAs targeting exon 10 of eIL6ST. In some embodiments, the CRISPR gene-editing system for the treatment of gout comprises one or more sgRNAs targeting exon 11 of eIL6ST In some embodiments, the CRISPR gene-editing system for the treatment of gout comprises one or more sgRNAs targeting exon 12 of eIL6ST. In some embodiments, the CRISPR gene-editing system for the treatment of gout comprises one or more sgRNAs targeting exon 13 of eIL6ST. In some embodiments, the CRISPR gene-editing system for the treatment of gout comprises one or more sgRNAs targeting exon 14 of eIL6ST. In some embodiments, the CRISPR gene-editing system for the treatment of gout comprises one or more sgRNAs targeting exon 15 of eIL6ST. In some embodiments, the CRISPR gene-editing system for the treatment of gout comprises one or more sgRNAs targeting exon 16 of eIL6ST. In some embodiments, the CRISPR gene-editing system for the treatment of gout comprises one or more sgRNAs targeting exon 17 of

eIL6ST. In some embodiments, the CRISPR gene-editing system for the treatment of gout comprises one or more sgRNAs targeting exon 18 of eIL6ST.

[00319] In some embodiments, the CRISPR gene-editing system for the treatment of gout comprises one or more sgRNAs targeting exon 1 of fIL6ST. In some embodiments, the CRISPR gene-editing system for the treatment of gout comprises one or more sgRNAs targeting exon 2 of fIL6ST. In some embodiments, the CRISPR gene-editing system for the treatment of gout comprises one or more sgRNAs targeting exon 3 of fIL6ST. In some embodiments, the CRISPR gene-editing system for the treatment of gout comprises one or more sgRNAs targeting exon 4 of fIL6ST. In some embodiments, the CRISPR gene-editing system for the treatment of gout comprises one or more sgRNAs targeting exon 5 of fIL6ST. In some embodiments, the CRISPR gene-editing system for the treatment of gout comprises one or more sgRNAs targeting exon 6 of fIL6ST. In some embodiments, the CRISPR gene-editing system for the treatment of gout comprises one or more sgRNAs targeting exon 7 of fIL6ST. In some embodiments, the CRISPR gene-editing system for the treatment of gout comprises one or more sgRNAs targeting exon 8 of fIL6ST. In some embodiments, the CRISPR gene-editing system for the treatment of gout comprises one or more sgRNAs targeting exon 9 of fIL6ST. In some embodiments, the CRISPR gene-editing system for the treatment of gout comprises one or more sgRNAs targeting exon 10 of fIL6ST. In some embodiments, the CRISPR gene-editing system for the treatment of gout comprises one or more sgRNAs targeting exon 11 of fIL6ST In some embodiments, the CRISPR gene-editing system for the treatment of gout comprises one or more sgRNAs targeting exon 12 of fIL6ST. In some embodiments, the CRISPR gene-editing system for the treatment of gout comprises one or more sgRNAs targeting exon 13 of fIL6ST. In some embodiments, the CRISPR gene-editing system for the treatment of gout comprises one or more sgRNAs targeting exon 14 of fIL6ST. In some embodiments, the CRISPR gene-editing system for the treatment of gout comprises one or more sgRNAs targeting exon 15 of fIL6ST. In some embodiments, the CRISPR gene-editing system for the treatment of gout comprises one or more sgRNAs targeting exon 16 of fIL6ST. In some embodiments, the CRISPR gene-editing system for the treatment of gout comprises one or more sgRNAs targeting exon 17 of fIL6ST. In some embodiments, the CRISPR gene-editing system for the treatment of gout comprises one or more sgRNAs targeting exon 18 of fIL6ST. In some embodiments, the CRISPR gene-editing system for the treatment of gout comprises one or more sgRNAs targeting exon 19 of fIL6ST.

In some embodiments, the CRISPR gene-editing system for the treatment of gout comprises one or more sgRNAs targeting exon 20 of fIL6ST.

[00320] In some embodiments, the CRISPR gene-editing system for the treatment of gout comprises one or more sgRNAs targeting TNFRSF1A. In some embodiments, the CRISPR gene-editing system for the treatment of gout comprises one or more sgRNAs targeting hTNFRSF1A. In some embodiments, the CRISPR gene-editing system for the treatment of gout comprises one or more sgRNAs targeting cTNFRSF1A. In some embodiments, the CRISPR gene-editing system for the treatment of gout comprises one or more sgRNAs targeting eTNFRSF1A. In some embodiments, the CRISPR gene-editing system for the treatment of gout comprises one or more sgRNAs targeting fTNFRSF1A.

[00321] In some embodiments, the CRISPR gene-editing system for the treatment of gout comprises one or more sgRNAs targeting exon 1 of hTNFRSF1A. In some embodiments, the CRISPR gene-editing system for the treatment of gout comprises one or more sgRNAs targeting exon 2 of hTNFRSF1A. In some embodiments, the CRISPR gene-editing system for the treatment of gout comprises one or more sgRNAs targeting exon 3 of hTNFRSF1A. In some embodiments, the CRISPR gene-editing system for the treatment of gout comprises one or more sgRNAs targeting exon 4 of hTNFRSF1A. In some embodiments, the CRISPR gene-editing system for the treatment of gout comprises one or more sgRNAs targeting exon 5 of hTNFRSF1A. In some embodiments, the CRISPR gene-editing system for the treatment of gout comprises one or more sgRNAs targeting exon 6 of hTNFRSF1A. In some embodiments, the CRISPR gene-editing system for the treatment of gout comprises one or more sgRNAs targeting exon 7 of hTNFRSF1A. In some embodiments, the CRISPR gene-editing system for the treatment of gout comprises one or more sgRNAs targeting exon 8 of hTNFRSF1A. In some embodiments, the CRISPR gene-editing system for the treatment of gout comprises one or more sgRNAs targeting exon 9 of hTNFRSF1A. In some embodiments, the CRISPR gene-editing system for the treatment of gout comprises one or more sgRNAs targeting exon 10 of hTNFRSF1A. In some embodiments, the CRISPR gene-editing system for the treatment of gout comprises one or more sgRNAs targeting exon 11 of hTNFRSF1A.

[00322] In some embodiments, the CRISPR gene-editing system for the treatment of gout comprises one or more sgRNAs targeting exon 1 of cTNFRSF1A. In some embodiments, the CRISPR gene-editing system for the treatment of gout comprises one or more sgRNAs targeting exon 2 of cTNFRSF1A. In some embodiments, the CRISPR gene-editing system

for the treatment of gout comprises one or more sgRNAs targeting exon 3 of cTNFRSF1A. In some embodiments, the CRISPR gene-editing system for the treatment of gout comprises one or more sgRNAs targeting exon 4 of cTNFRSF1A. In some embodiments, the CRISPR gene-editing system for the treatment of gout comprises one or more sgRNAs targeting exon 5 of cTNFRSF1A. In some embodiments, the CRISPR gene-editing system for the treatment of gout comprises one or more sgRNAs targeting exon 6 of cTNFRSF1A. In some embodiments, the CRISPR gene-editing system for the treatment of gout comprises one or more sgRNAs targeting exon 7 of cTNFRSF1A. In some embodiments, the CRISPR gene-editing system for the treatment of gout comprises one or more sgRNAs targeting exon 8 of cTNFRSF1A. In some embodiments, the CRISPR gene-editing system for the treatment of gout comprises one or more sgRNAs targeting exon 9 of cTNFRSF1A. In some embodiments, the CRISPR gene-editing system for the treatment of gout comprises one or more sgRNAs targeting exon 10 of cTNFRSF1A. In some embodiments, the CRISPR gene-editing system for the treatment of gout comprises one or more sgRNAs targeting exon 11 of cTNFRSF1A.

[00323] In some embodiments, the CRISPR gene-editing system for the treatment of gout comprises one or more sgRNAs targeting exon 1 of eTNFRSF1A. In some embodiments, the CRISPR gene-editing system for the treatment of gout comprises one or more sgRNAs targeting exon 2 of eTNFRSF1A. In some embodiments, the CRISPR gene-editing system for the treatment of gout comprises one or more sgRNAs targeting exon 3 of eTNFRSF1A. In some embodiments, the CRISPR gene-editing system for the treatment of gout comprises one or more sgRNAs targeting exon 4 of eTNFRSF1A. In some embodiments, the CRISPR gene-editing system for the treatment of gout comprises one or more sgRNAs targeting exon 5 of eTNFRSF1A. In some embodiments, the CRISPR gene-editing system for the treatment of gout comprises one or more sgRNAs targeting exon 6 of eTNFRSF1A. In some embodiments, the CRISPR gene-editing system for the treatment of gout comprises one or more sgRNAs targeting exon 7 of eTNFRSF1A. In some embodiments, the CRISPR gene-editing system for the treatment of gout comprises one or more sgRNAs targeting exon 8 of eTNFRSF1A. In some embodiments, the CRISPR gene-editing system for the treatment of gout comprises one or more sgRNAs targeting exon 9 of eTNFRSF1A. In some embodiments, the CRISPR gene-editing system for the treatment of gout comprises one or more sgRNAs targeting exon 10 of eTNFRSF1A.

[00324] In some embodiments, the CRISPR gene-editing system for the treatment of gout comprises one or more sgRNAs targeting exon 1 of fTNFRSF1A. In some embodiments, the CRISPR gene-editing system for the treatment of gout comprises one or more sgRNAs targeting exon 2 of fTNFRSF1A. In some embodiments, the CRISPR gene-editing system for the treatment of gout comprises one or more sgRNAs targeting exon 3 of fTNFRSF1A. In some embodiments, the CRISPR gene-editing system for the treatment of gout comprises one or more sgRNAs targeting exon 4 of fTNFRSF1A. In some embodiments, the CRISPR gene-editing system for the treatment of gout comprises one or more sgRNAs targeting exon 5 of fTNFRSF1A. In some embodiments, the CRISPR gene-editing system for the treatment of gout comprises one or more sgRNAs targeting exon 6 of fTNFRSF1A. In some embodiments, the CRISPR gene-editing system for the treatment of gout comprises one or more sgRNAs targeting exon 7 of fTNFRSF1A. In some embodiments, the CRISPR gene-editing system for the treatment of gout comprises one or more sgRNAs targeting exon 8 of fTNFRSF1A. In some embodiments, the CRISPR gene-editing system for the treatment of gout comprises one or more sgRNAs targeting exon 9 of fTNFRSF1A. In some embodiments, the CRISPR gene-editing system for the treatment of gout comprises one or more sgRNAs targeting exon 10 of fTNFRSF1A.

[00325] In some embodiments, the CRISPR gene-editing system for the treatment of gout comprises one or more sgRNAs targeting TNFRSF1B. In some embodiments, the CRISPR gene-editing system for the treatment of gout comprises one or more sgRNAs targeting hTNFRSF1B. In some embodiments, the CRISPR gene-editing system for the treatment of gout comprises one or more sgRNAs targeting cTNFRSF1B. In some embodiments, the CRISPR gene-editing system for the treatment of gout comprises one or more sgRNAs targeting eTNFRSF1B. In some embodiments, the CRISPR gene-editing system for the treatment of gout comprises one or more sgRNAs targeting fTNFRSF1B.

[00326] In some embodiments, the CRISPR gene-editing system for the treatment of gout comprises one or more sgRNAs targeting exon 1 of hTNFRSF1B. In some embodiments, the CRISPR gene-editing system for the treatment of gout comprises one or more sgRNAs targeting exon 2 of hTNFRSF1B. In some embodiments, the CRISPR gene-editing system for the treatment of gout comprises one or more sgRNAs targeting exon 3 of hTNFRSF1B. In some embodiments, the CRISPR gene-editing system for the treatment of gout comprises one or more sgRNAs targeting exon 4 of hTNFRSF1B. In some embodiments, the CRISPR gene-editing system for the treatment of gout comprises one or more sgRNAs targeting exon

5 of hTNFRSF1B. In some embodiments, the CRISPR gene-editing system for the treatment of gout comprises one or more sgRNAs targeting exon 6 of hTNFRSF1B. In some embodiments, the CRISPR gene-editing system for the treatment of gout comprises one or more sgRNAs targeting exon 7 of hTNFRSF1B. In some embodiments, the CRISPR gene-editing system for the treatment of gout comprises one or more sgRNAs targeting exon 8 of hTNFRSF1B. In some embodiments, the CRISPR gene-editing system for the treatment of gout comprises one or more sgRNAs targeting exon 9 of hTNFRSF1B. In some embodiments, the CRISPR gene-editing system for the treatment of gout comprises one or more sgRNAs targeting exon 10 of hTNFRSF1B. In some embodiments, the CRISPR gene-editing system for the treatment of gout comprises one or more sgRNAs targeting exon 11 of hTNFRSF1B In some embodiments, the CRISPR gene-editing system for the treatment of gout comprises one or more sgRNAs targeting exon 12 of hTNFRSF1B. In some embodiments, the CRISPR gene-editing system for the treatment of gout comprises one or more sgRNAs targeting exon 13 of hTNFRSF1B.

[00327] In some embodiments, the CRISPR gene-editing system for the treatment of gout comprises one or more sgRNAs targeting exon 1 of cTNFRSF1B. In some embodiments, the CRISPR gene-editing system for the treatment of gout comprises one or more sgRNAs targeting exon 2 of cTNFRSF1B. In some embodiments, the CRISPR gene-editing system for the treatment of gout comprises one or more sgRNAs targeting exon 3 of cTNFRSF1B. In some embodiments, the CRISPR gene-editing system for the treatment of gout comprises one or more sgRNAs targeting exon 4 of cTNFRSF1B. In some embodiments, the CRISPR gene-editing system for the treatment of gout comprises one or more sgRNAs targeting exon 5 of cTNFRSF1B. In some embodiments, the CRISPR gene-editing system for the treatment of gout comprises one or more sgRNAs targeting exon 6 of cTNFRSF1B. In some embodiments, the CRISPR gene-editing system for the treatment of gout comprises one or more sgRNAs targeting exon 7 of cTNFRSF1B. In some embodiments, the CRISPR gene-editing system for the treatment of gout comprises one or more sgRNAs targeting exon 8 of cTNFRSF1B. In some embodiments, the CRISPR gene-editing system for the treatment of gout comprises one or more sgRNAs targeting exon 9 of cTNFRSF1B. In some embodiments, the CRISPR gene-editing system for the treatment of gout comprises one or more sgRNAs targeting exon 10 of cTNFRSF1B. In some embodiments, the CRISPR gene-editing system for the treatment of gout comprises one or more sgRNAs targeting exon 11 of cTNFRSF1B.

[00328] In some embodiments, the CRISPR gene-editing system for the treatment of gout comprises one or more sgRNAs targeting exon 1 of eTNFRSF1B. In some embodiments, the CRISPR gene-editing system for the treatment of gout comprises one or more sgRNAs targeting exon 2 of eTNFRSF1B. In some embodiments, the CRISPR gene-editing system for the treatment of gout comprises one or more sgRNAs targeting exon 3 of eTNFRSF1B. In some embodiments, the CRISPR gene-editing system for the treatment of gout comprises one or more sgRNAs targeting exon 4 of eTNFRSF1B. In some embodiments, the CRISPR gene-editing system for the treatment of gout comprises one or more sgRNAs targeting exon 5 of eTNFRSF1B. In some embodiments, the CRISPR gene-editing system for the treatment of gout comprises one or more sgRNAs targeting exon 6 of eTNFRSF1B. In some embodiments, the CRISPR gene-editing system for the treatment of gout comprises one or more sgRNAs targeting exon 7 of eTNFRSF1B. In some embodiments, the CRISPR gene-editing system for the treatment of gout comprises one or more sgRNAs targeting exon 8 of eTNFRSF1B. In some embodiments, the CRISPR gene-editing system for the treatment of gout comprises one or more sgRNAs targeting exon 9 of eTNFRSF1B. In some embodiments, the CRISPR gene-editing system for the treatment of gout comprises one or more sgRNAs targeting exon 10 of eTNFRSF1B. In some embodiments, the CRISPR gene-editing system for the treatment of gout comprises one or more sgRNAs targeting exon 11 of eTNFRSF1B.

[00329] In some embodiments, the CRISPR gene-editing system for the treatment of gout comprises one or more sgRNAs targeting exon 1 of fTNFRSF1B. In some embodiments, the CRISPR gene-editing system for the treatment of gout comprises one or more sgRNAs targeting exon 2 of fTNFRSF1B. In some embodiments, the CRISPR gene-editing system for the treatment of gout comprises one or more sgRNAs targeting exon 3 of fTNFRSF1B. In some embodiments, the CRISPR gene-editing system for the treatment of gout comprises one or more sgRNAs targeting exon 4 of fTNFRSF1B. In some embodiments, the CRISPR gene-editing system for the treatment of gout comprises one or more sgRNAs targeting exon 5 of fTNFRSF1B. In some embodiments, the CRISPR gene-editing system for the treatment of gout comprises one or more sgRNAs targeting exon 6 of fTNFRSF1B. In some embodiments, the CRISPR gene-editing system for the treatment of gout comprises one or more sgRNAs targeting exon 7 of fTNFRSF1B. In some embodiments, the CRISPR gene-editing system for the treatment of gout comprises one or more sgRNAs targeting exon 8 of fTNFRSF1B. In some embodiments, the CRISPR gene-editing system for the treatment of

gout comprises one or more sgRNAs targeting exon 9 of fTNFRSF1B. In some embodiments, the CRISPR gene-editing system for the treatment of gout comprises one or more sgRNAs targeting exon 10 of fTNFRSF1B.

[00330] In some embodiments, the CRISPR gene-editing system for the treatment of gout comprises one or more sgRNAs targeting TNFRSF3. In some embodiments, the CRISPR gene-editing system for the treatment of gout comprises one or more sgRNAs targeting hTNFRSF3. In some embodiments, the CRISPR gene-editing system for the treatment of gout comprises one or more sgRNAs targeting cTNFRSF3. In some embodiments, the CRISPR gene-editing system for the treatment of gout comprises one or more sgRNAs targeting eTNFRSF3. In some embodiments, the CRISPR gene-editing system for the treatment of gout comprises one or more sgRNAs targeting fTNFRSF3.

[00331] In some embodiments, the CRISPR gene-editing system for the treatment of gout comprises one or more sgRNAs targeting exon 1 of hTNFRSF3. In some embodiments, the CRISPR gene-editing system for the treatment of gout comprises one or more sgRNAs targeting exon 2 of hTNFRSF3. In some embodiments, the CRISPR gene-editing system for the treatment of gout comprises one or more sgRNAs targeting exon 3 of hTNFRSF3. In some embodiments, the CRISPR gene-editing system for the treatment of gout comprises one or more sgRNAs targeting exon 4 of hTNFRSF3. In some embodiments, the CRISPR gene-editing system for the treatment of gout comprises one or more sgRNAs targeting exon 5 of hTNFRSF3. In some embodiments, the CRISPR gene-editing system for the treatment of gout comprises one or more sgRNAs targeting exon 6 of hTNFRSF3. In some embodiments, the CRISPR gene-editing system for the treatment of gout comprises one or more sgRNAs targeting exon 7 of hTNFRSF3. In some embodiments, the CRISPR gene-editing system for the treatment of gout comprises one or more sgRNAs targeting exon 8 of hTNFRSF3. In some embodiments, the CRISPR gene-editing system for the treatment of gout comprises one or more sgRNAs targeting exon 9 of hTNFRSF3. In some embodiments, the CRISPR gene-editing system for the treatment of gout comprises one or more sgRNAs targeting exon 10 of hTNFRSF3. In some embodiments, the CRISPR gene-editing system for the treatment of gout comprises one or more sgRNAs targeting exon 11 of hTNFRSF3. In some embodiments, the CRISPR gene-editing system for the treatment of gout comprises one or more sgRNAs targeting exon 12 of hTNFRSF3.

[00332] In some embodiments, the CRISPR gene-editing system for the treatment of gout comprises one or more sgRNAs targeting exon 1 of cTNFRSF3. In some embodiments, the

CRISPR gene-editing system for the treatment of gout comprises one or more sgRNAs targeting exon 2 of cTNFRSF3. In some embodiments, the CRISPR gene-editing system for the treatment of gout comprises one or more sgRNAs targeting exon 3 of cTNFRSF3. In some embodiments, the CRISPR gene-editing system for the treatment of gout comprises one or more sgRNAs targeting exon 4 of cTNFRSF3. In some embodiments, the CRISPR gene-editing system for the treatment of gout comprises one or more sgRNAs targeting exon 5 of cTNFRSF3. In some embodiments, the CRISPR gene-editing system for the treatment of gout comprises one or more sgRNAs targeting exon 6 of cTNFRSF3. In some embodiments, the CRISPR gene-editing system for the treatment of gout comprises one or more sgRNAs targeting exon 7 of cTNFRSF3. In some embodiments, the CRISPR gene-editing system for the treatment of gout comprises one or more sgRNAs targeting exon 8 of cTNFRSF3. In some embodiments, the CRISPR gene-editing system for the treatment of gout comprises one or more sgRNAs targeting exon 9 of cTNFRSF3. In some embodiments, the CRISPR gene-editing system for the treatment of gout comprises one or more sgRNAs targeting exon 10 of cTNFRSF3.

[00333] In some embodiments, the CRISPR gene-editing system for the treatment of gout comprises one or more sgRNAs targeting exon 1 of eTNFRSF3. In some embodiments, the CRISPR gene-editing system for the treatment of gout comprises one or more sgRNAs targeting exon 2 of eTNFRSF3. In some embodiments, the CRISPR gene-editing system for the treatment of gout comprises one or more sgRNAs targeting exon 3 of eTNFRSF3. In some embodiments, the CRISPR gene-editing system for the treatment of gout comprises one or more sgRNAs targeting exon 4 of eTNFRSF3. In some embodiments, the CRISPR gene-editing system for the treatment of gout comprises one or more sgRNAs targeting exon 5 of eTNFRSF3. In some embodiments, the CRISPR gene-editing system for the treatment of gout comprises one or more sgRNAs targeting exon 6 of eTNFRSF3. In some embodiments, the CRISPR gene-editing system for the treatment of gout comprises one or more sgRNAs targeting exon 7 of eTNFRSF3. In some embodiments, the CRISPR gene-editing system for the treatment of gout comprises one or more sgRNAs targeting exon 8 of eTNFRSF3. In some embodiments, the CRISPR gene-editing system for the treatment of gout comprises one or more sgRNAs targeting exon 9 of eTNFRSF3. In some embodiments, the CRISPR gene-editing system for the treatment of gout comprises one or more sgRNAs targeting exon 10 of eTNFRSF3.

[00334] In some embodiments, the CRISPR gene-editing system for the treatment of gout comprises one or more sgRNAs targeting exon 1 of fTNFRSF3. In some embodiments, the CRISPR gene-editing system for the treatment of gout comprises one or more sgRNAs targeting exon 2 of fTNFRSF3. In some embodiments, the CRISPR gene-editing system for the treatment of gout comprises one or more sgRNAs targeting exon 3 of fTNFRSF3. In some embodiments, the CRISPR gene-editing system for the treatment of gout comprises one or more sgRNAs targeting exon 4 of fTNFRSF3. In some embodiments, the CRISPR gene-editing system for the treatment of gout comprises one or more sgRNAs targeting exon 5 of fTNFRSF3. In some embodiments, the CRISPR gene-editing system for the treatment of gout comprises one or more sgRNAs targeting exon 6 of fTNFRSF3. In some embodiments, the CRISPR gene-editing system for the treatment of gout comprises one or more sgRNAs targeting exon 7 of fTNFRSF3. In some embodiments, the CRISPR gene-editing system for the treatment of gout comprises one or more sgRNAs targeting exon 8 of fTNFRSF3. In some embodiments, the CRISPR gene-editing system for the treatment of gout comprises one or more sgRNAs targeting exon 9 of fTNFRSF3. In some embodiments, the CRISPR gene-editing system for the treatment of gout comprises one or more sgRNAs targeting exon 10 of fTNFRSF3.

[00335] In some embodiments, the CRISPR gene-editing system for the treatment of gout comprises one or more sgRNAs targeting TNFRSF4. In some embodiments, the CRISPR gene-editing system for the treatment of gout comprises one or more sgRNAs targeting hTNFRSF4. In some embodiments, the CRISPR gene-editing system for the treatment of gout comprises one or more sgRNAs targeting cTNFRSF4. In some embodiments, the CRISPR gene-editing system for the treatment of gout comprises one or more sgRNAs targeting eTNFRSF4. In some embodiments, the CRISPR gene-editing system for the treatment of gout comprises one or more sgRNAs targeting fTNFRSF4.

[00336] In some embodiments, the CRISPR gene-editing system for the treatment of gout comprises one or more sgRNAs targeting exon 1 of hTNFRSF4. In some embodiments, the CRISPR gene-editing system for the treatment of gout comprises one or more sgRNAs targeting exon 2 of hTNFRSF4. In some embodiments, the CRISPR gene-editing system for the treatment of gout comprises one or more sgRNAs targeting exon 3 of hTNFRSF4. In some embodiments, the CRISPR gene-editing system for the treatment of gout comprises one or more sgRNAs targeting exon 4 of hTNFRSF4. In some embodiments, the CRISPR gene-editing system for the treatment of gout comprises one or more sgRNAs targeting exon 5 of

hTNFRSF4. In some embodiments, the CRISPR gene-editing system for the treatment of gout comprises one or more sgRNAs targeting exon 6 of hTNFRSF4.

[00337] In some embodiments, the CRISPR gene-editing system for the treatment of gout comprises one or more sgRNAs targeting exon 1 of cTNFRSF4. In some embodiments, the CRISPR gene-editing system for the treatment of gout comprises one or more sgRNAs targeting exon 2 of cTNFRSF4. In some embodiments, the CRISPR gene-editing system for the treatment of gout comprises one or more sgRNAs targeting exon 3 of cTNFRSF4. In some embodiments, the CRISPR gene-editing system for the treatment of gout comprises one or more sgRNAs targeting exon 4 of cTNFRSF4. In some embodiments, the CRISPR gene-editing system for the treatment of gout comprises one or more sgRNAs targeting exon 5 of cTNFRSF4. In some embodiments, the CRISPR gene-editing system for the treatment of gout comprises one or more sgRNAs targeting exon 6 of cTNFRSF4. In some embodiments, the CRISPR gene-editing system for the treatment of gout comprises one or more sgRNAs targeting exon 7 of cTNFRSF4.

[00338] In some embodiments, the CRISPR gene-editing system for the treatment of gout comprises one or more sgRNAs targeting exon 1 of eTNFRSF4. In some embodiments, the CRISPR gene-editing system for the treatment of gout comprises one or more sgRNAs targeting exon 2 of eTNFRSF4. In some embodiments, the CRISPR gene-editing system for the treatment of gout comprises one or more sgRNAs targeting exon 3 of eTNFRSF4. In some embodiments, the CRISPR gene-editing system for the treatment of gout comprises one or more sgRNAs targeting exon 4 of eTNFRSF4. In some embodiments, the CRISPR gene-editing system for the treatment of gout comprises one or more sgRNAs targeting exon 5 of eTNFRSF4. In some embodiments, the CRISPR gene-editing system for the treatment of gout comprises one or more sgRNAs targeting exon 6 of eTNFRSF4. In some embodiments, the CRISPR gene-editing system for the treatment of gout comprises one or more sgRNAs targeting exon 7 of eTNFRSF4.

[00339] In some embodiments, the CRISPR gene-editing system for the treatment of gout comprises one or more sgRNAs targeting exon 1 of fTNFRSF4. In some embodiments, the CRISPR gene-editing system for the treatment of gout comprises one or more sgRNAs targeting exon 2 of fTNFRSF4. In some embodiments, the CRISPR gene-editing system for the treatment of gout comprises one or more sgRNAs targeting exon 3 of fTNFRSF4. In some embodiments, the CRISPR gene-editing system for the treatment of gout comprises one or more sgRNAs targeting exon 4 of fTNFRSF4. In some embodiments, the CRISPR gene-

editing system for the treatment of gout comprises one or more sgRNAs targeting exon 5 of fTNFRSF4. In some embodiments, the CRISPR gene-editing system for the treatment of gout comprises one or more sgRNAs targeting exon 6 of fTNFRSF4. In some embodiments, the CRISPR gene-editing system for the treatment of gout comprises one or more sgRNAs targeting exon 7 of fTNFRSF4.

[00340] In some embodiments, the CRISPR gene-editing system for the treatment of gout comprises one or more sgRNAs targeting TNFRSF11A. In some embodiments, the CRISPR gene-editing system for the treatment of gout comprises one or more sgRNAs targeting hTNFRSF11A. In some embodiments, the CRISPR gene-editing system for the treatment of gout comprises one or more sgRNAs targeting cTNFRSF11A. In some embodiments, the CRISPR gene-editing system for the treatment of gout comprises one or more sgRNAs targeting eTNFRSF11A. In some embodiments, the CRISPR gene-editing system for the treatment of gout comprises one or more sgRNAs targeting fTNFRSF11A.

[00341] In some embodiments, the CRISPR gene-editing system for the treatment of gout comprises one or more sgRNAs targeting exon 1 of hTNFRSF11A. In some embodiments, the CRISPR gene-editing system for the treatment of gout comprises one or more sgRNAs targeting exon 2 of hTNFRSF11A. In some embodiments, the CRISPR gene-editing system for the treatment of gout comprises one or more sgRNAs targeting exon 3 of hTNFRSF11A. In some embodiments, the CRISPR gene-editing system for the treatment of gout comprises one or more sgRNAs targeting exon 4 of hTNFRSF11A. In some embodiments, the CRISPR gene-editing system for the treatment of gout comprises one or more sgRNAs targeting exon 5 of hTNFRSF11A. In some embodiments, the CRISPR gene-editing system for the treatment of gout comprises one or more sgRNAs targeting exon 6 of hTNFRSF11A. In some embodiments, the CRISPR gene-editing system for the treatment of gout comprises one or more sgRNAs targeting exon 7 of hTNFRSF11A. In some embodiments, the CRISPR gene-editing system for the treatment of gout comprises one or more sgRNAs targeting exon 8 of hTNFRSF11A. In some embodiments, the CRISPR gene-editing system for the treatment of gout comprises one or more sgRNAs targeting exon 9 of hTNFRSF11A. In some embodiments, the CRISPR gene-editing system for the treatment of gout comprises one or more sgRNAs targeting exon 10 of hTNFRSF11A. In some embodiments, the CRISPR gene-editing system for the treatment of gout comprises one or more sgRNAs targeting exon 11 of hTNFRSF11A. In some embodiments, the CRISPR gene-editing system for the treatment of gout comprises one or more sgRNAs targeting exon 12 of hTNFRSF11A.

[00342] In some embodiments, the CRISPR gene-editing system for the treatment of gout comprises one or more sgRNAs targeting exon 1 of cTNFRSF11A. In some embodiments, the CRISPR gene-editing system for the treatment of gout comprises one or more sgRNAs targeting exon 2 of cTNFRSF11A. In some embodiments, the CRISPR gene-editing system for the treatment of gout comprises one or more sgRNAs targeting exon 3 of cTNFRSF11A. In some embodiments, the CRISPR gene-editing system for the treatment of gout comprises one or more sgRNAs targeting exon 4 of cTNFRSF11A. In some embodiments, the CRISPR gene-editing system for the treatment of gout comprises one or more sgRNAs targeting exon 5 of cTNFRSF11A. In some embodiments, the CRISPR gene-editing system for the treatment of gout comprises one or more sgRNAs targeting exon 6 of cTNFRSF11A. In some embodiments, the CRISPR gene-editing system for the treatment of gout comprises one or more sgRNAs targeting exon 7 of cTNFRSF11A. In some embodiments, the CRISPR gene-editing system for the treatment of gout comprises one or more sgRNAs targeting exon 8 of cTNFRSF11A. In some embodiments, the CRISPR gene-editing system for the treatment of gout comprises one or more sgRNAs targeting exon 9 of cTNFRSF11A. In some embodiments, the CRISPR gene-editing system for the treatment of gout comprises one or more sgRNAs targeting exon 10 of cTNFRSF11A. In some embodiments, the CRISPR gene-editing system for the treatment of gout comprises one or more sgRNAs targeting exon 11 of cTNFRSF11A.

[00343] In some embodiments, the CRISPR gene-editing system for the treatment of gout comprises one or more sgRNAs targeting exon 1 of eTNFRSF11A. In some embodiments, the CRISPR gene-editing system for the treatment of gout comprises one or more sgRNAs targeting exon 2 of eTNFRSF11A. In some embodiments, the CRISPR gene-editing system for the treatment of gout comprises one or more sgRNAs targeting exon 3 of eTNFRSF11A. In some embodiments, the CRISPR gene-editing system for the treatment of gout comprises one or more sgRNAs targeting exon 4 of eTNFRSF11A. In some embodiments, the CRISPR gene-editing system for the treatment of gout comprises one or more sgRNAs targeting exon 5 of eTNFRSF11A. In some embodiments, the CRISPR gene-editing system for the treatment of gout comprises one or more sgRNAs targeting exon 6 of eTNFRSF11A. In some embodiments, the CRISPR gene-editing system for the treatment of gout comprises one or more sgRNAs targeting exon 7 of eTNFRSF11A. In some embodiments, the CRISPR gene-editing system for the treatment of gout comprises one or more sgRNAs targeting exon 8 of eTNFRSF11A. In some embodiments, the CRISPR gene-editing system for the

treatment of gout comprises one or more sgRNAs targeting exon 9 of eTNFRSF11A. In some embodiments, the CRISPR gene-editing system for the treatment of gout comprises one or more sgRNAs targeting exon 10 of eTNFRSF11A.

[00344] In some embodiments, the CRISPR gene-editing system for the treatment of gout comprises one or more sgRNAs targeting exon 1 of fTNFRSF11A. In some embodiments, the CRISPR gene-editing system for the treatment of gout comprises one or more sgRNAs targeting exon 2 of fTNFRSF11A. In some embodiments, the CRISPR gene-editing system for the treatment of gout comprises one or more sgRNAs targeting exon 3 of fTNFRSF11A. In some embodiments, the CRISPR gene-editing system for the treatment of gout comprises one or more sgRNAs targeting exon 4 of fTNFRSF11A. In some embodiments, the CRISPR gene-editing system for the treatment of gout comprises one or more sgRNAs targeting exon 5 of fTNFRSF11A. In some embodiments, the CRISPR gene-editing system for the treatment of gout comprises one or more sgRNAs targeting exon 6 of fTNFRSF11A. In some embodiments, the CRISPR gene-editing system for the treatment of gout comprises one or more sgRNAs targeting exon 7 of fTNFRSF11A. In some embodiments, the CRISPR gene-editing system for the treatment of gout comprises one or more sgRNAs targeting exon 8 of fTNFRSF11A. In some embodiments, the CRISPR gene-editing system for the treatment of gout comprises one or more sgRNAs targeting exon 9 of fTNFRSF11A. In some embodiments, the CRISPR gene-editing system for the treatment of gout comprises one or more sgRNAs targeting exon 10 of fTNFRSF11A. In some embodiments, the CRISPR gene-editing system for the treatment of gout comprises one or more sgRNAs targeting exon 11 of fTNFRSF11A.

V. Back or spine conditions or disorders

A. Introduction

[00345] Back or spine conditions or disorders, including low back pain, cervical pain, sacral pain, thoracic pain. and pain or inflammation associated with discogenic disorders e.g., degenerative disc disease (DDD) or internal disc disruption (IDD), are a major cause of morbidity and disability worldwide for which few long-term options for amelioration currently exist. Andersson GB. Epidemiological features of chronic low-back pain. *Lancet.* 1999;354:581-585. Presently available treatments include surgical or less invasive options that often fail to offer long-term palliation. Ju, et al. *Global Spine Journal* (2020): 2192568220963058. All vertebrate species are affected by back or spine conditions or

disorders, including working animals, domestic pets, and their owners. All suffer from the associated discomfort, pain, and disability, depending on the degree of disease progression.

[00346] Back or spine conditions or disorders, such as low back pain, are complex diseases characterized by a multitude of inputs contributing to a progressive course of disability. Among these contributors are morphological irregularities (e.g., disc disruptions), inflammation, changes in the localized cellular environment (e.g., vascularization and/or innervation) and degenerative changes. Peng, Bao-Gan. *World Journal of Orthopedics* 4.2 (2013): 42. Each contributing factor is driven by differential expression of various gene products, including at least pro-inflammatory cytokines, growth factors, pain signaling molecules, and other effector biomolecules. There is a pressing need for new methods and compositions to treat this spectrum of disease and its associated disability.

[00347] The present disclosure provides compositions and methods for back or spine conditions or disorders. Particularly, said conditions are treated by reducing pro-inflammatory signaling mediated by inflammatory cytokines, such as, IL1α, IL1β, TNF-α, IL6, IL8, IL18, IL33, matrix metalloproteinases (MMPs), or TGFB1, or TGFB2, binding to their cognate receptor(s). In some embodiments, such conditions or disorders include disorders of the intervertebral discs (IVDs). In some embodiments, the condition or disorder is DDD. In some embodiments, the condition or disorder is IDD. In some embodiments, the condition or disorder is low back pain.

[00348] Among the advantages of the present disclosure over treatments currently available for mammals afflicted with back or spine conditions or disorders include the period of relief from symptoms. Upon local administration (e.g., intradiscal injection) and subsequent genetic editing of a cell (e.g., a chondrocyte, a tenocyte, an osteocyte, a monocyte, a macrophage or the cells of the nucleus pulposus or annulus fibrosus), pro-inflammatory signaling is silenced through the targeted gene for the life of that cell. By contrast, biologic treatments require periodic dosing, which may magnify the impact of any side effects, which can be severe. Among various genetic approaches, the present disclosure is also superior due to the resistance to leakiness built in by virtue of modifying a protein receptor, rather than ablating its expression altogether.

B. Low back pain

[00349] In one aspect, the present disclosure encompasses treatments for low back pain. In some embodiments, the low back pain treatment comprises a therapeutically effective amount of a Clustered Regularly Interspaced Short Palindromic Repeats (CRISPR) gene-editing system, the system comprising: (i) a CRISPR Associated (Cas) protein; and (ii) at least one guide RNA targeting IL1R1. In some embodiments, the low back pain treatment comprises a CRISPR gene-editing system targeting hIL1R1. In some embodiments, the low back pain treatment comprises a CRISPR gene-editing system targeting cIL1R1. In some embodiments, the low back pain treatment comprises a CRISP gene-editing system R targeting eIL1R1. In some embodiments, the low back pain treatment comprises a CRISPR gene-editing system targeting fIL1R1.

[00350] In some embodiments, the CRISPR gene-editing system for the treatment of low back pain comprises one or more sgRNAs targeting exon 1 of hIL1R1. In some embodiments, the CRISPR gene-editing system for the treatment of low back pain comprises one or more sgRNAs targeting exon 2 of hIL1R1. In some embodiments, the CRISPR gene-editing system for the treatment of low back pain comprises one or more sgRNAs targeting exon 3 of hIL1R1. In some embodiments, the CRISPR gene-editing system for the treatment of low back pain comprises one or more sgRNAs targeting exon 4 of hIL1R1. In some embodiments, the CRISPR gene-editing system for the treatment of low back pain comprises one or more sgRNAs targeting exon 5 of hIL1R1. In some embodiments, the CRISPR gene-editing system for the treatment of low back pain comprises one or more sgRNAs targeting exon 6 of hIL1R1. In some embodiments, the CRISPR gene-editing system for the treatment of low back pain comprises one or more sgRNAs targeting exon 7 of hIL1R1. In some embodiments, the CRISPR gene-editing system for the treatment of low back pain comprises one or more sgRNAs targeting exon 8 of hIL1R1. In some embodiments, the CRISPR gene-editing system for the treatment of low back pain comprises one or more sgRNAs targeting exon 9 of hIL1R1. In some embodiments, the CRISPR gene-editing system for the treatment of low back pain comprises one or more sgRNAs targeting exon 10 of hIL1R1. In some embodiments, the CRISPR gene-editing system for the treatment of low back pain comprises one or more sgRNAs targeting exon 11 of hIL1R1. In some embodiments, the CRISPR gene-editing system for the treatment of low back pain comprises one or more sgRNAs targeting exon 12 of hIL1R1. In some embodiments, the CRISPR gene-editing system for the treatment of low back pain comprises one or more sgRNAs targeting exon 13 of hIL1R1. In some embodiments, the CRISPR gene-editing system for the treatment of low back pain

comprises one or more sgRNAs targeting exon 14 of hIL1R1. In some embodiments, the CRISPR gene-editing system for the treatment of low back pain comprises one or more sgRNAs targeting exon 15 of hIL1R1. In some embodiments, the CRISPR gene-editing system for the treatment of low back pain comprises one or more sgRNAs targeting exon 16 of hIL1R1. In some embodiments, the CRISPR gene-editing system for the treatment of low back pain comprises one or more sgRNAs targeting exon 17 of hIL1R1. In some embodiments, the CRISPR gene-editing system for the treatment of low back pain comprises one or more sgRNAs targeting exon 18 of hIL1R1. In some embodiments, the CRISPR gene-editing system for the treatment of low back pain comprises one or more sgRNAs targeting exon 19 of hIL1R1. In some embodiments, the CRISPR gene-editing system for the treatment of low back pain comprises one or more sgRNAs targeting exon 20 of hIL1R1. In some embodiments, the CRISPR gene-editing system for the treatment of low back pain comprises one or more sgRNAs targeting exon 21 of hIL1R1.

[00351] In some embodiments, the CRISPR gene-editing system for the treatment of low back pain comprises one or more sgRNAs targeting exon 1 of cIL1R1. In some embodiments, the CRISPR gene-editing system for the treatment of low back pain comprises one or more sgRNAs targeting exon 2 of cIL1R1. In some embodiments, the CRISPR gene-editing system for the treatment of low back pain comprises one or more sgRNAs targeting exon 3 of cIL1R1. In some embodiments, the CRISPR gene-editing system for the treatment of low back pain comprises one or more sgRNAs targeting exon 4 of cIL1R1. In some embodiments, the CRISPR gene-editing system for the treatment of low back pain comprises one or more sgRNAs targeting exon 5 of cIL1R1. In some embodiments, the CRISPR gene-editing system for the treatment of low back pain comprises one or more sgRNAs targeting exon 6 of cIL1R1. In some embodiments, the CRISPR gene-editing system for the treatment of low back pain comprises one or more sgRNAs targeting exon 7 of cIL1R1. In some embodiments, the CRISPR gene-editing system for the treatment of low back pain comprises one or more sgRNAs targeting exon 8 of cIL1R1. In some embodiments, the CRISPR gene-editing system for the treatment of low back pain comprises one or more sgRNAs targeting exon 9 of cIL1R1. In some embodiments, the CRISPR gene-editing system for the treatment of low back pain comprises one or more sgRNAs targeting exon 10 of cIL1R1. In some embodiments, the CRISPR gene-editing system for the treatment of low back pain comprises one or more sgRNAs targeting exon 11 of cIL1R1. In some embodiments, the CRISPR gene-editing system for the treatment of low back pain comprises one or more sgRNAs targeting

exon 12 of cIL1R1. In some embodiments, the CRISPR gene-editing system for the treatment of low back pain comprises one or more sgRNAs targeting exon 13 of cIL1R1. In some embodiments, the CRISPR gene-editing system for the treatment of low back pain comprises one or more sgRNAs targeting exon 14 of cIL1R1. In some embodiments, the CRISPR gene-editing system for the treatment of low back pain comprises one or more sgRNAs targeting exon 15 of cIL1R1. In some embodiments, the CRISPR gene-editing system for the treatment of low back pain comprises one or more sgRNAs targeting exon 16 of cIL1R1.

[00352] In some embodiments, the CRISPR gene-editing system for the treatment of low back pain comprises one or more sgRNAs targeting exon 1 of eIL1R1. In some embodiments, the CRISPR gene-editing system for the treatment of low back pain comprises one or more sgRNAs targeting exon 2 of eIL1R1. In some embodiments, the CRISPR gene-editing system for the treatment of low back pain comprises one or more sgRNAs targeting exon 3 of eIL1R1. In some embodiments, the CRISPR gene-editing system for the treatment of low back pain comprises one or more sgRNAs targeting exon 4 of eIL1R1. In some embodiments, the CRISPR gene-editing system for the treatment of low back pain comprises one or more sgRNAs targeting exon 5 of eIL1R1. In some embodiments, the CRISPR gene-editing system for the treatment of low back pain comprises one or more sgRNAs targeting exon 6 of eIL1R1. In some embodiments, the CRISPR gene-editing system for the treatment of low back pain comprises one or more sgRNAs targeting exon 7 of eIL1R1. In some embodiments, the CRISPR gene-editing system for the treatment of low back pain comprises one or more sgRNAs targeting exon 8 of eIL1R1. In some embodiments, the CRISPR gene-editing system for the treatment of low back pain comprises one or more sgRNAs targeting exon 9 of eIL1R1. In some embodiments, the CRISPR gene-editing system for the treatment of low back pain comprises one or more sgRNAs targeting exon 10 of eIL1R1. In some embodiments, the CRISPR gene-editing system for the treatment of low back pain comprises one or more sgRNAs targeting exon 11 of eIL1R1. In some embodiments, the CRISPR gene-editing system for the treatment of low back pain comprises one or more sgRNAs targeting exon 12 of eIL1R1. In some embodiments, the CRISPR gene-editing system for the treatment of low back pain comprises one or more sgRNAs targeting exon 13 of eIL1R1. In some embodiments, the CRISPR gene-editing system for the treatment of low back pain comprises one or more sgRNAs targeting exon 14 of eIL1R1. In some embodiments, the

CRISPR gene-editing system for the treatment of low back pain comprises one or more sgRNAs targeting exon 15 of eIL1R1.

[00353] In some embodiments, the CRISPR gene-editing system for the treatment of low back pain comprises one or more sgRNAs targeting exon 1 of fIL1R1. In some embodiments, the CRISPR gene-editing system for the treatment of low back pain comprises one or more sgRNAs targeting exon 2 of fIL1R1. In some embodiments, the CRISPR gene-editing system for the treatment of low back pain comprises one or more sgRNAs targeting exon 3 of fIL1R1. In some embodiments, the CRISPR gene-editing system for the treatment of low back pain comprises one or more sgRNAs targeting exon 4 of fIL1R1. In some embodiments, the CRISPR gene-editing system for the treatment of low back pain comprises one or more sgRNAs targeting exon 5 of fIL1R1. In some embodiments, the CRISPR gene-editing system for the treatment of low back pain comprises one or more sgRNAs targeting exon 6 of fIL1R1. In some embodiments, the CRISPR gene-editing system for the treatment of low back pain comprises one or more sgRNAs targeting exon 7 of fIL1R1. In some embodiments, the CRISPR gene-editing system for the treatment of low back pain comprises one or more sgRNAs targeting exon 8 of fIL1R1. In some embodiments, the CRISPR gene-editing system for the treatment of low back pain comprises one or more sgRNAs targeting exon 9 of fIL1R1. In some embodiments, the CRISPR gene-editing system for the treatment of low back pain comprises one or more sgRNAs targeting exon 10 of fIL1R1. In some embodiments, the CRISPR gene-editing system for the treatment of low back pain comprises one or more sgRNAs targeting exon 11 of fIL1R1. In some embodiments, the CRISPR gene-editing system for the treatment of low back pain comprises one or more sgRNAs targeting exon 12 of fIL1R1. In some embodiments, the CRISPR gene-editing system for the treatment of low back pain comprises one or more sgRNAs targeting exon 13 of fIL1R1. In some embodiments, the CRISPR gene-editing system for the treatment of low back pain comprises one or more sgRNAs targeting exon 14 of fIL1R1. In some embodiments, the CRISPR gene-editing system for the treatment of low back pain comprises one or more sgRNAs targeting exon 15 of fIL1R1. In some embodiments, the CRISPR gene-editing system for the treatment of low back pain comprises one or more sgRNAs targeting exon 16 of fIL1R1. In some embodiments, the CRISPR gene-editing system for the treatment of low back pain comprises one or more sgRNAs targeting exon 17 of fIL1R1. In some embodiments, the CRISPR gene-editing system for the treatment of low back pain comprises one or more sgRNAs targeting exon 18 of fIL1R1.

[00354] In some embodiments, the CRISPR gene-editing system for the treatment of low back pain comprises one or more sgRNAs targeting IL1RAP. In some embodiments, the CRISPR gene-editing system for the treatment of low back pain comprises one or more sgRNAs targeting hIL1RAP. In some embodiments, the CRISPR gene-editing system for the treatment of low back pain comprises one or more sgRNAs targeting cIL1RAP. In some embodiments, the CRISPR gene-editing system for the treatment of low back pain comprises one or more sgRNAs targeting eIL1RAP. In some embodiments, the CRISPR gene-editing system for the treatment of low back pain comprises one or more sgRNAs targeting fIL1RAP.

[00355] In some embodiments, the CRISPR gene-editing system for the treatment of low back pain comprises one or more sgRNAs targeting exon 1 of hIL1RAP. In some embodiments, the CRISPR gene-editing system for the treatment of low back pain comprises one or more sgRNAs targeting exon 2 of hIL1RAP. In some embodiments, the CRISPR gene-editing system for the treatment of low back pain comprises one or more sgRNAs targeting exon 3 of hIL1RAP. In some embodiments, the CRISPR gene-editing system for the treatment of low back pain comprises one or more sgRNAs targeting exon 4 of hIL1RAP. In some embodiments, the CRISPR gene-editing system for the treatment of low back pain comprises one or more sgRNAs targeting exon 5 of hIL1RAP. In some embodiments, the CRISPR gene-editing system for the treatment of low back pain comprises one or more sgRNAs targeting exon 6 of hIL1RAP. In some embodiments, the CRISPR gene-editing system for the treatment of low back pain comprises one or more sgRNAs targeting exon 7 of hIL1RAP. In some embodiments, the CRISPR gene-editing system for the treatment of low back pain comprises one or more sgRNAs targeting exon 8 of hIL1RAP. In some embodiments, the CRISPR gene-editing system for the treatment of low back pain comprises one or more sgRNAs targeting exon 9 of hIL1RAP. In some embodiments, the CRISPR gene-editing system for the treatment of low back pain comprises one or more sgRNAs targeting exon 10 of hIL1RAP. In some embodiments, the CRISPR gene-editing system for the treatment of low back pain comprises one or more sgRNAs targeting exon 11 of hIL1RAP. In some embodiments, the CRISPR gene-editing system for the treatment of low back pain comprises one or more sgRNAs targeting exon 12 of hIL1RAP. In some embodiments, the CRISPR gene-editing system for the treatment of low back pain comprises one or more sgRNAs targeting exon 13 of hIL1RAP. In some embodiments, the CRISPR gene-editing system for the treatment of low back pain comprises one or more sgRNAs

targeting exon 14 of hIL1RAP. In some embodiments, the CRISPR gene-editing system for the treatment of low back pain comprises one or more sgRNAs targeting exon 15 of hIL1RAP. In some embodiments, the CRISPR gene-editing system for the treatment of low back pain comprises one or more sgRNAs targeting exon 16 of hIL1RAP. In some embodiments, the CRISPR gene-editing system for the treatment of low back pain comprises one or more sgRNAs targeting exon 17 of hIL1RAP.

[00356] In some embodiments, the CRISPR gene-editing system for the treatment of low back pain comprises one or more sgRNAs targeting exon 1 of cIL1RAP. In some embodiments, the CRISPR gene-editing system for the treatment of low back pain comprises one or more sgRNAs targeting exon 2 of cIL1RAP. In some embodiments, the CRISPR gene-editing system for the treatment of low back pain comprises one or more sgRNAs targeting exon 3 of cIL1RAP. In some embodiments, the CRISPR gene-editing system for the treatment of low back pain comprises one or more sgRNAs targeting exon 4 of cIL1RAP. In some embodiments, the CRISPR gene-editing system for the treatment of low back pain comprises one or more sgRNAs targeting exon 5 of cIL1RAP. In some embodiments, the CRISPR gene-editing system for the treatment of low back pain comprises one or more sgRNAs targeting exon 6 of cIL1RAP. In some embodiments, the CRISPR gene-editing system for the treatment of low back pain comprises one or more sgRNAs targeting exon 7 of cIL1RAP. In some embodiments, the CRISPR gene-editing system for the treatment of low back pain comprises one or more sgRNAs targeting exon 8 of cIL1RAP. In some embodiments, the CRISPR gene-editing system for the treatment of low back pain comprises one or more sgRNAs targeting exon 9 of cIL1RAP. In some embodiments, the CRISPR gene-editing system for the treatment of low back pain comprises one or more sgRNAs targeting exon 10 of cIL1RAP. In some embodiments, the CRISPR gene-editing system for the treatment of low back pain comprises one or more sgRNAs targeting exon 11 of cIL1RAP. In some embodiments, the CRISPR gene-editing system for the treatment of low back pain comprises one or more sgRNAs targeting exon 12 of cIL1RAP. In some embodiments, the CRISPR gene-editing system for the treatment of low back pain comprises one or more sgRNAs targeting exon 13 of cIL1RAP. In some embodiments, the CRISPR gene-editing system for the treatment of low back pain comprises one or more sgRNAs targeting exon 14 of cIL1RAP. In some embodiments, the CRISPR gene-editing system for the treatment of low back pain comprises one or more sgRNAs targeting exon 15 of cIL1RAP. In some

embodiments, the CRISPR gene-editing system for the treatment of low back pain comprises one or more sgRNAs targeting exon 16 of cIL1RAP.

[00357] In some embodiments, the CRISPR gene-editing system for the treatment of low back pain comprises one or more sgRNAs targeting exon 1 of eIL1RAP. In some embodiments, the CRISPR gene-editing system for the treatment of low back pain comprises one or more sgRNAs targeting exon 2 of eIL1RAP. In some embodiments, the CRISPR gene-editing system for the treatment of low back pain comprises one or more sgRNAs targeting exon 3 of eIL1RAP. In some embodiments, the CRISPR gene-editing system for the treatment of low back pain comprises one or more sgRNAs targeting exon 4 of eIL1RAP. In some embodiments, the CRISPR gene-editing system for the treatment of low back pain comprises one or more sgRNAs targeting exon 5 of eIL1RAP. In some embodiments, the CRISPR gene-editing system for the treatment of low back pain comprises one or more sgRNAs targeting exon 6 of eIL1RAP. In some embodiments, the CRISPR gene-editing system for the treatment of low back pain comprises one or more sgRNAs targeting exon 7 of eIL1RAP. In some embodiments, the CRISPR gene-editing system for the treatment of low back pain comprises one or more sgRNAs targeting exon 8 of eIL1RAP. In some embodiments, the CRISPR gene-editing system for the treatment of low back pain comprises one or more sgRNAs targeting exon 9 of eIL1RAP. In some embodiments, the CRISPR gene-editing system for the treatment of low back pain comprises one or more sgRNAs targeting exon 10 of eIL1RAP. In some embodiments, the CRISPR gene-editing system for the treatment of low back pain comprises one or more sgRNAs targeting exon 11 of eIL1RAP. In some embodiments, the CRISPR gene-editing system for the treatment of low back pain comprises one or more sgRNAs targeting exon 12 of eIL1RAP. In some embodiments, the CRISPR gene-editing system for the treatment of low back pain comprises one or more sgRNAs targeting exon 13 of eIL1RAP.

[00358] In some embodiments, the CRISPR gene-editing system for the treatment of low back pain comprises one or more sgRNAs targeting exon 1 of fIL1RAP. In some embodiments, the CRISPR gene-editing system for the treatment of low back pain comprises one or more sgRNAs targeting exon 2 of fIL1RAP. In some embodiments, the CRISPR gene-editing system for the treatment of low back pain comprises one or more sgRNAs targeting exon 3 of fIL1RAP. In some embodiments, the CRISPR gene-editing system for the treatment of low back pain comprises one or more sgRNAs targeting exon 4 of fIL1RAP. In some embodiments, the CRISPR gene-editing system for the treatment of low back pain

comprises one or more sgRNAs targeting exon 5 of fIL1RAP. In some embodiments, the CRISPR gene-editing system for the treatment of low back pain comprises one or more sgRNAs targeting exon 6 of fIL1RAP. In some embodiments, the CRISPR gene-editing system for the treatment of low back pain comprises one or more sgRNAs targeting exon 7 of fIL1RAP. In some embodiments, the CRISPR gene-editing system for the treatment of low back pain comprises one or more sgRNAs targeting exon 8 of fIL1RAP. In some embodiments, the CRISPR gene-editing system for the treatment of low back pain comprises one or more sgRNAs targeting exon 9 of fIL1RAP. In some embodiments, the CRISPR gene-editing system for the treatment of low back pain comprises one or more sgRNAs targeting exon 10 of fIL1RAP. In some embodiments, the CRISPR gene-editing system for the treatment of low back pain comprises one or more sgRNAs targeting exon 11 of fIL1RAP. In some embodiments, the CRISPR gene-editing system for the treatment of low back pain comprises one or more sgRNAs targeting exon 12 of fIL1RAP. In some embodiments, the CRISPR gene-editing system for the treatment of low back pain comprises one or more sgRNAs targeting exon 13 of fIL1RAP. In some embodiments, the CRISPR gene-editing system for the treatment of low back pain comprises one or more sgRNAs targeting exon 14 of fIL1RAP.

[00359] In some embodiments, the CRISPR gene-editing system for the treatment of low back pain comprises one or more sgRNAs targeting TGFBR1. In some embodiments, the CRISPR gene-editing system for the treatment of low back pain comprises one or more sgRNAs targeting hTGFBR1. In some embodiments, the CRISPR gene-editing system for the treatment of low back pain comprises one or more sgRNAs targeting cTGFBR1. In some embodiments, the CRISPR gene-editing system for the treatment of low back pain comprises one or more sgRNAs targeting e TGFBR1. In some embodiments, the CRISPR gene-editing system for the treatment of low back pain comprises one or more sgRNAs targeting fTGFBR1.

[00360] In some embodiments, the CRISPR gene-editing system for the treatment of low back pain comprises one or more sgRNAs targeting exon 1 of hTGFBR1. In some embodiments, the CRISPR gene-editing system for the treatment of low back pain comprises one or more sgRNAs targeting exon 2 of hTGFBR1. In some embodiments, the CRISPR gene-editing system for the treatment of low back pain comprises one or more sgRNAs targeting exon 3 of hTGFBR1. In some embodiments, the CRISPR gene-editing system for the treatment of low back pain comprises one or more sgRNAs targeting exon 4 of

hTGFBR1. In some embodiments, the CRISPR gene-editing system for the treatment of low back pain comprises one or more sgRNAs targeting exon 5 of hTGFBR1. In some embodiments, the CRISPR gene-editing system for the treatment of low back pain comprises one or more sgRNAs targeting exon 6 of hTGFBR1. In some embodiments, the CRISPR gene-editing system for the treatment of low back pain comprises one or more sgRNAs targeting exon 7 of hTGFBR1. In some embodiments, the CRISPR gene-editing system for the treatment of low back pain comprises one or more sgRNAs targeting exon 8 of hTGFBR1. In some embodiments, the CRISPR gene-editing system for the treatment of low back pain comprises one or more sgRNAs targeting exon 9 of hTGFBR1. In some embodiments, the CRISPR gene-editing system for the treatment of low back pain comprises one or more sgRNAs targeting exon 10 of hTGFBR1. In some embodiments, the CRISPR gene-editing system for the treatment of low back pain comprises one or more sgRNAs targeting exon 11 of hTGFBR1.

[00361] In some embodiments, the CRISPR gene-editing system for the treatment of low back pain comprises one or more sgRNAs targeting exon 1 of cTGFBR1. In some embodiments, the CRISPR gene-editing system for the treatment of low back pain comprises one or more sgRNAs targeting exon 2 of cTGFBR1. In some embodiments, the CRISPR gene-editing system for the treatment of low back pain comprises one or more sgRNAs targeting exon 3 of cTGFBR1. In some embodiments, the CRISPR gene-editing system for the treatment of low back pain comprises one or more sgRNAs targeting exon 4 of cTGFBR1. In some embodiments, the CRISPR gene-editing system for the treatment of low back pain comprises one or more sgRNAs targeting exon 5 of cTGFBR1. In some embodiments, the CRISPR gene-editing system for the treatment of low back pain comprises one or more sgRNAs targeting exon 6 of cTGFBR1. In some embodiments, the CRISPR gene-editing system for the treatment of low back pain comprises one or more sgRNAs targeting exon 7 of cTGFBR1. In some embodiments, the CRISPR gene-editing system for the treatment of low back pain comprises one or more sgRNAs targeting exon 8 of cTGFBR1. In some embodiments, the CRISPR gene-editing system for the treatment of low back pain comprises one or more sgRNAs targeting exon 9 of cTGFBR1.

[00362] In some embodiments, the CRISPR gene-editing system for the treatment of low back pain comprises one or more sgRNAs targeting exon 1 of eTGFBR1. In some embodiments, the CRISPR gene-editing system for the treatment of low back pain comprises one or more sgRNAs targeting exon 2 of eTGFBR1. In some embodiments, the CRISPR

gene-editing system for the treatment of low back pain comprises one or more sgRNAs targeting exon 3 of eTGFBR1. In some embodiments, the CRISPR gene-editing system for the treatment of low back pain comprises one or more sgRNAs targeting exon 4 of eTGFBR1. In some embodiments, the CRISPR gene-editing system for the treatment of low back pain comprises one or more sgRNAs targeting exon 5 of eTGFBR1. In some embodiments, the CRISPR gene-editing system for the treatment of low back pain comprises one or more sgRNAs targeting exon 6 of eTGFBR1. In some embodiments, the CRISPR gene-editing system for the treatment of low back pain comprises one or more sgRNAs targeting exon 7 of eTGFBR1. In some embodiments, the CRISPR gene-editing system for the treatment of low back pain comprises one or more sgRNAs targeting exon 8 of eTGFBR1. In some embodiments, the CRISPR gene-editing system for the treatment of low back pain comprises one or more sgRNAs targeting exon 9 of eTGFBR1. In some embodiments, the CRISPR gene-editing system for the treatment of low back pain comprises one or more sgRNAs targeting exon 10 of eTGFBR1. In some embodiments, the CRISPR gene-editing system for the treatment of low back pain comprises one or more sgRNAs targeting exon 11 of eTGFBR1. In some embodiments, the CRISPR gene-editing system for the treatment of low back pain comprises one or more sgRNAs targeting exon 12 of eTGFBR1.

[00363] In some embodiments, the CRISPR gene-editing system for the treatment of low back pain comprises one or more sgRNAs targeting exon 1 of fTGFBR1. In some embodiments, the CRISPR gene-editing system for the treatment of low back pain comprises one or more sgRNAs targeting exon 2 of fTGFBR1. In some embodiments, the CRISPR gene-editing system for the treatment of low back pain comprises one or more sgRNAs targeting exon 3 of fTGFBR1. In some embodiments, the CRISPR gene-editing system for the treatment of low back pain comprises one or more sgRNAs targeting exon 4 of fTGFBR1. In some embodiments, the CRISPR gene-editing system for the treatment of low back pain comprises one or more sgRNAs targeting exon 5 of fTGFBR1. In some embodiments, the CRISPR gene-editing system for the treatment of low back pain comprises one or more sgRNAs targeting exon 6 of fTGFBR1. In some embodiments, the CRISPR gene-editing system for the treatment of low back pain comprises one or more sgRNAs targeting exon 7 of fTGFBR1. In some embodiments, the CRISPR gene-editing system for the treatment of low back pain comprises one or more sgRNAs targeting exon 8 of fTGFBR1. In some embodiments, the CRISPR gene-editing system for the treatment of low back pain comprises

one or more sgRNAs targeting exon 9 of fTGFBR1. In some embodiments, the CRISPR gene-editing system for the treatment of low back pain comprises one or more sgRNAs targeting exon 10 of fTGFBR1. In some embodiments, the CRISPR gene-editing system for the treatment of low back pain comprises one or more sgRNAs targeting exon 11 of fTGFBR1.

[00364] In some embodiments, the CRISPR gene-editing system for the treatment of low back pain comprises one or more sgRNAs targeting TGFBR2. In some embodiments, the CRISPR gene-editing system for the treatment of low back pain comprises one or more sgRNAs targeting hTGFBR2. In some embodiments, the CRISPR gene-editing system for the treatment of low back pain comprises one or more sgRNAs targeting cTGFBR2. In some embodiments, the CRISPR gene-editing system for the treatment of low back pain comprises one or more sgRNAs targeting eTGFBR2. In some embodiments, the CRISPR gene-editing system for the treatment of low back pain comprises one or more sgRNAs targeting fTGFBR2.

[00365] In some embodiments, the CRISPR gene-editing system for the treatment of low back pain comprises one or more sgRNAs targeting exon 1 of hTGFBR2. In some embodiments, the CRISPR gene-editing system for the treatment of low back pain comprises one or more sgRNAs targeting exon 2 of hTGFBR2. In some embodiments, the CRISPR gene-editing system for the treatment of low back pain comprises one or more sgRNAs targeting exon 3 of hTGFBR2. In some embodiments, the CRISPR gene-editing system for the treatment of low back pain comprises one or more sgRNAs targeting exon 4 of hTGFBR2. In some embodiments, the CRISPR gene-editing system for the treatment of low back pain comprises one or more sgRNAs targeting exon 5 of hTGFBR2. In some embodiments, the CRISPR gene-editing system for the treatment of low back pain comprises one or more sgRNAs targeting exon 6 of hTGFBR2. In some embodiments, the CRISPR gene-editing system for the treatment of low back pain comprises one or more sgRNAs targeting exon 7 of hTGFBR2. In some embodiments, the CRISPR gene-editing system for the treatment of low back pain comprises one or more sgRNAs targeting exon 8 of hTGFBR2. In some embodiments, the CRISPR gene-editing system for the treatment of low back pain comprises one or more sgRNAs targeting exon 9 of hTGFBR2.

[00366] In some embodiments, the CRISPR gene-editing system for the treatment of low back pain comprises one or more sgRNAs targeting exon 1 of cTGFBR2. In some embodiments, the CRISPR gene-editing system for the treatment of low back pain comprises

one or more sgRNAs targeting exon 2 of cTGFBR2. In some embodiments, the CRISPR gene-editing system for the treatment of low back pain comprises one or more sgRNAs targeting exon 3 of cTGFBR2. In some embodiments, the CRISPR gene-editing system for the treatment of low back pain comprises one or more sgRNAs targeting exon 4 of cTGFBR2. In some embodiments, the CRISPR gene-editing system for the treatment of low back pain comprises one or more sgRNAs targeting exon 5 of cTGFBR2. In some embodiments, the CRISPR gene-editing system for the treatment of low back pain comprises one or more sgRNAs targeting exon 6 of cTGFBR2. In some embodiments, the CRISPR gene-editing system for the treatment of low back pain comprises one or more sgRNAs targeting exon 7 of cTGFBR2. In some embodiments, the CRISPR gene-editing system for the treatment of low back pain comprises one or more sgRNAs targeting exon 8 of cTGFBR2.

[00367] In some embodiments, the CRISPR gene-editing system for the treatment of low back pain comprises one or more sgRNAs targeting exon 1 of eTGFBR2. In some embodiments, the CRISPR gene-editing system for the treatment of low back pain comprises one or more sgRNAs targeting exon 2 of eTGFBR2. In some embodiments, the CRISPR gene-editing system for the treatment of low back pain comprises one or more sgRNAs targeting exon 3 of eTGFBR2. In some embodiments, the CRISPR gene-editing system for the treatment of low back pain comprises one or more sgRNAs targeting exon 4 of eTGFBR2. In some embodiments, the CRISPR gene-editing system for the treatment of low back pain comprises one or more sgRNAs targeting exon 5 of eTGFBR2. In some embodiments, the CRISPR gene-editing system for the treatment of low back pain comprises one or more sgRNAs targeting exon 6 of eTGFBR2. In some embodiments, the CRISPR gene-editing system for the treatment of low back pain comprises one or more sgRNAs targeting exon 7 of eTGFBR2. In some embodiments, the CRISPR gene-editing system for the treatment of low back pain comprises one or more sgRNAs targeting exon 8 of eTGFBR2. In some embodiments, the CRISPR gene-editing system for the treatment of low back pain comprises one or more sgRNAs targeting exon 9 of eTGFBR2. In some embodiments, the CRISPR gene-editing system for the treatment of low back pain comprises one or more sgRNAs targeting exon 10 of eTGFBR2.

[00368] In some embodiments, the CRISPR gene-editing system for the treatment of low back pain comprises one or more sgRNAs targeting exon 1 of fTGFBR2. In some embodiments, the CRISPR gene-editing system for the treatment of low back pain comprises

one or more sgRNAs targeting exon 2 of fTGFBR2. In some embodiments, the CRISPR gene-editing system for the treatment of low back pain comprises one or more sgRNAs targeting exon 3 of fTGFBR2. In some embodiments, the CRISPR gene-editing system for the treatment of low back pain comprises one or more sgRNAs targeting exon 4 of fTGFBR2. In some embodiments, the CRISPR gene-editing system for the treatment of low back pain comprises one or more sgRNAs targeting exon 5 of fTGFBR2. In some embodiments, the CRISPR gene-editing system for the treatment of low back pain comprises one or more sgRNAs targeting exon 6 of fTGFBR2. In some embodiments, the CRISPR gene-editing system for the treatment of low back pain comprises one or more sgRNAs targeting exon 7 of fTGFBR2. In some embodiments, the CRISPR gene-editing system for the treatment of low back pain comprises one or more sgRNAs targeting exon 8 of fTGFBR2.

[00369] In some embodiments, the CRISPR gene-editing system for the treatment of low back pain comprises one or more sgRNAs targeting IL6R. In some embodiments, the CRISPR gene-editing system for the treatment of low back pain comprises one or more sgRNAs targeting hIL6R. In some embodiments, the CRISPR gene-editing system for the treatment of low back pain comprises one or more sgRNAs targeting cIL6R. In some embodiments, the CRISPR gene-editing system for the treatment of low back pain comprises one or more sgRNAs targeting eIL6R. In some embodiments, the CRISPR gene-editing system for the treatment of low back pain comprises one or more sgRNAs targeting fIL6R.

[00370] In some embodiments, the CRISPR gene-editing system for the treatment of low back pain comprises one or more sgRNAs targeting exon 1 of hIL6R. In some embodiments, the CRISPR gene-editing system for the treatment of low back pain comprises one or more sgRNAs targeting exon 2 of hIL6R. In some embodiments, the CRISPR gene-editing system for the treatment of low back pain comprises one or more sgRNAs targeting exon 3 of hIL6R. In some embodiments, the CRISPR gene-editing system for the treatment of low back pain comprises one or more sgRNAs targeting exon 4 of hIL6R. In some embodiments, the CRISPR gene-editing system for the treatment of low back pain comprises one or more sgRNAs targeting exon 5 of hIL6R. In some embodiments, the CRISPR gene-editing system for the treatment of low back pain comprises one or more sgRNAs targeting exon 6 of hIL6R. In some embodiments, the CRISPR gene-editing system for the treatment of low back pain comprises one or more sgRNAs targeting exon 7 of hIL6R. In some embodiments, the CRISPR gene-editing system for the treatment of low back pain comprises one or more sgRNAs targeting exon 8 of hIL6R. In some embodiments, the CRISPR gene-editing system

for the treatment of low back pain comprises one or more sgRNAs targeting exon 9 of hIL6R. In some embodiments, the CRISPR gene-editing system for the treatment of low back pain comprises one or more sgRNAs targeting exon 10 of hIL6R. In some embodiments, the CRISPR gene-editing system for the treatment of low back pain comprises one or more sgRNAs targeting exon 11 of hIL6R In some embodiments, the CRISPR gene-editing system for the treatment of low back pain comprises one or more sgRNAs targeting exon 12 of hIL6R. In some embodiments, the CRISPR gene-editing system for the treatment of low back pain comprises one or more sgRNAs targeting exon 13 of hIL6R. In some embodiments, the CRISPR gene-editing system for the treatment of low back pain comprises one or more sgRNAs targeting exon 14 of hIL6R. In some embodiments, the CRISPR gene-editing system for the treatment of low back pain comprises one or more sgRNAs targeting exon 15 of hIL6R.

[00371] In some embodiments, the CRISPR gene-editing system for the treatment of low back pain comprises one or more sgRNAs targeting exon 1 of cIL6R. In some embodiments, the CRISPR gene-editing system for the treatment of low back pain comprises one or more sgRNAs targeting exon 2 of cIL6R. In some embodiments, the CRISPR gene-editing system for the treatment of low back pain comprises one or more sgRNAs targeting exon 3 of cIL6R. In some embodiments, the CRISPR gene-editing system for the treatment of low back pain comprises one or more sgRNAs targeting exon 4 of cIL6R. In some embodiments, the CRISPR gene-editing system for the treatment of low back pain comprises one or more sgRNAs targeting exon 5 of cIL6R. In some embodiments, the CRISPR gene-editing system for the treatment of low back pain comprises one or more sgRNAs targeting exon 6 of cIL6R. In some embodiments, the CRISPR gene-editing system for the treatment of low back pain comprises one or more sgRNAs targeting exon 7 of cIL6R. In some embodiments, the CRISPR gene-editing system for the treatment of low back pain comprises one or more sgRNAs targeting exon 8 of cIL6R. In some embodiments, the CRISPR gene-editing system for the treatment of low back pain comprises one or more sgRNAs targeting exon 9 of cIL6R. In some embodiments, the CRISPR gene-editing system for the treatment of low back pain comprises one or more sgRNAs targeting exon 10 of cIL6R. In some embodiments, the CRISPR gene-editing system for the treatment of low back pain comprises one or more sgRNAs targeting exon 11 of cIL6R. In some embodiments, the CRISPR gene-editing system for the treatment of low back pain comprises one or more sgRNAs targeting exon 12 of

cIL6R. In some embodiments, the CRISPR gene-editing system for the treatment of low back pain comprises one or more sgRNAs targeting exon 13 of cIL6R.

[00372] In some embodiments, the CRISPR gene-editing system for the treatment of low back pain comprises one or more sgRNAs targeting exon 1 of eIL6R. In some embodiments, the CRISPR gene-editing system for the treatment of low back pain comprises one or more sgRNAs targeting exon 2 of eIL6R. In some embodiments, the CRISPR gene-editing system for the treatment of low back pain comprises one or more sgRNAs targeting exon 3 of eIL6R. In some embodiments, the CRISPR gene-editing system for the treatment of low back pain comprises one or more sgRNAs targeting exon 4 of eIL6R. In some embodiments, the CRISPR gene-editing system for the treatment of low back pain comprises one or more sgRNAs targeting exon 5 of eIL6R. In some embodiments, the CRISPR gene-editing system for the treatment of low back pain comprises one or more sgRNAs targeting exon 6 of eIL6R. In some embodiments, the CRISPR gene-editing system for the treatment of low back pain comprises one or more sgRNAs targeting exon 7 of eIL6R. In some embodiments, the CRISPR gene-editing system for the treatment of low back pain comprises one or more sgRNAs targeting exon 8 of eIL6R. In some embodiments, the CRISPR gene-editing system for the treatment of low back pain comprises one or more sgRNAs targeting exon 9 of eIL6R. In some embodiments, the CRISPR gene-editing system for the treatment of low back pain comprises one or more sgRNAs targeting exon 10 of eIL6R. In some embodiments, the CRISPR gene-editing system for the treatment of low back pain comprises one or more sgRNAs targeting exon 11 of eIL6R.

[00373] In some embodiments, the CRISPR gene-editing system for the treatment of low back pain comprises one or more sgRNAs targeting exon 1 of fIL6R. In some embodiments, the CRISPR gene-editing system for the treatment of low back pain comprises one or more sgRNAs targeting exon 2 of fIL6R. In some embodiments, the CRISPR gene-editing system for the treatment of low back pain comprises one or more sgRNAs targeting exon 3 of fIL6R. In some embodiments, the CRISPR gene-editing system for the treatment of low back pain comprises one or more sgRNAs targeting exon 4 of fIL6R. In some embodiments, the CRISPR gene-editing system for the treatment of low back pain comprises one or more sgRNAs targeting exon 5 of fIL6R. In some embodiments, the CRISPR gene-editing system for the treatment of low back pain comprises one or more sgRNAs targeting exon 6 of fIL6R. In some embodiments, the CRISPR gene-editing system for the treatment of low back pain comprises one or more sgRNAs targeting exon 7 of fIL6R. In some embodiments, the

CRISPR gene-editing system for the treatment of low back pain comprises one or more sgRNAs targeting exon 8 of fIL6R. In some embodiments, the CRISPR gene-editing system for the treatment of low back pain comprises one or more sgRNAs targeting exon 9 of fIL6R. In some embodiments, the CRISPR gene-editing system for the treatment of low back pain comprises one or more sgRNAs targeting exon 10 of fIL6R.

[00374] In some embodiments, the CRISPR gene-editing system for the treatment of low back pain comprises one or more sgRNAs targeting IL6ST. In some embodiments, the CRISPR gene-editing system for the treatment of low back pain comprises one or more sgRNAs targeting hIL6ST. In some embodiments, the CRISPR gene-editing system for the treatment of low back pain comprises one or more sgRNAs targeting cIL6ST. In some embodiments, the CRISPR gene-editing system for the treatment of low back pain comprises one or more sgRNAs targeting eIL6ST. In some embodiments, the CRISPR gene-editing system for the treatment of low back pain comprises one or more sgRNAs targeting fIL6ST.

[00375] In some embodiments, the CRISPR gene-editing system for the treatment of low back pain comprises one or more sgRNAs targeting exon 1 of hIL6ST. In some embodiments, the CRISPR gene-editing system for the treatment of low back pain comprises one or more sgRNAs targeting exon 2 of hIL6ST. In some embodiments, the CRISPR gene-editing system for the treatment of low back pain comprises one or more sgRNAs targeting exon 3 of hIL6ST. In some embodiments, the CRISPR gene-editing system for the treatment of low back pain comprises one or more sgRNAs targeting exon 4 of hIL6ST. In some embodiments, the CRISPR gene-editing system for the treatment of low back pain comprises one or more sgRNAs targeting exon 5 of hIL6ST. In some embodiments, the CRISPR gene-editing system for the treatment of low back pain comprises one or more sgRNAs targeting exon 6 of hIL6ST. In some embodiments, the CRISPR gene-editing system for the treatment of low back pain comprises one or more sgRNAs targeting exon 7 of hIL6ST. In some embodiments, the CRISPR gene-editing system for the treatment of low back pain comprises one or more sgRNAs targeting exon 8 of hIL6ST. In some embodiments, the CRISPR gene-editing system for the treatment of low back pain comprises one or more sgRNAs targeting exon 9 of hIL6ST. In some embodiments, the CRISPR gene-editing system for the treatment of low back pain comprises one or more sgRNAs targeting exon 10 of hIL6ST. In some embodiments, the CRISPR gene-editing system for the treatment of low back pain comprises one or more sgRNAs targeting exon 11 of hIL6ST. In some embodiments, the CRISPR gene-editing system for the treatment of low back pain comprises one or more sgRNAs targeting

exon 12 of hIL6ST. In some embodiments, the CRISPR gene-editing system for the treatment of low back pain comprises one or more sgRNAs targeting exon 13 of hIL6ST. In some embodiments, the CRISPR gene-editing system for the treatment of low back pain comprises one or more sgRNAs targeting exon 14 of hIL6ST. In some embodiments, the CRISPR gene-editing system for the treatment of low back pain comprises one or more sgRNAs targeting exon 15 of hIL6ST. In some embodiments, the CRISPR gene-editing system for the treatment of low back pain comprises one or more sgRNAs targeting exon 16 of hIL6ST. In some embodiments, the CRISPR gene-editing system for the treatment of low back pain comprises one or more sgRNAs targeting exon 17 of hIL6ST. In some embodiments, the CRISPR gene-editing system for the treatment of low back pain comprises one or more sgRNAs targeting exon 18 of hIL6ST. In some embodiments, the CRISPR gene-editing system for the treatment of low back pain comprises one or more sgRNAs targeting exon 19 of hIL6ST.

[00376] In some embodiments, the CRISPR gene-editing system for the treatment of low back pain comprises one or more sgRNAs targeting exon 1 of cIL6ST. In some embodiments, the CRISPR gene-editing system for the treatment of low back pain comprises one or more sgRNAs targeting exon 2 of cIL6ST. In some embodiments, the CRISPR gene-editing system for the treatment of low back pain comprises one or more sgRNAs targeting exon 3 of cIL6ST. In some embodiments, the CRISPR gene-editing system for the treatment of low back pain comprises one or more sgRNAs targeting exon 4 of cIL6ST. In some embodiments, the CRISPR gene-editing system for the treatment of low back pain comprises one or more sgRNAs targeting exon 5 of cIL6ST. In some embodiments, the CRISPR gene-editing system for the treatment of low back pain comprises one or more sgRNAs targeting exon 6 of cIL6ST. In some embodiments, the CRISPR gene-editing system for the treatment of low back pain comprises one or more sgRNAs targeting exon 7 of cIL6ST. In some embodiments, the CRISPR gene-editing system for the treatment of low back pain comprises one or more sgRNAs targeting exon 8 of cIL6ST. In some embodiments, the CRISPR gene-editing system for the treatment of low back pain comprises one or more sgRNAs targeting exon 9 of cIL6ST. In some embodiments, the CRISPR gene-editing system for the treatment of low back pain comprises one or more sgRNAs targeting exon 10 of cIL6ST. In some embodiments, the CRISPR gene-editing system for the treatment of low back pain comprises one or more sgRNAs targeting exon 11 of cIL6ST In some embodiments, the CRISPR gene-editing system for the treatment of low back pain comprises one or more sgRNAs targeting exon 12 of cIL6ST. In some embodiments, the CRISPR gene-editing system for the treatment

of low back pain comprises one or more sgRNAs targeting exon 13 of cIL6ST. In some embodiments, the CRISPR gene-editing system for the treatment of low back pain comprises one or more sgRNAs targeting exon 14 of cIL6ST. In some embodiments, the CRISPR gene-editing system for the treatment of low back pain comprises one or more sgRNAs targeting exon 15 of cIL6ST. In some embodiments, the CRISPR gene-editing system for the treatment of low back pain comprises one or more sgRNAs targeting exon 16 of cIL6ST. In some embodiments, the CRISPR gene-editing system for the treatment of low back pain comprises one or more sgRNAs targeting exon 17 of cIL6ST. In some embodiments, the CRISPR gene-editing system for the treatment of low back pain comprises one or more sgRNAs targeting exon 18 of cIL6ST.

[00377] In some embodiments, the CRISPR gene-editing system for the treatment of low back pain comprises one or more sgRNAs targeting exon 1 of eIL6ST. In some embodiments, the CRISPR gene-editing system for the treatment of low back pain comprises one or more sgRNAs targeting exon 2 of eIL6ST. In some embodiments, the CRISPR gene-editing system for the treatment of low back pain comprises one or more sgRNAs targeting exon 3 of eIL6ST. In some embodiments, the CRISPR gene-editing system for the treatment of low back pain comprises one or more sgRNAs targeting exon 4 of eIL6ST. In some embodiments, the CRISPR gene-editing system for the treatment of low back pain comprises one or more sgRNAs targeting exon 5 of eIL6ST. In some embodiments, the CRISPR gene-editing system for the treatment of low back pain comprises one or more sgRNAs targeting exon 6 of eIL6ST. In some embodiments, the CRISPR gene-editing system for the treatment of low back pain comprises one or more sgRNAs targeting exon 7 of eIL6ST. In some embodiments, the CRISPR gene-editing system for the treatment of low back pain comprises one or more sgRNAs targeting exon 8 of eIL6ST. In some embodiments, the CRISPR gene-editing system for the treatment of low back pain comprises one or more sgRNAs targeting exon 9 of eIL6ST. In some embodiments, the CRISPR gene-editing system for the treatment of low back pain comprises one or more sgRNAs targeting exon 10 of eIL6ST. In some embodiments, the CRISPR gene-editing system for the treatment of low back pain comprises one or more sgRNAs targeting exon 11 of eIL6ST In some embodiments, the CRISPR gene-editing system for the treatment of low back pain comprises one or more sgRNAs targeting exon 12 of eIL6ST. In some embodiments, the CRISPR gene-editing system for the treatment of low back pain comprises one or more sgRNAs targeting exon 13 of eIL6ST. In some embodiments, the CRISPR gene-editing system for the treatment of low back pain comprises

one or more sgRNAs targeting exon 14 of eIL6ST. In some embodiments, the CRISPR gene-editing system for the treatment of low back pain comprises one or more sgRNAs targeting exon 15 of eIL6ST. In some embodiments, the CRISPR gene-editing system for the treatment of low back pain comprises one or more sgRNAs targeting exon 16 of eIL6ST. In some embodiments, the CRISPR gene-editing system for the treatment of low back pain comprises one or more sgRNAs targeting exon 17 of eIL6ST. In some embodiments, the CRISPR gene-editing system for the treatment of low back pain comprises one or more sgRNAs targeting exon 18 of eIL6ST.

[00378] In some embodiments, the CRISPR gene-editing system for the treatment of low back pain comprises one or more sgRNAs targeting exon 1 of fIL6ST. In some embodiments, the CRISPR gene-editing system for the treatment of low back pain comprises one or more sgRNAs targeting exon 2 of fIL6ST. In some embodiments, the CRISPR gene-editing system for the treatment of low back pain comprises one or more sgRNAs targeting exon 3 of fIL6ST. In some embodiments, the CRISPR gene-editing system for the treatment of low back pain comprises one or more sgRNAs targeting exon 4 of fIL6ST. In some embodiments, the CRISPR gene-editing system for the treatment of low back pain comprises one or more sgRNAs targeting exon 5 of fIL6ST. In some embodiments, the CRISPR gene-editing system for the treatment of low back pain comprises one or more sgRNAs targeting exon 6 of fIL6ST. In some embodiments, the CRISPR gene-editing system for the treatment of low back pain comprises one or more sgRNAs targeting exon 7 of fIL6ST. In some embodiments, the CRISPR gene-editing system for the treatment of low back pain comprises one or more sgRNAs targeting exon 8 of fIL6ST. In some embodiments, the CRISPR gene-editing system for the treatment of low back pain comprises one or more sgRNAs targeting exon 9 of fIL6ST. In some embodiments, the CRISPR gene-editing system for the treatment of low back pain comprises one or more sgRNAs targeting exon 10 of fIL6ST. In some embodiments, the CRISPR gene-editing system for the treatment of low back pain comprises one or more sgRNAs targeting exon 11 of fIL6ST In some embodiments, the CRISPR gene-editing system for the treatment of low back pain comprises one or more sgRNAs targeting exon 12 of fIL6ST. In some embodiments, the CRISPR gene-editing system for the treatment of low back pain comprises one or more sgRNAs targeting exon 13 of fIL6ST. In some embodiments, the CRISPR gene-editing system for the treatment of low back pain comprises one or more sgRNAs targeting exon 14 of fIL6ST. In some embodiments, the CRISPR gene-editing system for the treatment of low back pain comprises one or more sgRNAs targeting

exon 15 of fIL6ST. In some embodiments, the CRISPR gene-editing system for the treatment of low back pain comprises one or more sgRNAs targeting exon 16 of fIL6ST. In some embodiments, the CRISPR gene-editing system for the treatment of low back pain comprises one or more sgRNAs targeting exon 17 of fIL6ST. In some embodiments, the CRISPR gene-editing system for the treatment of low back pain comprises one or more sgRNAs targeting exon 18 of fIL6ST. In some embodiments, the CRISPR gene-editing system for the treatment of low back pain comprises one or more sgRNAs targeting exon 19 of fIL6ST. In some embodiments, the CRISPR gene-editing system for the treatment of low back pain comprises one or more sgRNAs targeting exon 20 of fIL6ST.

[00379] In some embodiments, the CRISPR gene-editing system for the treatment of low back pain comprises one or more sgRNAs targeting TNFRSF1A. In some embodiments, the CRISPR gene-editing system for the treatment of low back pain comprises one or more sgRNAs targeting hTNFRSF1A. In some embodiments, the CRISPR gene-editing system for the treatment of low back pain comprises one or more sgRNAs targeting cTNFRSF1A. In some embodiments, the CRISPR gene-editing system for the treatment of low back pain comprises one or more sgRNAs targeting eTNFRSF1A. In some embodiments, the CRISPR gene-editing system for the treatment of low back pain comprises one or more sgRNAs targeting fTNFRSF1A.

[00380] In some embodiments, the CRISPR gene-editing system for the treatment of low back pain comprises one or more sgRNAs targeting exon 1 of hTNFRSF1A. In some embodiments, the CRISPR gene-editing system for the treatment of low back pain comprises one or more sgRNAs targeting exon 2 of hTNFRSF1A. In some embodiments, the CRISPR gene-editing system for the treatment of low back pain comprises one or more sgRNAs targeting exon 3 of hTNFRSF1A. In some embodiments, the CRISPR gene-editing system for the treatment of low back pain comprises one or more sgRNAs targeting exon 4 of hTNFRSF1A. In some embodiments, the CRISPR gene-editing system for the treatment of low back pain comprises one or more sgRNAs targeting exon 5 of hTNFRSF1A. In some embodiments, the CRISPR gene-editing system for the treatment of low back pain comprises one or more sgRNAs targeting exon 6 of hTNFRSF1A. In some embodiments, the CRISPR gene-editing system for the treatment of low back pain comprises one or more sgRNAs targeting exon 7 of hTNFRSF1A. In some embodiments, the CRISPR gene-editing system for the treatment of low back pain comprises one or more sgRNAs targeting exon 8 of hTNFRSF1A. In some embodiments, the CRISPR gene-editing system for the treatment of

low back pain comprises one or more sgRNAs targeting exon 9 of hTNFRSF1A. In some embodiments, the CRISPR gene-editing system for the treatment of low back pain comprises one or more sgRNAs targeting exon 10 of hTNFRSF1A. In some embodiments, the CRISPR gene-editing system for the treatment of low back pain comprises one or more sgRNAs targeting exon 11 of hTNFRSF1A.

[00381] In some embodiments, the CRISPR gene-editing system for the treatment of low back pain comprises one or more sgRNAs targeting exon 1 of cTNFRSF1A. In some embodiments, the CRISPR gene-editing system for the treatment of low back pain comprises one or more sgRNAs targeting exon 2 of cTNFRSF1A. In some embodiments, the CRISPR gene-editing system for the treatment of low back pain comprises one or more sgRNAs targeting exon 3 of cTNFRSF1A. In some embodiments, the CRISPR gene-editing system for the treatment of low back pain comprises one or more sgRNAs targeting exon 4 of cTNFRSF1A. In some embodiments, the CRISPR gene-editing system for the treatment of low back pain comprises one or more sgRNAs targeting exon 5 of cTNFRSF1A. In some embodiments, the CRISPR gene-editing system for the treatment of low back pain comprises one or more sgRNAs targeting exon 6 of cTNFRSF1A. In some embodiments, the CRISPR gene-editing system for the treatment of low back pain comprises one or more sgRNAs targeting exon 7 of cTNFRSF1A. In some embodiments, the CRISPR gene-editing system for the treatment of low back pain comprises one or more sgRNAs targeting exon 8 of cTNFRSF1A. In some embodiments, the CRISPR gene-editing system for the treatment of low back pain comprises one or more sgRNAs targeting exon 9 of cTNFRSF1A. In some embodiments, the CRISPR gene-editing system for the treatment of low back pain comprises one or more sgRNAs targeting exon 10 of cTNFRSF1A. In some embodiments, the CRISPR gene-editing system for the treatment of low back pain comprises one or more sgRNAs targeting exon 11 of cTNFRSF1A.

[00382] In some embodiments, the CRISPR gene-editing system for the treatment of low back pain comprises one or more sgRNAs targeting exon 1 of eTNFRSF1A. In some embodiments, the CRISPR gene-editing system for the treatment of low back pain comprises one or more sgRNAs targeting exon 2 of eTNFRSF1A. In some embodiments, the CRISPR gene-editing system for the treatment of low back pain comprises one or more sgRNAs targeting exon 3 of eTNFRSF1A. In some embodiments, the CRISPR gene-editing system for the treatment of low back pain comprises one or more sgRNAs targeting exon 4 of eTNFRSF1A. In some embodiments, the CRISPR gene-editing system for the treatment of

low back pain comprises one or more sgRNAs targeting exon 5 of eTNFRSF1A. In some embodiments, the CRISPR gene-editing system for the treatment of low back pain comprises one or more sgRNAs targeting exon 6 of eTNFRSF1A. In some embodiments, the CRISPR gene-editing system for the treatment of low back pain comprises one or more sgRNAs targeting exon 7 of eTNFRSF1A. In some embodiments, the CRISPR gene-editing system for the treatment of low back pain comprises one or more sgRNAs targeting exon 8 of eTNFRSF1A. In some embodiments, the CRISPR gene-editing system for the treatment of low back pain comprises one or more sgRNAs targeting exon 9 of eTNFRSF1A. In some embodiments, the CRISPR gene-editing system for the treatment of low back pain comprises one or more sgRNAs targeting exon 10 of eTNFRSF1A.

[00383] In some embodiments, the CRISPR gene-editing system for the treatment of low back pain comprises one or more sgRNAs targeting exon 1 of fTNFRSF1A. In some embodiments, the CRISPR gene-editing system for the treatment of low back pain comprises one or more sgRNAs targeting exon 2 of fTNFRSF1A. In some embodiments, the CRISPR gene-editing system for the treatment of low back pain comprises one or more sgRNAs targeting exon 3 of fTNFRSF1A. In some embodiments, the CRISPR gene-editing system for the treatment of low back pain comprises one or more sgRNAs targeting exon 4 of fTNFRSF1A. In some embodiments, the CRISPR gene-editing system for the treatment of low back pain comprises one or more sgRNAs targeting exon 5 of fTNFRSF1A. In some embodiments, the CRISPR gene-editing system for the treatment of low back pain comprises one or more sgRNAs targeting exon 6 of fTNFRSF1A. In some embodiments, the CRISPR gene-editing system for the treatment of low back pain comprises one or more sgRNAs targeting exon 7 of fTNFRSF1A. In some embodiments, the CRISPR gene-editing system for the treatment of low back pain comprises one or more sgRNAs targeting exon 8 of fTNFRSF1A. In some embodiments, the CRISPR gene-editing system for the treatment of low back pain comprises one or more sgRNAs targeting exon 9 of fTNFRSF1A. In some embodiments, the CRISPR gene-editing system for the treatment of low back pain comprises one or more sgRNAs targeting exon 10 of fTNFRSF1A.

[00384] In some embodiments, the CRISPR gene-editing system for the treatment of low back pain comprises one or more sgRNAs targeting TNFRSF1B. In some embodiments, the CRISPR gene-editing system for the treatment of low back pain comprises one or more sgRNAs targeting hTNFRSF1B. In some embodiments, the CRISPR gene-editing system for the treatment of low back pain comprises one or more sgRNAs targeting cTNFRSF1B. In

some embodiments, the CRISPR gene-editing system for the treatment of low back pain comprises one or more sgRNAs targeting eTNFRSF1B. In some embodiments, the CRISPR gene-editing system for the treatment of low back pain comprises one or more sgRNAs targeting fTNFRSF1B.

[00385] In some embodiments, the CRISPR gene-editing system for the treatment of low back pain comprises one or more sgRNAs targeting exon 1 of hTNFRSF1B. In some embodiments, the CRISPR gene-editing system for the treatment of low back pain comprises one or more sgRNAs targeting exon 2 of hTNFRSF1B. In some embodiments, the CRISPR gene-editing system for the treatment of low back pain comprises one or more sgRNAs targeting exon 3 of hTNFRSF1B. In some embodiments, the CRISPR gene-editing system for the treatment of low back pain comprises one or more sgRNAs targeting exon 4 of hTNFRSF1B. In some embodiments, the CRISPR gene-editing system for the treatment of low back pain comprises one or more sgRNAs targeting exon 5 of hTNFRSF1B. In some embodiments, the CRISPR gene-editing system for the treatment of low back pain comprises one or more sgRNAs targeting exon 6 of hTNFRSF1B. In some embodiments, the CRISPR gene-editing system for the treatment of low back pain comprises one or more sgRNAs targeting exon 7 of hTNFRSF1B. In some embodiments, the CRISPR gene-editing system for the treatment of low back pain comprises one or more sgRNAs targeting exon 8 of hTNFRSF1B. In some embodiments, the CRISPR gene-editing system for the treatment of low back pain comprises one or more sgRNAs targeting exon 9 of hTNFRSF1B. In some embodiments, the CRISPR gene-editing system for the treatment of low back pain comprises one or more sgRNAs targeting exon 10 of hTNFRSF1B. In some embodiments, the CRISPR gene-editing system for the treatment of low back pain comprises one or more sgRNAs targeting exon 11 of hTNFRSF1B In some embodiments, the CRISPR gene-editing system for the treatment of low back pain comprises one or more sgRNAs targeting exon 12 of hTNFRSF1B. In some embodiments, the CRISPR gene-editing system for the treatment of low back pain comprises one or more sgRNAs targeting exon 13 of hTNFRSF1B.

[00386] In some embodiments, the CRISPR gene-editing system for the treatment of low back pain comprises one or more sgRNAs targeting exon 1 of cTNFRSF1B. In some embodiments, the CRISPR gene-editing system for the treatment of low back pain comprises one or more sgRNAs targeting exon 2 of cTNFRSF1B. In some embodiments, the CRISPR gene-editing system for the treatment of low back pain comprises one or more sgRNAs targeting exon 3 of cTNFRSF1B. In some embodiments, the CRISPR gene-editing system

for the treatment of low back pain comprises one or more sgRNAs targeting exon 4 of cTNFRSF1B. In some embodiments, the CRISPR gene-editing system for the treatment of low back pain comprises one or more sgRNAs targeting exon 5 of cTNFRSF1B. In some embodiments, the CRISPR gene-editing system for the treatment of low back pain comprises one or more sgRNAs targeting exon 6 of cTNFRSF1B. In some embodiments, the CRISPR gene-editing system for the treatment of low back pain comprises one or more sgRNAs targeting exon 7 of cTNFRSF1B. In some embodiments, the CRISPR gene-editing system for the treatment of low back pain comprises one or more sgRNAs targeting exon 8 of cTNFRSF1B. In some embodiments, the CRISPR gene-editing system for the treatment of low back pain comprises one or more sgRNAs targeting exon 9 of cTNFRSF1B. In some embodiments, the CRISPR gene-editing system for the treatment of low back pain comprises one or more sgRNAs targeting exon 10 of cTNFRSF1B. In some embodiments, the CRISPR gene-editing system for the treatment of low back pain comprises one or more sgRNAs targeting exon 11 of cTNFRSF1B.

[00387] In some embodiments, the CRISPR gene-editing system for the treatment of low back pain comprises one or more sgRNAs targeting exon 1 of eTNFRSF1B. In some embodiments, the CRISPR gene-editing system for the treatment of low back pain comprises one or more sgRNAs targeting exon 2 of eTNFRSF1B. In some embodiments, the CRISPR gene-editing system for the treatment of low back pain comprises one or more sgRNAs targeting exon 3 of eTNFRSF1B. In some embodiments, the CRISPR gene-editing system for the treatment of low back pain comprises one or more sgRNAs targeting exon 4 of eTNFRSF1B. In some embodiments, the CRISPR gene-editing system for the treatment of low back pain comprises one or more sgRNAs targeting exon 5 of eTNFRSF1B. In some embodiments, the CRISPR gene-editing system for the treatment of low back pain comprises one or more sgRNAs targeting exon 6 of eTNFRSF1B. In some embodiments, the CRISPR gene-editing system for the treatment of low back pain comprises one or more sgRNAs targeting exon 7 of eTNFRSF1B. In some embodiments, the CRISPR gene-editing system for the treatment of low back pain comprises one or more sgRNAs targeting exon 8 of eTNFRSF1B. In some embodiments, the CRISPR gene-editing system for the treatment of low back pain comprises one or more sgRNAs targeting exon 9 of eTNFRSF1B. In some embodiments, the CRISPR gene-editing system for the treatment of low back pain comprises one or more sgRNAs targeting exon 10 of eTNFRSF1B. In some embodiments, the CRISPR

gene-editing system for the treatment of low back pain comprises one or more sgRNAs targeting exon 11 of eTNFRSF1B.

[00388] In some embodiments, the CRISPR gene-editing system for the treatment of low back pain comprises one or more sgRNAs targeting exon 1 of fTNFRSF1B. In some embodiments, the CRISPR gene-editing system for the treatment of low back pain comprises one or more sgRNAs targeting exon 2 of fTNFRSF1B. In some embodiments, the CRISPR gene-editing system for the treatment of low back pain comprises one or more sgRNAs targeting exon 3 of fTNFRSF1B. In some embodiments, the CRISPR gene-editing system for the treatment of low back pain comprises one or more sgRNAs targeting exon 4 of fTNFRSF1B. In some embodiments, the CRISPR gene-editing system for the treatment of low back pain comprises one or more sgRNAs targeting exon 5 of fTNFRSF1B. In some embodiments, the CRISPR gene-editing system for the treatment of low back pain comprises one or more sgRNAs targeting exon 6 of fTNFRSF1B. In some embodiments, the CRISPR gene-editing system for the treatment of low back pain comprises one or more sgRNAs targeting exon 7 of fTNFRSF1B. In some embodiments, the CRISPR gene-editing system for the treatment of low back pain comprises one or more sgRNAs targeting exon 8 of fTNFRSF1B. In some embodiments, the CRISPR gene-editing system for the treatment of low back pain comprises one or more sgRNAs targeting exon 9 of fTNFRSF1B. In some embodiments, the CRISPR gene-editing system for the treatment of low back pain comprises one or more sgRNAs targeting exon 10 of fTNFRSF1B.

[00389] In some embodiments, the CRISPR gene-editing system for the treatment of low back pain comprises one or more sgRNAs targeting TNFRSF3. In some embodiments, the CRISPR gene-editing system for the treatment of low back pain comprises one or more sgRNAs targeting hTNFRSF3. In some embodiments, the CRISPR gene-editing system for the treatment of low back pain comprises one or more sgRNAs targeting cTNFRSF3. In some embodiments, the CRISPR gene-editing system for the treatment of low back pain comprises one or more sgRNAs targeting eTNFRSF3. In some embodiments, the CRISPR gene-editing system for the treatment of low back pain comprises one or more sgRNAs targeting fTNFRSF3.

[00390] In some embodiments, the CRISPR gene-editing system for the treatment of low back pain comprises one or more sgRNAs targeting exon 1 of hTNFRSF3. In some embodiments, the CRISPR gene-editing system for the treatment of low back pain comprises one or more sgRNAs targeting exon 2 of hTNFRSF3. In some embodiments, the CRISPR

gene-editing system for the treatment of low back pain comprises one or more sgRNAs targeting exon 3 of hTNFRSF3. In some embodiments, the CRISPR gene-editing system for the treatment of low back pain comprises one or more sgRNAs targeting exon 4 of hTNFRSF3. In some embodiments, the CRISPR gene-editing system for the treatment of low back pain comprises one or more sgRNAs targeting exon 5 of hTNFRSF3. In some embodiments, the CRISPR gene-editing system for the treatment of low back pain comprises one or more sgRNAs targeting exon 6 of hTNFRSF3. In some embodiments, the CRISPR gene-editing system for the treatment of low back pain comprises one or more sgRNAs targeting exon 7 of hTNFRSF3. In some embodiments, the CRISPR gene-editing system for the treatment of low back pain comprises one or more sgRNAs targeting exon 8 of hTNFRSF3. In some embodiments, the CRISPR gene-editing system for the treatment of low back pain comprises one or more sgRNAs targeting exon 9 of hTNFRSF3. In some embodiments, the CRISPR gene-editing system for the treatment of low back pain comprises one or more sgRNAs targeting exon 10 of hTNFRSF3. In some embodiments, the CRISPR gene-editing system for the treatment of low back pain comprises one or more sgRNAs targeting exon 11 of hTNFRSF3. In some embodiments, the CRISPR gene-editing system for the treatment of low back pain comprises one or more sgRNAs targeting exon 12 of hTNFRSF3.

[00391] In some embodiments, the CRISPR gene-editing system for the treatment of low back pain comprises one or more sgRNAs targeting exon 1 of cTNFRSF3. In some embodiments, the CRISPR gene-editing system for the treatment of low back pain comprises one or more sgRNAs targeting exon 2 of cTNFRSF3. In some embodiments, the CRISPR gene-editing system for the treatment of low back pain comprises one or more sgRNAs targeting exon 3 of cTNFRSF3. In some embodiments, the CRISPR gene-editing system for the treatment of low back pain comprises one or more sgRNAs targeting exon 4 of cTNFRSF3. In some embodiments, the CRISPR gene-editing system for the treatment of low back pain comprises one or more sgRNAs targeting exon 5 of cTNFRSF3. In some embodiments, the CRISPR gene-editing system for the treatment of low back pain comprises one or more sgRNAs targeting exon 6 of cTNFRSF3. In some embodiments, the CRISPR gene-editing system for the treatment of low back pain comprises one or more sgRNAs targeting exon 7 of cTNFRSF3. In some embodiments, the CRISPR gene-editing system for the treatment of low back pain comprises one or more sgRNAs targeting exon 8 of cTNFRSF3. In some embodiments, the CRISPR gene-editing system for the treatment of

low back pain comprises one or more sgRNAs targeting exon 9 of cTNFRSF3. In some embodiments, the CRISPR gene-editing system for the treatment of low back pain comprises one or more sgRNAs targeting exon 10 of cTNFRSF3.

[00392] In some embodiments, the CRISPR gene-editing system for the treatment of low back pain comprises one or more sgRNAs targeting exon 1 of eTNFRSF3. In some embodiments, the CRISPR gene-editing system for the treatment of low back pain comprises one or more sgRNAs targeting exon 2 of eTNFRSF3. In some embodiments, the CRISPR gene-editing system for the treatment of low back pain comprises one or more sgRNAs targeting exon 3 of eTNFRSF3. In some embodiments, the CRISPR gene-editing system for the treatment of low back pain comprises one or more sgRNAs targeting exon 4 of eTNFRSF3. In some embodiments, the CRISPR gene-editing system for the treatment of low back pain comprises one or more sgRNAs targeting exon 5 of eTNFRSF3. In some embodiments, the CRISPR gene-editing system for the treatment of low back pain comprises one or more sgRNAs targeting exon 6 of eTNFRSF3. In some embodiments, the CRISPR gene-editing system for the treatment of low back pain comprises one or more sgRNAs targeting exon 7 of eTNFRSF3. In some embodiments, the CRISPR gene-editing system for the treatment of low back pain comprises one or more sgRNAs targeting exon 8 of eTNFRSF3. In some embodiments, the CRISPR gene-editing system for the treatment of low back pain comprises one or more sgRNAs targeting exon 9 of eTNFRSF3. In some embodiments, the CRISPR gene-editing system for the treatment of low back pain comprises one or more sgRNAs targeting exon 10 of eTNFRSF3.

[00393] In some embodiments, the CRISPR gene-editing system for the treatment of low back pain comprises one or more sgRNAs targeting exon 1 of fTNFRSF3. In some embodiments, the CRISPR gene-editing system for the treatment of low back pain comprises one or more sgRNAs targeting exon 2 of fTNFRSF3. In some embodiments, the CRISPR gene-editing system for the treatment of low back pain comprises one or more sgRNAs targeting exon 3 of fTNFRSF3. In some embodiments, the CRISPR gene-editing system for the treatment of low back pain comprises one or more sgRNAs targeting exon 4 of fTNFRSF3. In some embodiments, the CRISPR gene-editing system for the treatment of low back pain comprises one or more sgRNAs targeting exon 5 of fTNFRSF3. In some embodiments, the CRISPR gene-editing system for the treatment of low back pain comprises one or more sgRNAs targeting exon 6 of fTNFRSF3. In some embodiments, the CRISPR gene-editing system for the treatment of low back pain comprises one or more sgRNAs

targeting exon 7 of fTNFRSF3. In some embodiments, the CRISPR gene-editing system for the treatment of low back pain comprises one or more sgRNAs targeting exon 8 of fTNFRSF3. In some embodiments, the CRISPR gene-editing system for the treatment of low back pain comprises one or more sgRNAs targeting exon 9 of fTNFRSF3. In some embodiments, the CRISPR gene-editing system for the treatment of low back pain comprises one or more sgRNAs targeting exon 10 of fTNFRSF3.

[00394] In some embodiments, the CRISPR gene-editing system for the treatment of low back pain comprises one or more sgRNAs targeting TNFRSF4. In some embodiments, the CRISPR gene-editing system for the treatment of low back pain comprises one or more sgRNAs targeting hTNFRSF4. In some embodiments, the CRISPR gene-editing system for the treatment of low back pain comprises one or more sgRNAs targeting cTNFRSF4. In some embodiments, the CRISPR gene-editing system for the treatment of low back pain comprises one or more sgRNAs targeting eTNFRSF4. In some embodiments, the CRISPR gene-editing system for the treatment of low back pain comprises one or more sgRNAs targeting fTNFRSF4.

[00395] In some embodiments, the CRISPR gene-editing system for the treatment of low back pain comprises one or more sgRNAs targeting exon 1 of hTNFRSF4. In some embodiments, the CRISPR gene-editing system for the treatment of low back pain comprises one or more sgRNAs targeting exon 2 of hTNFRSF4. In some embodiments, the CRISPR gene-editing system for the treatment of low back pain comprises one or more sgRNAs targeting exon 3 of hTNFRSF4. In some embodiments, the CRISPR gene-editing system for the treatment of low back pain comprises one or more sgRNAs targeting exon 4 of hTNFRSF4. In some embodiments, the CRISPR gene-editing system for the treatment of low back pain comprises one or more sgRNAs targeting exon 5 of hTNFRSF4. In some embodiments, the CRISPR gene-editing system for the treatment of low back pain comprises one or more sgRNAs targeting exon 6 of hTNFRSF4.

[00396] In some embodiments, the CRISPR gene-editing system for the treatment of low back pain comprises one or more sgRNAs targeting exon 1 of cTNFRSF4. In some embodiments, the CRISPR gene-editing system for the treatment of low back pain comprises one or more sgRNAs targeting exon 2 of cTNFRSF4. In some embodiments, the CRISPR gene-editing system for the treatment of low back pain comprises one or more sgRNAs targeting exon 3 of cTNFRSF4. In some embodiments, the CRISPR gene-editing system for the treatment of low back pain comprises one or more sgRNAs targeting exon 4 of

cTNFRSF4. In some embodiments, the CRISPR gene-editing system for the treatment of low back pain comprises one or more sgRNAs targeting exon 5 of cTNFRSF4. In some embodiments, the CRISPR gene-editing system for the treatment of low back pain comprises one or more sgRNAs targeting exon 6 of cTNFRSF4. In some embodiments, the CRISPR gene-editing system for the treatment of low back pain comprises one or more sgRNAs targeting exon 7 of cTNFRSF4.

[00397] In some embodiments, the CRISPR gene-editing system for the treatment of low back pain comprises one or more sgRNAs targeting exon 1 of eTNFRSF4. In some embodiments, the CRISPR gene-editing system for the treatment of low back pain comprises one or more sgRNAs targeting exon 2 of eTNFRSF4. In some embodiments, the CRISPR gene-editing system for the treatment of low back pain comprises one or more sgRNAs targeting exon 3 of eTNFRSF4. In some embodiments, the CRISPR gene-editing system for the treatment of low back pain comprises one or more sgRNAs targeting exon 4 of eTNFRSF4. In some embodiments, the CRISPR gene-editing system for the treatment of low back pain comprises one or more sgRNAs targeting exon 5 of eTNFRSF4. In some embodiments, the CRISPR gene-editing system for the treatment of low back pain comprises one or more sgRNAs targeting exon 6 of eTNFRSF4. In some embodiments, the CRISPR gene-editing system for the treatment of low back pain comprises one or more sgRNAs targeting exon 7 of eTNFRSF4.

[00398] In some embodiments, the CRISPR gene-editing system for the treatment of low back pain comprises one or more sgRNAs targeting exon 1 of fTNFRSF4. In some embodiments, the CRISPR gene-editing system for the treatment of low back pain comprises one or more sgRNAs targeting exon 2 of fTNFRSF4. In some embodiments, the CRISPR gene-editing system for the treatment of low back pain comprises one or more sgRNAs targeting exon 3 of fTNFRSF4. In some embodiments, the CRISPR gene-editing system for the treatment of low back pain comprises one or more sgRNAs targeting exon 4 of fTNFRSF4. In some embodiments, the CRISPR gene-editing system for the treatment of low back pain comprises one or more sgRNAs targeting exon 5 of fTNFRSF4. In some embodiments, the CRISPR gene-editing system for the treatment of low back pain comprises one or more sgRNAs targeting exon 6 of fTNFRSF4. In some embodiments, the CRISPR gene-editing system for the treatment of low back pain comprises one or more sgRNAs targeting exon 7 of fTNFRSF4.

[00399] In some embodiments, the CRISPR gene-editing system for the treatment of low back pain comprises one or more sgRNAs targeting TNFRSF11A. In some embodiments, the CRISPR gene-editing system for the treatment of low back pain comprises one or more sgRNAs targeting hTNFRSF11A. In some embodiments, the CRISPR gene-editing system for the treatment of low back pain comprises one or more sgRNAs targeting cTNFRSF11A. In some embodiments, the CRISPR gene-editing system for the treatment of low back pain comprises one or more sgRNAs targeting eTNFRSF11A. In some embodiments, the CRISPR gene-editing system for the treatment of low back pain comprises one or more sgRNAs targeting fTNFRSF11A.

[00400] In some embodiments, the CRISPR gene-editing system for the treatment of low back pain comprises one or more sgRNAs targeting exon 1 of hTNFRSF11A. In some embodiments, the CRISPR gene-editing system for the treatment of low back pain comprises one or more sgRNAs targeting exon 2 of hTNFRSF11A. In some embodiments, the CRISPR gene-editing system for the treatment of low back pain comprises one or more sgRNAs targeting exon 3 of hTNFRSF11A. In some embodiments, the CRISPR gene-editing system for the treatment of low back pain comprises one or more sgRNAs targeting exon 4 of hTNFRSF11A. In some embodiments, the CRISPR gene-editing system for the treatment of low back pain comprises one or more sgRNAs targeting exon 5 of hTNFRSF11A. In some embodiments, the CRISPR gene-editing system for the treatment of low back pain comprises one or more sgRNAs targeting exon 6 of hTNFRSF11A. In some embodiments, the CRISPR gene-editing system for the treatment of low back pain comprises one or more sgRNAs targeting exon 7 of hTNFRSF11A. In some embodiments, the CRISPR gene-editing system for the treatment of low back pain comprises one or more sgRNAs targeting exon 8 of hTNFRSF11A. In some embodiments, the CRISPR gene-editing system for the treatment of low back pain comprises one or more sgRNAs targeting exon 9 of hTNFRSF11A. In some embodiments, the CRISPR gene-editing system for the treatment of low back pain comprises one or more sgRNAs targeting exon 10 of hTNFRSF11A. In some embodiments, the CRISPR gene-editing system for the treatment of low back pain comprises one or more sgRNAs targeting exon 11 of hTNFRSF11A. In some embodiments, the CRISPR gene-editing system for the treatment of low back pain comprises one or more sgRNAs targeting exon 12 of hTNFRSF11A.

[00401] In some embodiments, the CRISPR gene-editing system for the treatment of low back pain comprises one or more sgRNAs targeting exon 1 of cTNFRSF11A. In some

embodiments, the CRISPR gene-editing system for the treatment of low back pain comprises one or more sgRNAs targeting exon 2 of cTNFRSF11A. In some embodiments, the CRISPR gene-editing system for the treatment of low back pain comprises one or more sgRNAs targeting exon 3 of cTNFRSF11A. In some embodiments, the CRISPR gene-editing system for the treatment of low back pain comprises one or more sgRNAs targeting exon 4 of cTNFRSF11A. In some embodiments, the CRISPR gene-editing system for the treatment of low back pain comprises one or more sgRNAs targeting exon 5 of cTNFRSF11A. In some embodiments, the CRISPR gene-editing system for the treatment of low back pain comprises one or more sgRNAs targeting exon 6 of cTNFRSF11A. In some embodiments, the CRISPR gene-editing system for the treatment of low back pain comprises one or more sgRNAs targeting exon 7 of cTNFRSF11A. In some embodiments, the CRISPR gene-editing system for the treatment of low back pain comprises one or more sgRNAs targeting exon 8 of cTNFRSF11A. In some embodiments, the CRISPR gene-editing system for the treatment of low back pain comprises one or more sgRNAs targeting exon 9 of cTNFRSF11A. In some embodiments, the CRISPR gene-editing system for the treatment of low back pain comprises one or more sgRNAs targeting exon 10 of cTNFRSF11A. In some embodiments, the CRISPR gene-editing system for the treatment of low back pain comprises one or more sgRNAs targeting exon 11 of cTNFRSF11A.

[00402] In some embodiments, the CRISPR gene-editing system for the treatment of low back pain comprises one or more sgRNAs targeting exon 1 of eTNFRSF11A. In some embodiments, the CRISPR gene-editing system for the treatment of low back pain comprises one or more sgRNAs targeting exon 2 of eTNFRSF11A. In some embodiments, the CRISPR gene-editing system for the treatment of low back pain comprises one or more sgRNAs targeting exon 3 of eTNFRSF11A. In some embodiments, the CRISPR gene-editing system for the treatment of low back pain comprises one or more sgRNAs targeting exon 4 of eTNFRSF11A. In some embodiments, the CRISPR gene-editing system for the treatment of low back pain comprises one or more sgRNAs targeting exon 5 of eTNFRSF11A. In some embodiments, the CRISPR gene-editing system for the treatment of low back pain comprises one or more sgRNAs targeting exon 6 of eTNFRSF11A. In some embodiments, the CRISPR gene-editing system for the treatment of low back pain comprises one or more sgRNAs targeting exon 7 of eTNFRSF11A. In some embodiments, the CRISPR gene-editing system for the treatment of low back pain comprises one or more sgRNAs targeting exon 8 of eTNFRSF11A. In some embodiments, the CRISPR gene-editing system for the treatment of

low back pain comprises one or more sgRNAs targeting exon 9 of eTNFRSF11A. In some embodiments, the CRISPR gene-editing system for the treatment of low back pain comprises one or more sgRNAs targeting exon 10 of eTNFRSF11A.

[00403] In some embodiments, the CRISPR gene-editing system for the treatment of low back pain comprises one or more sgRNAs targeting exon 1 of fTNFRSF11A. In some embodiments, the CRISPR gene-editing system for the treatment of low back pain comprises one or more sgRNAs targeting exon 2 of fTNFRSF11A. In some embodiments, the CRISPR gene-editing system for the treatment of low back pain comprises one or more sgRNAs targeting exon 3 of fTNFRSF11A. In some embodiments, the CRISPR gene-editing system for the treatment of low back pain comprises one or more sgRNAs targeting exon 4 of fTNFRSF11A. In some embodiments, the CRISPR gene-editing system for the treatment of low back pain comprises one or more sgRNAs targeting exon 5 of fTNFRSF11A. In some embodiments, the CRISPR gene-editing system for the treatment of low back pain comprises one or more sgRNAs targeting exon 6 of fTNFRSF11A. In some embodiments, the CRISPR gene-editing system for the treatment of low back pain comprises one or more sgRNAs targeting exon 7 of fTNFRSF11A. In some embodiments, the CRISPR gene-editing system for the treatment of low back pain comprises one or more sgRNAs targeting exon 8 of fTNFRSF11A. In some embodiments, the CRISPR gene-editing system for the treatment of low back pain comprises one or more sgRNAs targeting exon 9 of fTNFRSF11A. In some embodiments, the CRISPR gene-editing system for the treatment of low back pain comprises one or more sgRNAs targeting exon 10 of fTNFRSF11A. In some embodiments, the CRISPR gene-editing system for the treatment of low back pain comprises one or more sgRNAs targeting exon 11 of fTNFRSF11A.

C. DDD

[00404] In one aspect, the present disclosure encompasses treatments for degenerative disc disorder (DDD). In some embodiments, the DDD treatment comprises a therapeutically effective amount of a Clustered Regularly Interspaced Short Palindromic Repeats (CRISPR) gene-editing system, the system comprising: (i) a CRISPR Associated (Cas) protein; and (ii) at least one guide RNA targeting IL1R1. In some embodiments, the DDD treatment comprises a CRISPR gene-editing system targeting hIL1R1. In some embodiments, the DDD treatment comprises a CRISPR gene-editing system targeting cIL1R1. In some embodiments, the DDD treatment comprises a CRISP gene-editing system R targeting

eIL1R1. In some embodiments, the DDD treatment comprises a CRISPR gene-editing system targeting fIL1R1.

[00405] In some embodiments, the CRISPR gene-editing system for the treatment of DDD comprises one or more sgRNAs targeting exon 1 of hIL1R1. In some embodiments, the CRISPR gene-editing system for the treatment of DDD comprises one or more sgRNAs targeting exon 2 of hIL1R1. In some embodiments, the CRISPR gene-editing system for the treatment of DDD comprises one or more sgRNAs targeting exon 3 of hIL1R1. In some embodiments, the CRISPR gene-editing system for the treatment of DDD comprises one or more sgRNAs targeting exon 4 of hIL1R1. In some embodiments, the CRISPR gene-editing system for the treatment of DDD comprises one or more sgRNAs targeting exon 5 of hIL1R1. In some embodiments, the CRISPR gene-editing system for the treatment of DDD comprises one or more sgRNAs targeting exon 6 of hIL1R1. In some embodiments, the CRISPR gene-editing system for the treatment of DDD comprises one or more sgRNAs targeting exon 7 of hIL1R1. In some embodiments, the CRISPR gene-editing system for the treatment of DDD comprises one or more sgRNAs targeting exon 8 of hIL1R1. In some embodiments, the CRISPR gene-editing system for the treatment of DDD comprises one or more sgRNAs targeting exon 9 of hIL1R1. In some embodiments, the CRISPR gene-editing system for the treatment of DDD comprises one or more sgRNAs targeting exon 10 of hIL1R1. In some embodiments, the CRISPR gene-editing system for the treatment of DDD comprises one or more sgRNAs targeting exon 11 of hIL1R1. In some embodiments, the CRISPR gene-editing system for the treatment of DDD comprises one or more sgRNAs targeting exon 12 of hIL1R1. In some embodiments, the CRISPR gene-editing system for the treatment of DDD comprises one or more sgRNAs targeting exon 13 of hIL1R1. In some embodiments, the CRISPR gene-editing system for the treatment of DDD comprises one or more sgRNAs targeting exon 14 of hIL1R1. In some embodiments, the CRISPR gene-editing system for the treatment of DDD comprises one or more sgRNAs targeting exon 15 of hIL1R1. In some embodiments, the CRISPR gene-editing system for the treatment of DDD comprises one or more sgRNAs targeting exon 16 of hIL1R1. In some embodiments, the CRISPR gene-editing system for the treatment of DDD comprises one or more sgRNAs targeting exon 17 of hIL1R1. In some embodiments, the CRISPR gene-editing system for the treatment of DDD comprises one or more sgRNAs targeting exon 18 of hIL1R1. In some embodiments, the CRISPR gene-editing system for the treatment of DDD comprises one or more sgRNAs targeting exon 19 of hIL1R1. In some embodiments, the CRISPR gene-

editing system for the treatment of DDD comprises one or more sgRNAs targeting exon 20 of hIL1R1. In some embodiments, the CRISPR gene-editing system for the treatment of DDD comprises one or more sgRNAs targeting exon 21 of hIL1R1.

[00406] In some embodiments, the CRISPR gene-editing system for the treatment of DDD comprises one or more sgRNAs targeting exon 1 of cIL1R1. In some embodiments, the CRISPR gene-editing system for the treatment of DDD comprises one or more sgRNAs targeting exon 2 of cIL1R1. In some embodiments, the CRISPR gene-editing system for the treatment of DDD comprises one or more sgRNAs targeting exon 3 of cIL1R1. In some embodiments, the CRISPR gene-editing system for the treatment of DDD comprises one or more sgRNAs targeting exon 4 of cIL1R1. In some embodiments, the CRISPR gene-editing system for the treatment of DDD comprises one or more sgRNAs targeting exon 5 of cIL1R1. In some embodiments, the CRISPR gene-editing system for the treatment of DDD comprises one or more sgRNAs targeting exon 6 of cIL1R1. In some embodiments, the CRISPR gene-editing system for the treatment of DDD comprises one or more sgRNAs targeting exon 7 of cIL1R1. In some embodiments, the CRISPR gene-editing system for the treatment of DDD comprises one or more sgRNAs targeting exon 8 of cIL1R1. In some embodiments, the CRISPR gene-editing system for the treatment of DDD comprises one or more sgRNAs targeting exon 9 of cIL1R1. In some embodiments, the CRISPR gene-editing system for the treatment of DDD comprises one or more sgRNAs targeting exon 10 of cIL1R1. In some embodiments, the CRISPR gene-editing system for the treatment of DDD comprises one or more sgRNAs targeting exon 11 of cIL1R1. In some embodiments, the CRISPR gene-editing system for the treatment of DDD comprises one or more sgRNAs targeting exon 12 of cIL1R1. In some embodiments, the CRISPR gene-editing system for the treatment of DDD comprises one or more sgRNAs targeting exon 13 of cIL1R1. In some embodiments, the CRISPR gene-editing system for the treatment of DDD comprises one or more sgRNAs targeting exon 14 of cIL1R1. In some embodiments, the CRISPR gene-editing system for the treatment of DDD comprises one or more sgRNAs targeting exon 15 of cIL1R1. In some embodiments, the CRISPR gene-editing system for the treatment of DDD comprises one or more sgRNAs targeting exon 16 of cIL1R1.

[00407] In some embodiments, the CRISPR gene-editing system for the treatment of DDD comprises one or more sgRNAs targeting exon 1 of eIL1R1. In some embodiments, the CRISPR gene-editing system for the treatment of DDD comprises one or more sgRNAs targeting exon 2 of eIL1R1. In some embodiments, the CRISPR gene-editing system for the

treatment of DDD comprises one or more sgRNAs targeting exon 3 of eIL1R1. In some embodiments, the CRISPR gene-editing system for the treatment of DDD comprises one or more sgRNAs targeting exon 4 of eIL1R1. In some embodiments, the CRISPR gene-editing system for the treatment of DDD comprises one or more sgRNAs targeting exon 5 of eIL1R1. In some embodiments, the CRISPR gene-editing system for the treatment of DDD comprises one or more sgRNAs targeting exon 6 of eIL1R1. In some embodiments, the CRISPR gene-editing system for the treatment of DDD comprises one or more sgRNAs targeting exon 7 of eIL1R1. In some embodiments, the CRISPR gene-editing system for the treatment of DDD comprises one or more sgRNAs targeting exon 8 of eIL1R1. In some embodiments, the CRISPR gene-editing system for the treatment of DDD comprises one or more sgRNAs targeting exon 9 of eIL1R1. In some embodiments, the CRISPR gene-editing system for the treatment of DDD comprises one or more sgRNAs targeting exon 10 of eIL1R1. In some embodiments, the CRISPR gene-editing system for the treatment of DDD comprises one or more sgRNAs targeting exon 11 of eIL1R1. In some embodiments, the CRISPR gene-editing system for the treatment of DDD comprises one or more sgRNAs targeting exon 12 of eIL1R1. In some embodiments, the CRISPR gene-editing system for the treatment of DDD comprises one or more sgRNAs targeting exon 13 of eIL1R1. In some embodiments, the CRISPR gene-editing system for the treatment of DDD comprises one or more sgRNAs targeting exon 14 of eIL1R1. In some embodiments, the CRISPR gene-editing system for the treatment of DDD comprises one or more sgRNAs targeting exon 15 of eIL1R1.

[00408] In some embodiments, the CRISPR gene-editing system for the treatment of DDD comprises one or more sgRNAs targeting exon 1 of fIL1R1. In some embodiments, the CRISPR gene-editing system for the treatment of DDD comprises one or more sgRNAs targeting exon 2 of fIL1R1. In some embodiments, the CRISPR gene-editing system for the treatment of DDD comprises one or more sgRNAs targeting exon 3 of fIL1R1. In some embodiments, the CRISPR gene-editing system for the treatment of DDD comprises one or more sgRNAs targeting exon 4 of fIL1R1. In some embodiments, the CRISPR gene-editing system for the treatment of DDD comprises one or more sgRNAs targeting exon 5 of fIL1R1. In some embodiments, the CRISPR gene-editing system for the treatment of DDD comprises one or more sgRNAs targeting exon 6 of fIL1R1. In some embodiments, the CRISPR gene-editing system for the treatment of DDD comprises one or more sgRNAs targeting exon 7 of fIL1R1. In some embodiments, the CRISPR gene-editing system for the treatment of DDD comprises one or more sgRNAs targeting exon 8 of fIL1R1. In some embodiments, the

CRISPR gene-editing system for the treatment of DDD comprises one or more sgRNAs targeting exon 9 of fIL1R1. In some embodiments, the CRISPR gene-editing system for the treatment of DDD comprises one or more sgRNAs targeting exon 10 of fIL1R1. In some embodiments, the CRISPR gene-editing system for the treatment of DDD comprises one or more sgRNAs targeting exon 11 of fIL1R1. In some embodiments, the CRISPR gene-editing system for the treatment of DDD comprises one or more sgRNAs targeting exon 12 of fIL1R1. In some embodiments, the CRISPR gene-editing system for the treatment of DDD comprises one or more sgRNAs targeting exon 13 of fIL1R1. In some embodiments, the CRISPR gene-editing system for the treatment of DDD comprises one or more sgRNAs targeting exon 14 of fIL1R1. In some embodiments, the CRISPR gene-editing system for the treatment of DDD comprises one or more sgRNAs targeting exon 15 of fIL1R1. In some embodiments, the CRISPR gene-editing system for the treatment of DDD comprises one or more sgRNAs targeting exon 16 of fIL1R1. In some embodiments, the CRISPR gene-editing system for the treatment of DDD comprises one or more sgRNAs targeting exon 17 of fIL1R1. In some embodiments, the CRISPR gene-editing system for the treatment of DDD comprises one or more sgRNAs targeting exon 18 of fIL1R1.

[00409] In some embodiments, the CRISPR gene-editing system for the treatment of DDD comprises one or more sgRNAs targeting IL1RAP. In some embodiments, the CRISPR gene-editing system for the treatment of DDD comprises one or more sgRNAs targeting hIL1RAP. In some embodiments, the CRISPR gene-editing system for the treatment of DDD comprises one or more sgRNAs targeting cIL1RAP. In some embodiments, the CRISPR gene-editing system for the treatment of DDD comprises one or more sgRNAs targeting eIL1RAP. In some embodiments, the CRISPR gene-editing system for the treatment of DDD comprises one or more sgRNAs targeting fIL1RAP.

[00410] In some embodiments, the CRISPR gene-editing system for the treatment of DDD comprises one or more sgRNAs targeting exon 1 of hIL1RAP. In some embodiments, the CRISPR gene-editing system for the treatment of DDD comprises one or more sgRNAs targeting exon 2 of hIL1RAP. In some embodiments, the CRISPR gene-editing system for the treatment of DDD comprises one or more sgRNAs targeting exon 3 of hIL1RAP. In some embodiments, the CRISPR gene-editing system for the treatment of DDD comprises one or more sgRNAs targeting exon 4 of hIL1RAP. In some embodiments, the CRISPR gene-editing system for the treatment of DDD comprises one or more sgRNAs targeting exon 5 of hIL1RAP. In some embodiments, the CRISPR gene-editing system for the treatment of

DDD comprises one or more sgRNAs targeting exon 6 of hIL1RAP. In some embodiments, the CRISPR gene-editing system for the treatment of DDD comprises one or more sgRNAs targeting exon 7 of hIL1RAP. In some embodiments, the CRISPR gene-editing system for the treatment of DDD comprises one or more sgRNAs targeting exon 8 of hIL1RAP. In some embodiments, the CRISPR gene-editing system for the treatment of DDD comprises one or more sgRNAs targeting exon 9 of hIL1RAP. In some embodiments, the CRISPR gene-editing system for the treatment of DDD comprises one or more sgRNAs targeting exon 10 of hIL1RAP. In some embodiments, the CRISPR gene-editing system for the treatment of DDD comprises one or more sgRNAs targeting exon 11 of hIL1RAP. In some embodiments, the CRISPR gene-editing system for the treatment of DDD comprises one or more sgRNAs targeting exon 12 of hIL1RAP. In some embodiments, the CRISPR gene-editing system for the treatment of DDD comprises one or more sgRNAs targeting exon 13 of hIL1RAP. In some embodiments, the CRISPR gene-editing system for the treatment of DDD comprises one or more sgRNAs targeting exon 14 of hIL1RAP. In some embodiments, the CRISPR gene-editing system for the treatment of DDD comprises one or more sgRNAs targeting exon 15 of hIL1RAP. In some embodiments, the CRISPR gene-editing system for the treatment of DDD comprises one or more sgRNAs targeting exon 16 of hIL1RAP. In some embodiments, the CRISPR gene-editing system for the treatment of DDD comprises one or more sgRNAs targeting exon 17 of hIL1RAP.

[00411] In some embodiments, the CRISPR gene-editing system for the treatment of DDD comprises one or more sgRNAs targeting exon 1 of cIL1RAP. In some embodiments, the CRISPR gene-editing system for the treatment of DDD comprises one or more sgRNAs targeting exon 2 of cIL1RAP. In some embodiments, the CRISPR gene-editing system for the treatment of DDD comprises one or more sgRNAs targeting exon 3 of cIL1RAP. In some embodiments, the CRISPR gene-editing system for the treatment of DDD comprises one or more sgRNAs targeting exon 4 of cIL1RAP. In some embodiments, the CRISPR gene-editing system for the treatment of DDD comprises one or more sgRNAs targeting exon 5 of cIL1RAP. In some embodiments, the CRISPR gene-editing system for the treatment of DDD comprises one or more sgRNAs targeting exon 6 of cIL1RAP. In some embodiments, the CRISPR gene-editing system for the treatment of DDD comprises one or more sgRNAs targeting exon 7 of cIL1RAP. In some embodiments, the CRISPR gene-editing system for the treatment of DDD comprises one or more sgRNAs targeting exon 8 of cIL1RAP. In some embodiments, the CRISPR gene-editing system for the treatment of DDD comprises

one or more sgRNAs targeting exon 9 of cIL1RAP. In some embodiments, the CRISPR gene-editing system for the treatment of DDD comprises one or more sgRNAs targeting exon 10 of cIL1RAP. In some embodiments, the CRISPR gene-editing system for the treatment of DDD comprises one or more sgRNAs targeting exon 11 of cIL1RAP. In some embodiments, the CRISPR gene-editing system for the treatment of DDD comprises one or more sgRNAs targeting exon 12 of cIL1RAP. In some embodiments, the CRISPR gene-editing system for the treatment of DDD comprises one or more sgRNAs targeting exon 13 of cIL1RAP. In some embodiments, the CRISPR gene-editing system for the treatment of DDD comprises one or more sgRNAs targeting exon 14 of cIL1RAP. In some embodiments, the CRISPR gene-editing system for the treatment of DDD comprises one or more sgRNAs targeting exon 15 of cIL1RAP. In some embodiments, the CRISPR gene-editing system for the treatment of DDD comprises one or more sgRNAs targeting exon 16 of cIL1RAP.

[00412] In some embodiments, the CRISPR gene-editing system for the treatment of DDD comprises one or more sgRNAs targeting exon 1 of eIL1RAP. In some embodiments, the CRISPR gene-editing system for the treatment of DDD comprises one or more sgRNAs targeting exon 2 of eIL1RAP. In some embodiments, the CRISPR gene-editing system for the treatment of DDD comprises one or more sgRNAs targeting exon 3 of eIL1RAP. In some embodiments, the CRISPR gene-editing system for the treatment of DDD comprises one or more sgRNAs targeting exon 4 of eIL1RAP. In some embodiments, the CRISPR gene-editing system for the treatment of DDD comprises one or more sgRNAs targeting exon 5 of eIL1RAP. In some embodiments, the CRISPR gene-editing system for the treatment of DDD comprises one or more sgRNAs targeting exon 6 of eIL1RAP. In some embodiments, the CRISPR gene-editing system for the treatment of DDD comprises one or more sgRNAs targeting exon 7 of eIL1RAP. In some embodiments, the CRISPR gene-editing system for the treatment of DDD comprises one or more sgRNAs targeting exon 8 of eIL1RAP. In some embodiments, the CRISPR gene-editing system for the treatment of DDD comprises one or more sgRNAs targeting exon 9 of eIL1RAP. In some embodiments, the CRISPR gene-editing system for the treatment of DDD comprises one or more sgRNAs targeting exon 10 of eIL1RAP. In some embodiments, the CRISPR gene-editing system for the treatment of DDD comprises one or more sgRNAs targeting exon 11 of eIL1RAP. In some embodiments, the CRISPR gene-editing system for the treatment of DDD comprises one or more sgRNAs targeting exon 12 of eIL1RAP. In some embodiments, the CRISPR gene-editing system for the treatment of DDD comprises one or more sgRNAs targeting exon 13 of eIL1RAP.

[00413] In some embodiments, the CRISPR gene-editing system for the treatment of DDD comprises one or more sgRNAs targeting exon 1 of fIL1RAP. In some embodiments, the CRISPR gene-editing system for the treatment of DDD comprises one or more sgRNAs targeting exon 2 of fIL1RAP. In some embodiments, the CRISPR gene-editing system for the treatment of DDD comprises one or more sgRNAs targeting exon 3 of fIL1RAP. In some embodiments, the CRISPR gene-editing system for the treatment of DDD comprises one or more sgRNAs targeting exon 4 of fIL1RAP. In some embodiments, the CRISPR gene-editing system for the treatment of DDD comprises one or more sgRNAs targeting exon 5 of fIL1RAP. In some embodiments, the CRISPR gene-editing system for the treatment of DDD comprises one or more sgRNAs targeting exon 6 of fIL1RAP. In some embodiments, the CRISPR gene-editing system for the treatment of DDD comprises one or more sgRNAs targeting exon 7 of fIL1RAP. In some embodiments, the CRISPR gene-editing system for the treatment of DDD comprises one or more sgRNAs targeting exon 8 of fIL1RAP. In some embodiments, the CRISPR gene-editing system for the treatment of DDD comprises one or more sgRNAs targeting exon 9 of fIL1RAP. In some embodiments, the CRISPR gene-editing system for the treatment of DDD comprises one or more sgRNAs targeting exon 10 of fIL1RAP. In some embodiments, the CRISPR gene-editing system for the treatment of DDD comprises one or more sgRNAs targeting exon 11 of fIL1RAP. In some embodiments, the CRISPR gene-editing system for the treatment of DDD comprises one or more sgRNAs targeting exon 12 of fIL1RAP. In some embodiments, the CRISPR gene-editing system for the treatment of DDD comprises one or more sgRNAs targeting exon 13 of fIL1RAP. In some embodiments, the CRISPR gene-editing system for the treatment of DDD comprises one or more sgRNAs targeting exon 14 of fIL1RAP.

[00414] In some embodiments, the CRISPR gene-editing system for the treatment of DDD comprises one or more sgRNAs targeting TGFBR1. In some embodiments, the CRISPR gene-editing system for the treatment of DDD comprises one or more sgRNAs targeting hTGFBR1. In some embodiments, the CRISPR gene-editing system for the treatment of DDD comprises one or more sgRNAs targeting cTGFBR1. In some embodiments, the CRISPR gene-editing system for the treatment of DDD comprises one or more sgRNAs targeting e TGFBR1. In some embodiments, the CRISPR gene-editing system for the treatment of DDD comprises one or more sgRNAs targeting fTGFBR1.

[00415] In some embodiments, the CRISPR gene-editing system for the treatment of DDD comprises one or more sgRNAs targeting exon 1 of hTGFBR1. In some embodiments, the

CRISPR gene-editing system for the treatment of DDD comprises one or more sgRNAs targeting exon 2 of hTGFBR1. In some embodiments, the CRISPR gene-editing system for the treatment of DDD comprises one or more sgRNAs targeting exon 3 of hTGFBR1. In some embodiments, the CRISPR gene-editing system for the treatment of DDD comprises one or more sgRNAs targeting exon 4 of hTGFBR1. In some embodiments, the CRISPR gene-editing system for the treatment of DDD comprises one or more sgRNAs targeting exon 5 of hTGFBR1. In some embodiments, the CRISPR gene-editing system for the treatment of DDD comprises one or more sgRNAs targeting exon 6 of hTGFBR1. In some embodiments, the CRISPR gene-editing system for the treatment of DDD comprises one or more sgRNAs targeting exon 7 of hTGFBR1. In some embodiments, the CRISPR gene-editing system for the treatment of DDD comprises one or more sgRNAs targeting exon 8 of hTGFBR1. In some embodiments, the CRISPR gene-editing system for the treatment of DDD comprises one or more sgRNAs targeting exon 9 of hTGFBR1. In some embodiments, the CRISPR gene-editing system for the treatment of DDD comprises one or more sgRNAs targeting exon 10 of hTGFBR1. In some embodiments, the CRISPR gene-editing system for the treatment of DDD comprises one or more sgRNAs targeting exon 11 of hTGFBR1.

[00416] In some embodiments, the CRISPR gene-editing system for the treatment of DDD comprises one or more sgRNAs targeting exon 1 of cTGFBR1. In some embodiments, the CRISPR gene-editing system for the treatment of DDD comprises one or more sgRNAs targeting exon 2 of cTGFBR1. In some embodiments, the CRISPR gene-editing system for the treatment of DDD comprises one or more sgRNAs targeting exon 3 of cTGFBR1. In some embodiments, the CRISPR gene-editing system for the treatment of DDD comprises one or more sgRNAs targeting exon 4 of cTGFBR1. In some embodiments, the CRISPR gene-editing system for the treatment of DDD comprises one or more sgRNAs targeting exon 5 of cTGFBR1. In some embodiments, the CRISPR gene-editing system for the treatment of DDD comprises one or more sgRNAs targeting exon 6 of cTGFBR1. In some embodiments, the CRISPR gene-editing system for the treatment of DDD comprises one or more sgRNAs targeting exon 7 of cTGFBR1. In some embodiments, the CRISPR gene-editing system for the treatment of DDD comprises one or more sgRNAs targeting exon 8 of cTGFBR1. In some embodiments, the CRISPR gene-editing system for the treatment of DDD comprises one or more sgRNAs targeting exon 9 of cTGFBR1.

[00417] In some embodiments, the CRISPR gene-editing system for the treatment of DDD comprises one or more sgRNAs targeting exon 1 of eTGFBR1. In some embodiments, the

CRISPR gene-editing system for the treatment of DDD comprises one or more sgRNAs targeting exon 2 of eTGFBR1. In some embodiments, the CRISPR gene-editing system for the treatment of DDD comprises one or more sgRNAs targeting exon 3 of eTGFBR1. In some embodiments, the CRISPR gene-editing system for the treatment of DDD comprises one or more sgRNAs targeting exon 4 of eTGFBR1. In some embodiments, the CRISPR gene-editing system for the treatment of DDD comprises one or more sgRNAs targeting exon 5 of eTGFBR1. In some embodiments, the CRISPR gene-editing system for the treatment of DDD comprises one or more sgRNAs targeting exon 6 of eTGFBR1. In some embodiments, the CRISPR gene-editing system for the treatment of DDD comprises one or more sgRNAs targeting exon 7 of eTGFBR1. In some embodiments, the CRISPR gene-editing system for the treatment of DDD comprises one or more sgRNAs targeting exon 8 of eTGFBR1. In some embodiments, the CRISPR gene-editing system for the treatment of DDD comprises one or more sgRNAs targeting exon 9 of eTGFBR1. In some embodiments, the CRISPR gene-editing system for the treatment of DDD comprises one or more sgRNAs targeting exon 10 of eTGFBR1. In some embodiments, the CRISPR gene-editing system for the treatment of DDD comprises one or more sgRNAs targeting exon 11 of eTGFBR1. In some embodiments, the CRISPR gene-editing system for the treatment of DDD comprises one or more sgRNAs targeting exon 12 of eTGFBR1.

[00418] In some embodiments, the CRISPR gene-editing system for the treatment of DDD comprises one or more sgRNAs targeting exon 1 of fTGFBR1. In some embodiments, the CRISPR gene-editing system for the treatment of DDD comprises one or more sgRNAs targeting exon 2 of fTGFBR1. In some embodiments, the CRISPR gene-editing system for the treatment of DDD comprises one or more sgRNAs targeting exon 3 of fTGFBR1. In some embodiments, the CRISPR gene-editing system for the treatment of DDD comprises one or more sgRNAs targeting exon 4 of fTGFBR1. In some embodiments, the CRISPR gene-editing system for the treatment of DDD comprises one or more sgRNAs targeting exon 5 of fTGFBR1. In some embodiments, the CRISPR gene-editing system for the treatment of DDD comprises one or more sgRNAs targeting exon 6 of fTGFBR1. In some embodiments, the CRISPR gene-editing system for the treatment of DDD comprises one or more sgRNAs targeting exon 7 of fTGFBR1. In some embodiments, the CRISPR gene-editing system for the treatment of DDD comprises one or more sgRNAs targeting exon 8 of fTGFBR1. In some embodiments, the CRISPR gene-editing system for the treatment of DDD comprises one or more sgRNAs targeting exon 9 of fTGFBR1. In some embodiments, the CRISPR

gene-editing system for the treatment of DDD comprises one or more sgRNAs targeting exon 10 of fTGFBR1. In some embodiments, the CRISPR gene-editing system for the treatment of DDD comprises one or more sgRNAs targeting exon 11 of fTGFBR1.

[00419] In some embodiments, the CRISPR gene-editing system for the treatment of DDD comprises one or more sgRNAs targeting TGFBR2. In some embodiments, the CRISPR gene-editing system for the treatment of DDD comprises one or more sgRNAs targeting hTGFBR2. In some embodiments, the CRISPR gene-editing system for the treatment of DDD comprises one or more sgRNAs targeting cTGFBR2. In some embodiments, the CRISPR gene-editing system for the treatment of DDD comprises one or more sgRNAs targeting eTGFBR2. In some embodiments, the CRISPR gene-editing system for the treatment of DDD comprises one or more sgRNAs targeting fTGFBR2.

[00420] In some embodiments, the CRISPR gene-editing system for the treatment of DDD comprises one or more sgRNAs targeting exon 1 of hTGFBR2. In some embodiments, the CRISPR gene-editing system for the treatment of DDD comprises one or more sgRNAs targeting exon 2 of hTGFBR2. In some embodiments, the CRISPR gene-editing system for the treatment of DDD comprises one or more sgRNAs targeting exon 3 of hTGFBR2. In some embodiments, the CRISPR gene-editing system for the treatment of DDD comprises one or more sgRNAs targeting exon 4 of hTGFBR2. In some embodiments, the CRISPR gene-editing system for the treatment of DDD comprises one or more sgRNAs targeting exon 5 of hTGFBR2. In some embodiments, the CRISPR gene-editing system for the treatment of DDD comprises one or more sgRNAs targeting exon 6 of hTGFBR2. In some embodiments, the CRISPR gene-editing system for the treatment of DDD comprises one or more sgRNAs targeting exon 7 of hTGFBR2. In some embodiments, the CRISPR gene-editing system for the treatment of DDD comprises one or more sgRNAs targeting exon 8 of hTGFBR2. In some embodiments, the CRISPR gene-editing system for the treatment of DDD comprises one or more sgRNAs targeting exon 9 of hTGFBR2.

[00421] In some embodiments, the CRISPR gene-editing system for the treatment of DDD comprises one or more sgRNAs targeting exon 1 of cTGFBR2. In some embodiments, the CRISPR gene-editing system for the treatment of DDD comprises one or more sgRNAs targeting exon 2 of cTGFBR2. In some embodiments, the CRISPR gene-editing system for the treatment of DDD comprises one or more sgRNAs targeting exon 3 of cTGFBR2. In some embodiments, the CRISPR gene-editing system for the treatment of DDD comprises one or more sgRNAs targeting exon 4 of cTGFBR2. In some embodiments, the CRISPR

gene-editing system for the treatment of DDD comprises one or more sgRNAs targeting exon 5 of cTGFBR2. In some embodiments, the CRISPR gene-editing system for the treatment of DDD comprises one or more sgRNAs targeting exon 6 of cTGFBR2. In some embodiments, the CRISPR gene-editing system for the treatment of DDD comprises one or more sgRNAs targeting exon 7 of cTGFBR2. In some embodiments, the CRISPR gene-editing system for the treatment of DDD comprises one or more sgRNAs targeting exon 8 of cTGFBR2.

[00422] In some embodiments, the CRISPR gene-editing system for the treatment of DDD comprises one or more sgRNAs targeting exon 1 of eTGFBR2. In some embodiments, the CRISPR gene-editing system for the treatment of DDD comprises one or more sgRNAs targeting exon 2 of eTGFBR2. In some embodiments, the CRISPR gene-editing system for the treatment of DDD comprises one or more sgRNAs targeting exon 3 of eTGFBR2. In some embodiments, the CRISPR gene-editing system for the treatment of DDD comprises one or more sgRNAs targeting exon 4 of eTGFBR2. In some embodiments, the CRISPR gene-editing system for the treatment of DDD comprises one or more sgRNAs targeting exon 5 of eTGFBR2. In some embodiments, the CRISPR gene-editing system for the treatment of DDD comprises one or more sgRNAs targeting exon 6 of eTGFBR2. In some embodiments, the CRISPR gene-editing system for the treatment of DDD comprises one or more sgRNAs targeting exon 7 of eTGFBR2. In some embodiments, the CRISPR gene-editing system for the treatment of DDD comprises one or more sgRNAs targeting exon 8 of eTGFBR2. In some embodiments, the CRISPR gene-editing system for the treatment of DDD comprises one or more sgRNAs targeting exon 9 of eTGFBR2. In some embodiments, the CRISPR gene-editing system for the treatment of DDD comprises one or more sgRNAs targeting exon 10 of eTGFBR2.

[00423] In some embodiments, the CRISPR gene-editing system for the treatment of DDD comprises one or more sgRNAs targeting exon 1 of fTGFBR2. In some embodiments, the CRISPR gene-editing system for the treatment of DDD comprises one or more sgRNAs targeting exon 2 of fTGFBR2. In some embodiments, the CRISPR gene-editing system for the treatment of DDD comprises one or more sgRNAs targeting exon 3 of fTGFBR2. In some embodiments, the CRISPR gene-editing system for the treatment of DDD comprises one or more sgRNAs targeting exon 4 of fTGFBR2. In some embodiments, the CRISPR gene-editing system for the treatment of DDD comprises one or more sgRNAs targeting exon 5 of fTGFBR2. In some embodiments, the CRISPR gene-editing system for the treatment of DDD comprises one or more sgRNAs targeting exon 6 of fTGFBR2. In some embodiments,

the CRISPR gene-editing system for the treatment of DDD comprises one or more sgRNAs targeting exon 7 of fTGFBR2. In some embodiments, the CRISPR gene-editing system for the treatment of DDD comprises one or more sgRNAs targeting exon 8 of fTGFBR2.

[00424] In some embodiments, the CRISPR gene-editing system for the treatment of DDD comprises one or more sgRNAs targeting IL6R. In some embodiments, the CRISPR gene-editing system for the treatment of DDD comprises one or more sgRNAs targeting hIL6R. In some embodiments, the CRISPR gene-editing system for the treatment of DDD comprises one or more sgRNAs targeting cIL6R. In some embodiments, the CRISPR gene-editing system for the treatment of DDD comprises one or more sgRNAs targeting eIL6R. In some embodiments, the CRISPR gene-editing system for the treatment of DDD comprises one or more sgRNAs targeting fIL6R.

[00425] In some embodiments, the CRISPR gene-editing system for the treatment of DDD comprises one or more sgRNAs targeting exon 1 of hIL6R. In some embodiments, the CRISPR gene-editing system for the treatment of DDD comprises one or more sgRNAs targeting exon 2 of hIL6R. In some embodiments, the CRISPR gene-editing system for the treatment of DDD comprises one or more sgRNAs targeting exon 3 of hIL6R. In some embodiments, the CRISPR gene-editing system for the treatment of DDD comprises one or more sgRNAs targeting exon 4 of hIL6R. In some embodiments, the CRISPR gene-editing system for the treatment of DDD comprises one or more sgRNAs targeting exon 5 of hIL6R. In some embodiments, the CRISPR gene-editing system for the treatment of DDD comprises one or more sgRNAs targeting exon 6 of hIL6R. In some embodiments, the CRISPR gene-editing system for the treatment of DDD comprises one or more sgRNAs targeting exon 7 of hIL6R. In some embodiments, the CRISPR gene-editing system for the treatment of DDD comprises one or more sgRNAs targeting exon 8 of hIL6R. In some embodiments, the CRISPR gene-editing system for the treatment of DDD comprises one or more sgRNAs targeting exon 9 of hIL6R. In some embodiments, the CRISPR gene-editing system for the treatment of DDD comprises one or more sgRNAs targeting exon 10 of hIL6R. In some embodiments, the CRISPR gene-editing system for the treatment of DDD comprises one or more sgRNAs targeting exon 11 of hIL6R In some embodiments, the CRISPR gene-editing system for the treatment of DDD comprises one or more sgRNAs targeting exon 12 of hIL6R. In some embodiments, the CRISPR gene-editing system for the treatment of DDD comprises one or more sgRNAs targeting exon 13 of hIL6R. In some embodiments, the CRISPR gene-editing system for the treatment of DDD comprises one or more sgRNAs

targeting exon 14 of hIL6R. In some embodiments, the CRISPR gene-editing system for the treatment of DDD comprises one or more sgRNAs targeting exon 15 of hIL6R.

[00426] In some embodiments, the CRISPR gene-editing system for the treatment of DDD comprises one or more sgRNAs targeting exon 1 of cIL6R. In some embodiments, the CRISPR gene-editing system for the treatment of DDD comprises one or more sgRNAs targeting exon 2 of cIL6R. In some embodiments, the CRISPR gene-editing system for the treatment of DDD comprises one or more sgRNAs targeting exon 3 of cIL6R. In some embodiments, the CRISPR gene-editing system for the treatment of DDD comprises one or more sgRNAs targeting exon 4 of cIL6R. In some embodiments, the CRISPR gene-editing system for the treatment of DDD comprises one or more sgRNAs targeting exon 5 of cIL6R. In some embodiments, the CRISPR gene-editing system for the treatment of DDD comprises one or more sgRNAs targeting exon 6 of cIL6R. In some embodiments, the CRISPR gene-editing system for the treatment of DDD comprises one or more sgRNAs targeting exon 7 of cIL6R. In some embodiments, the CRISPR gene-editing system for the treatment of DDD comprises one or more sgRNAs targeting exon 8 of cIL6R. In some embodiments, the CRISPR gene-editing system for the treatment of DDD comprises one or more sgRNAs targeting exon 9 of cIL6R. In some embodiments, the CRISPR gene-editing system for the treatment of DDD comprises one or more sgRNAs targeting exon 10 of cIL6R. In some embodiments, the CRISPR gene-editing system for the treatment of DDD comprises one or more sgRNAs targeting exon 11 of cIL6R. In some embodiments, the CRISPR gene-editing system for the treatment of DDD comprises one or more sgRNAs targeting exon 12 of cIL6R. In some embodiments, the CRISPR gene-editing system for the treatment of DDD comprises one or more sgRNAs targeting exon 13 of cIL6R.

[00427] In some embodiments, the CRISPR gene-editing system for the treatment of DDD comprises one or more sgRNAs targeting exon 1 of eIL6R. In some embodiments, the CRISPR gene-editing system for the treatment of DDD comprises one or more sgRNAs targeting exon 2 of eIL6R. In some embodiments, the CRISPR gene-editing system for the treatment of DDD comprises one or more sgRNAs targeting exon 3 of eIL6R. In some embodiments, the CRISPR gene-editing system for the treatment of DDD comprises one or more sgRNAs targeting exon 4 of eIL6R. In some embodiments, the CRISPR gene-editing system for the treatment of DDD comprises one or more sgRNAs targeting exon 5 of eIL6R. In some embodiments, the CRISPR gene-editing system for the treatment of DDD comprises one or more sgRNAs targeting exon 6 of eIL6R. In some embodiments, the CRISPR gene-

editing system for the treatment of DDD comprises one or more sgRNAs targeting exon 7 of eIL6R. In some embodiments, the CRISPR gene-editing system for the treatment of DDD comprises one or more sgRNAs targeting exon 8 of eIL6R. In some embodiments, the CRISPR gene-editing system for the treatment of DDD comprises one or more sgRNAs targeting exon 9 of eIL6R. In some embodiments, the CRISPR gene-editing system for the treatment of DDD comprises one or more sgRNAs targeting exon 10 of eIL6R. In some embodiments, the CRISPR gene-editing system for the treatment of DDD comprises one or more sgRNAs targeting exon 11 of eIL6R.

[00428] In some embodiments, the CRISPR gene-editing system for the treatment of DDD comprises one or more sgRNAs targeting exon 1 of fIL6R. In some embodiments, the CRISPR gene-editing system for the treatment of DDD comprises one or more sgRNAs targeting exon 2 of fIL6R. In some embodiments, the CRISPR gene-editing system for the treatment of DDD comprises one or more sgRNAs targeting exon 3 of fIL6R. In some embodiments, the CRISPR gene-editing system for the treatment of DDD comprises one or more sgRNAs targeting exon 4 of fIL6R. In some embodiments, the CRISPR gene-editing system for the treatment of DDD comprises one or more sgRNAs targeting exon 5 of fIL6R. In some embodiments, the CRISPR gene-editing system for the treatment of DDD comprises one or more sgRNAs targeting exon 6 of fIL6R. In some embodiments, the CRISPR gene-editing system for the treatment of DDD comprises one or more sgRNAs targeting exon 7 of fIL6R. In some embodiments, the CRISPR gene-editing system for the treatment of DDD comprises one or more sgRNAs targeting exon 8 of fIL6R. In some embodiments, the CRISPR gene-editing system for the treatment of DDD comprises one or more sgRNAs targeting exon 9 of fIL6R. In some embodiments, the CRISPR gene-editing system for the treatment of DDD comprises one or more sgRNAs targeting exon 10 of fIL6R.

[00429] In some embodiments, the CRISPR gene-editing system for the treatment of DDD comprises one or more sgRNAs targeting IL6ST. In some embodiments, the CRISPR gene-editing system for the treatment of DDD comprises one or more sgRNAs targeting hIL6ST. In some embodiments, the CRISPR gene-editing system for the treatment of DDD comprises one or more sgRNAs targeting cIL6ST. In some embodiments, the CRISPR gene-editing system for the treatment of DDD comprises one or more sgRNAs targeting eIL6ST. In some embodiments, the CRISPR gene-editing system for the treatment of DDD comprises one or more sgRNAs targeting fIL6ST.

[00430] In some embodiments, the CRISPR gene-editing system for the treatment of DDD comprises one or more sgRNAs targeting exon 1 of hIL6ST. In some embodiments, the CRISPR gene-editing system for the treatment of DDD comprises one or more sgRNAs targeting exon 2 of hIL6ST. In some embodiments, the CRISPR gene-editing system for the treatment of DDD comprises one or more sgRNAs targeting exon 3 of hIL6ST. In some embodiments, the CRISPR gene-editing system for the treatment of DDD comprises one or more sgRNAs targeting exon 4 of hIL6ST. In some embodiments, the CRISPR gene-editing system for the treatment of DDD comprises one or more sgRNAs targeting exon 5 of hIL6ST. In some embodiments, the CRISPR gene-editing system for the treatment of DDD comprises one or more sgRNAs targeting exon 6 of hIL6ST. In some embodiments, the CRISPR gene-editing system for the treatment of DDD comprises one or more sgRNAs targeting exon 7 of hIL6ST. In some embodiments, the CRISPR gene-editing system for the treatment of DDD comprises one or more sgRNAs targeting exon 8 of hIL6ST. In some embodiments, the CRISPR gene-editing system for the treatment of DDD comprises one or more sgRNAs targeting exon 9 of hIL6ST. In some embodiments, the CRISPR gene-editing system for the treatment of DDD comprises one or more sgRNAs targeting exon 10 of hIL6ST. In some embodiments, the CRISPR gene-editing system for the treatment of DDD comprises one or more sgRNAs targeting exon 11 of hIL6ST. In some embodiments, the CRISPR gene-editing system for the treatment of DDD comprises one or more sgRNAs targeting exon 12 of hIL6ST. In some embodiments, the CRISPR gene-editing system for the treatment of DDD comprises one or more sgRNAs targeting exon 13 of hIL6ST. In some embodiments, the CRISPR gene-editing system for the treatment of DDD comprises one or more sgRNAs targeting exon 14 of hIL6ST. In some embodiments, the CRISPR gene-editing system for the treatment of DDD comprises one or more sgRNAs targeting exon 15 of hIL6ST. In some embodiments, the CRISPR gene-editing system for the treatment of DDD comprises one or more sgRNAs targeting exon 16 of hIL6ST. In some embodiments, the CRISPR gene-editing system for the treatment of DDD comprises one or more sgRNAs targeting exon 17 of hIL6ST. In some embodiments, the CRISPR gene-editing system for the treatment of DDD comprises one or more sgRNAs targeting exon 18 of hIL6ST. In some embodiments, the CRISPR gene-editing system for the treatment of DDD comprises one or more sgRNAs targeting exon 19 of hIL6ST.

[00431] In some embodiments, the CRISPR gene-editing system for the treatment of DDD comprises one or more sgRNAs targeting exon 1 of cIL6ST. In some embodiments, the

CRISPR gene-editing system for the treatment of DDD comprises one or more sgRNAs targeting exon 2 of cIL6ST. In some embodiments, the CRISPR gene-editing system for the treatment of DDD comprises one or more sgRNAs targeting exon 3 of cIL6ST. In some embodiments, the CRISPR gene-editing system for the treatment of DDD comprises one or more sgRNAs targeting exon 4 of cIL6ST. In some embodiments, the CRISPR gene-editing system for the treatment of DDD comprises one or more sgRNAs targeting exon 5 of cIL6ST. In some embodiments, the CRISPR gene-editing system for the treatment of DDD comprises one or more sgRNAs targeting exon 6 of cIL6ST. In some embodiments, the CRISPR gene-editing system for the treatment of DDD comprises one or more sgRNAs targeting exon 7 of cIL6ST. In some embodiments, the CRISPR gene-editing system for the treatment of DDD comprises one or more sgRNAs targeting exon 8 of cIL6ST. In some embodiments, the CRISPR gene-editing system for the treatment of DDD comprises one or more sgRNAs targeting exon 9 of cIL6ST. In some embodiments, the CRISPR gene-editing system for the treatment of DDD comprises one or more sgRNAs targeting exon 10 of cIL6ST. In some embodiments, the CRISPR gene-editing system for the treatment of DDD comprises one or more sgRNAs targeting exon 11 of cIL6ST In some embodiments, the CRISPR gene-editing system for the treatment of DDD comprises one or more sgRNAs targeting exon 12 of cIL6ST. In some embodiments, the CRISPR gene-editing system for the treatment of DDD comprises one or more sgRNAs targeting exon 13 of cIL6ST. In some embodiments, the CRISPR gene-editing system for the treatment of DDD comprises one or more sgRNAs targeting exon 14 of cIL6ST. In some embodiments, the CRISPR gene-editing system for the treatment of DDD comprises one or more sgRNAs targeting exon 15 of cIL6ST. In some embodiments, the CRISPR gene-editing system for the treatment of DDD comprises one or more sgRNAs targeting exon 16 of cIL6ST. In some embodiments, the CRISPR gene-editing system for the treatment of DDD comprises one or more sgRNAs targeting exon 17 of cIL6ST. In some embodiments, the CRISPR gene-editing system for the treatment of DDD comprises one or more sgRNAs targeting exon 18 of cIL6ST.

[00432] In some embodiments, the CRISPR gene-editing system for the treatment of DDD comprises one or more sgRNAs targeting exon 1 of eIL6ST. In some embodiments, the CRISPR gene-editing system for the treatment of DDD comprises one or more sgRNAs targeting exon 2 of eIL6ST. In some embodiments, the CRISPR gene-editing system for the treatment of DDD comprises one or more sgRNAs targeting exon 3 of eIL6ST. In some embodiments, the CRISPR gene-editing system for the treatment of DDD comprises one or

more sgRNAs targeting exon 4 of eIL6ST. In some embodiments, the CRISPR gene-editing system for the treatment of DDD comprises one or more sgRNAs targeting exon 5 of eIL6ST. In some embodiments, the CRISPR gene-editing system for the treatment of DDD comprises one or more sgRNAs targeting exon 6 of eIL6ST. In some embodiments, the CRISPR gene-editing system for the treatment of DDD comprises one or more sgRNAs targeting exon 7 of eIL6ST. In some embodiments, the CRISPR gene-editing system for the treatment of DDD comprises one or more sgRNAs targeting exon 8 of eIL6ST. In some embodiments, the CRISPR gene-editing system for the treatment of DDD comprises one or more sgRNAs targeting exon 9 of eIL6ST. In some embodiments, the CRISPR gene-editing system for the treatment of DDD comprises one or more sgRNAs targeting exon 10 of eIL6ST. In some embodiments, the CRISPR gene-editing system for the treatment of DDD comprises one or more sgRNAs targeting exon 11 of eIL6ST In some embodiments, the CRISPR gene-editing system for the treatment of DDD comprises one or more sgRNAs targeting exon 12 of eIL6ST. In some embodiments, the CRISPR gene-editing system for the treatment of DDD comprises one or more sgRNAs targeting exon 13 of eIL6ST. In some embodiments, the CRISPR gene-editing system for the treatment of DDD comprises one or more sgRNAs targeting exon 14 of eIL6ST. In some embodiments, the CRISPR gene-editing system for the treatment of DDD comprises one or more sgRNAs targeting exon 15 of eIL6ST. In some embodiments, the CRISPR gene-editing system for the treatment of DDD comprises one or more sgRNAs targeting exon 16 of eIL6ST. In some embodiments, the CRISPR gene-editing system for the treatment of DDD comprises one or more sgRNAs targeting exon 17 of eIL6ST. In some embodiments, the CRISPR gene-editing system for the treatment of DDD comprises one or more sgRNAs targeting exon 18 of eIL6ST.

[00433] In some embodiments, the CRISPR gene-editing system for the treatment of DDD comprises one or more sgRNAs targeting exon 1 of fIL6ST. In some embodiments, the CRISPR gene-editing system for the treatment of DDD comprises one or more sgRNAs targeting exon 2 of fIL6ST. In some embodiments, the CRISPR gene-editing system for the treatment of DDD comprises one or more sgRNAs targeting exon 3 of fIL6ST. In some embodiments, the CRISPR gene-editing system for the treatment of DDD comprises one or more sgRNAs targeting exon 4 of fIL6ST. In some embodiments, the CRISPR gene-editing system for the treatment of DDD comprises one or more sgRNAs targeting exon 5 of fIL6ST. In some embodiments, the CRISPR gene-editing system for the treatment of DDD comprises one or more sgRNAs targeting exon 6 of fIL6ST. In some embodiments, the CRISPR gene-

editing system for the treatment of DDD comprises one or more sgRNAs targeting exon 7 of fIL6ST. In some embodiments, the CRISPR gene-editing system for the treatment of DDD comprises one or more sgRNAs targeting exon 8 of fIL6ST. In some embodiments, the CRISPR gene-editing system for the treatment of DDD comprises one or more sgRNAs targeting exon 9 of fIL6ST. In some embodiments, the CRISPR gene-editing system for the treatment of DDD comprises one or more sgRNAs targeting exon 10 of fIL6ST. In some embodiments, the CRISPR gene-editing system for the treatment of DDD comprises one or more sgRNAs targeting exon 11 of fIL6ST In some embodiments, the CRISPR gene-editing system for the treatment of DDD comprises one or more sgRNAs targeting exon 12 of fIL6ST. In some embodiments, the CRISPR gene-editing system for the treatment of DDD comprises one or more sgRNAs targeting exon 13 of fIL6ST. In some embodiments, the CRISPR gene-editing system for the treatment of DDD comprises one or more sgRNAs targeting exon 14 of fIL6ST. In some embodiments, the CRISPR gene-editing system for the treatment of DDD comprises one or more sgRNAs targeting exon 15 of fIL6ST. In some embodiments, the CRISPR gene-editing system for the treatment of DDD comprises one or more sgRNAs targeting exon 16 of fIL6ST. In some embodiments, the CRISPR gene-editing system for the treatment of DDD comprises one or more sgRNAs targeting exon 17 of fIL6ST. In some embodiments, the CRISPR gene-editing system for the treatment of DDD comprises one or more sgRNAs targeting exon 18 of fIL6ST. In some embodiments, the CRISPR gene-editing system for the treatment of DDD comprises one or more sgRNAs targeting exon 19 of fIL6ST. In some embodiments, the CRISPR gene-editing system for the treatment of DDD comprises one or more sgRNAs targeting exon 20 of fIL6ST.

[00434] In some embodiments, the CRISPR gene-editing system for the treatment of DDD comprises one or more sgRNAs targeting TNFRSF1A. In some embodiments, the CRISPR gene-editing system for the treatment of DDD comprises one or more sgRNAs targeting hTNFRSF1A. In some embodiments, the CRISPR gene-editing system for the treatment of DDD comprises one or more sgRNAs targeting cTNFRSF1A. In some embodiments, the CRISPR gene-editing system for the treatment of DDD comprises one or more sgRNAs targeting eTNFRSF1A. In some embodiments, the CRISPR gene-editing system for the treatment of DDD comprises one or more sgRNAs targeting fTNFRSF1A.

[00435] In some embodiments, the CRISPR gene-editing system for the treatment of DDD comprises one or more sgRNAs targeting exon 1 of hTNFRSF1A. In some embodiments, the CRISPR gene-editing system for the treatment of DDD comprises one or more sgRNAs

targeting exon 2 of hTNFRSF1A. In some embodiments, the CRISPR gene-editing system for the treatment of DDD comprises one or more sgRNAs targeting exon 3 of hTNFRSF1A. In some embodiments, the CRISPR gene-editing system for the treatment of DDD comprises one or more sgRNAs targeting exon 4 of hTNFRSF1A. In some embodiments, the CRISPR gene-editing system for the treatment of DDD comprises one or more sgRNAs targeting exon 5 of hTNFRSF1A. In some embodiments, the CRISPR gene-editing system for the treatment of DDD comprises one or more sgRNAs targeting exon 6 of hTNFRSF1A. In some embodiments, the CRISPR gene-editing system for the treatment of DDD comprises one or more sgRNAs targeting exon 7 of hTNFRSF1A. In some embodiments, the CRISPR gene-editing system for the treatment of DDD comprises one or more sgRNAs targeting exon 8 of hTNFRSF1A. In some embodiments, the CRISPR gene-editing system for the treatment of DDD comprises one or more sgRNAs targeting exon 9 of hTNFRSF1A. In some embodiments, the CRISPR gene-editing system for the treatment of DDD comprises one or more sgRNAs targeting exon 10 of hTNFRSF1A. In some embodiments, the CRISPR gene-editing system for the treatment of DDD comprises one or more sgRNAs targeting exon 11 of hTNFRSF1A.

[00436] In some embodiments, the CRISPR gene-editing system for the treatment of DDD comprises one or more sgRNAs targeting exon 1 of cTNFRSF1A. In some embodiments, the CRISPR gene-editing system for the treatment of DDD comprises one or more sgRNAs targeting exon 2 of cTNFRSF1A. In some embodiments, the CRISPR gene-editing system for the treatment of DDD comprises one or more sgRNAs targeting exon 3 of cTNFRSF1A. In some embodiments, the CRISPR gene-editing system for the treatment of DDD comprises one or more sgRNAs targeting exon 4 of cTNFRSF1A. In some embodiments, the CRISPR gene-editing system for the treatment of DDD comprises one or more sgRNAs targeting exon 5 of cTNFRSF1A. In some embodiments, the CRISPR gene-editing system for the treatment of DDD comprises one or more sgRNAs targeting exon 6 of cTNFRSF1A. In some embodiments, the CRISPR gene-editing system for the treatment of DDD comprises one or more sgRNAs targeting exon 7 of cTNFRSF1A. In some embodiments, the CRISPR gene-editing system for the treatment of DDD comprises one or more sgRNAs targeting exon 8 of cTNFRSF1A. In some embodiments, the CRISPR gene-editing system for the treatment of DDD comprises one or more sgRNAs targeting exon 9 of cTNFRSF1A. In some embodiments, the CRISPR gene-editing system for the treatment of DDD comprises one or more sgRNAs targeting exon 10 of cTNFRSF1A. In some embodiments, the CRISPR gene-

editing system for the treatment of DDD comprises one or more sgRNAs targeting exon 11 of cTNFRSF1A.

[00437] In some embodiments, the CRISPR gene-editing system for the treatment of DDD comprises one or more sgRNAs targeting exon 1 of eTNFRSF1A. In some embodiments, the CRISPR gene-editing system for the treatment of DDD comprises one or more sgRNAs targeting exon 2 of eTNFRSF1A. In some embodiments, the CRISPR gene-editing system for the treatment of DDD comprises one or more sgRNAs targeting exon 3 of eTNFRSF1A. In some embodiments, the CRISPR gene-editing system for the treatment of DDD comprises one or more sgRNAs targeting exon 4 of eTNFRSF1A. In some embodiments, the CRISPR gene-editing system for the treatment of DDD comprises one or more sgRNAs targeting exon 5 of eTNFRSF1A. In some embodiments, the CRISPR gene-editing system for the treatment of DDD comprises one or more sgRNAs targeting exon 6 of eTNFRSF1A. In some embodiments, the CRISPR gene-editing system for the treatment of DDD comprises one or more sgRNAs targeting exon 7 of eTNFRSF1A. In some embodiments, the CRISPR gene-editing system for the treatment of DDD comprises one or more sgRNAs targeting exon 8 of eTNFRSF1A. In some embodiments, the CRISPR gene-editing system for the treatment of DDD comprises one or more sgRNAs targeting exon 9 of eTNFRSF1A. In some embodiments, the CRISPR gene-editing system for the treatment of DDD comprises one or more sgRNAs targeting exon 10 of eTNFRSF1A.

[00438] In some embodiments, the CRISPR gene-editing system for the treatment of DDD comprises one or more sgRNAs targeting exon 1 of fTNFRSF1A. In some embodiments, the CRISPR gene-editing system for the treatment of DDD comprises one or more sgRNAs targeting exon 2 of fTNFRSF1A. In some embodiments, the CRISPR gene-editing system for the treatment of DDD comprises one or more sgRNAs targeting exon 3 of fTNFRSF1A. In some embodiments, the CRISPR gene-editing system for the treatment of DDD comprises one or more sgRNAs targeting exon 4 of fTNFRSF1A. In some embodiments, the CRISPR gene-editing system for the treatment of DDD comprises one or more sgRNAs targeting exon 5 of fTNFRSF1A. In some embodiments, the CRISPR gene-editing system for the treatment of DDD comprises one or more sgRNAs targeting exon 6 of fTNFRSF1A. In some embodiments, the CRISPR gene-editing system for the treatment of DDD comprises one or more sgRNAs targeting exon 7 of fTNFRSF1A. In some embodiments, the CRISPR gene-editing system for the treatment of DDD comprises one or more sgRNAs targeting exon 8 of fTNFRSF1A. In some embodiments, the CRISPR gene-editing system for the treatment of

DDD comprises one or more sgRNAs targeting exon 9 of fTNFRSF1A. In some embodiments, the CRISPR gene-editing system for the treatment of DDD comprises one or more sgRNAs targeting exon 10 of fTNFRSF1A.

[00439] In some embodiments, the CRISPR gene-editing system for the treatment of DDD comprises one or more sgRNAs targeting TNFRSF1B. In some embodiments, the CRISPR gene-editing system for the treatment of DDD comprises one or more sgRNAs targeting hTNFRSF1B. In some embodiments, the CRISPR gene-editing system for the treatment of DDD comprises one or more sgRNAs targeting cTNFRSF1B. In some embodiments, the CRISPR gene-editing system for the treatment of DDD comprises one or more sgRNAs targeting eTNFRSF1B. In some embodiments, the CRISPR gene-editing system for the treatment of DDD comprises one or more sgRNAs targeting fTNFRSF1B.

[00440] In some embodiments, the CRISPR gene-editing system for the treatment of DDD comprises one or more sgRNAs targeting exon 1 of hTNFRSF1B. In some embodiments, the CRISPR gene-editing system for the treatment of DDD comprises one or more sgRNAs targeting exon 2 of hTNFRSF1B. In some embodiments, the CRISPR gene-editing system for the treatment of DDD comprises one or more sgRNAs targeting exon 3 of hTNFRSF1B. In some embodiments, the CRISPR gene-editing system for the treatment of DDD comprises one or more sgRNAs targeting exon 4 of hTNFRSF1B. In some embodiments, the CRISPR gene-editing system for the treatment of DDD comprises one or more sgRNAs targeting exon 5 of hTNFRSF1B. In some embodiments, the CRISPR gene-editing system for the treatment of DDD comprises one or more sgRNAs targeting exon 6 of hTNFRSF1B. In some embodiments, the CRISPR gene-editing system for the treatment of DDD comprises one or more sgRNAs targeting exon 7 of hTNFRSF1B. In some embodiments, the CRISPR gene-editing system for the treatment of DDD comprises one or more sgRNAs targeting exon 8 of hTNFRSF1B. In some embodiments, the CRISPR gene-editing system for the treatment of DDD comprises one or more sgRNAs targeting exon 9 of hTNFRSF1B. In some embodiments, the CRISPR gene-editing system for the treatment of DDD comprises one or more sgRNAs targeting exon 10 of hTNFRSF1B. In some embodiments, the CRISPR gene-editing system for the treatment of DDD comprises one or more sgRNAs targeting exon 11 of hTNFRSF1B In some embodiments, the CRISPR gene-editing system for the treatment of DDD comprises one or more sgRNAs targeting exon 12 of hTNFRSF1B. In some embodiments, the CRISPR gene-editing system for the treatment of DDD comprises one or more sgRNAs targeting exon 13 of hTNFRSF1B.

[00441] In some embodiments, the CRISPR gene-editing system for the treatment of DDD comprises one or more sgRNAs targeting exon 1 of cTNFRSF1B. In some embodiments, the CRISPR gene-editing system for the treatment of DDD comprises one or more sgRNAs targeting exon 2 of cTNFRSF1B. In some embodiments, the CRISPR gene-editing system for the treatment of DDD comprises one or more sgRNAs targeting exon 3 of cTNFRSF1B. In some embodiments, the CRISPR gene-editing system for the treatment of DDD comprises one or more sgRNAs targeting exon 4 of cTNFRSF1B. In some embodiments, the CRISPR gene-editing system for the treatment of DDD comprises one or more sgRNAs targeting exon 5 of cTNFRSF1B. In some embodiments, the CRISPR gene-editing system for the treatment of DDD comprises one or more sgRNAs targeting exon 6 of cTNFRSF1B. In some embodiments, the CRISPR gene-editing system for the treatment of DDD comprises one or more sgRNAs targeting exon 7 of cTNFRSF1B. In some embodiments, the CRISPR gene-editing system for the treatment of DDD comprises one or more sgRNAs targeting exon 8 of cTNFRSF1B. In some embodiments, the CRISPR gene-editing system for the treatment of DDD comprises one or more sgRNAs targeting exon 9 of cTNFRSF1B. In some embodiments, the CRISPR gene-editing system for the treatment of DDD comprises one or more sgRNAs targeting exon 10 of cTNFRSF1B. In some embodiments, the CRISPR gene-editing system for the treatment of DDD comprises one or more sgRNAs targeting exon 11 of cTNFRSF1B.

[00442] In some embodiments, the CRISPR gene-editing system for the treatment of DDD comprises one or more sgRNAs targeting exon 1 of eTNFRSF1B. In some embodiments, the CRISPR gene-editing system for the treatment of DDD comprises one or more sgRNAs targeting exon 2 of eTNFRSF1B. In some embodiments, the CRISPR gene-editing system for the treatment of DDD comprises one or more sgRNAs targeting exon 3 of eTNFRSF1B. In some embodiments, the CRISPR gene-editing system for the treatment of DDD comprises one or more sgRNAs targeting exon 4 of eTNFRSF1B. In some embodiments, the CRISPR gene-editing system for the treatment of DDD comprises one or more sgRNAs targeting exon 5 of eTNFRSF1B. In some embodiments, the CRISPR gene-editing system for the treatment of DDD comprises one or more sgRNAs targeting exon 6 of eTNFRSF1B. In some embodiments, the CRISPR gene-editing system for the treatment of DDD comprises one or more sgRNAs targeting exon 7 of eTNFRSF1B. In some embodiments, the CRISPR gene-editing system for the treatment of DDD comprises one or more sgRNAs targeting exon 8 of eTNFRSF1B. In some embodiments, the CRISPR gene-editing system for the treatment of

DDD comprises one or more sgRNAs targeting exon 9 of eTNFRSF1B. In some embodiments, the CRISPR gene-editing system for the treatment of DDD comprises one or more sgRNAs targeting exon 10 of eTNFRSF1B. In some embodiments, the CRISPR gene-editing system for the treatment of DDD comprises one or more sgRNAs targeting exon 11 of eTNFRSF1B.

[00443] In some embodiments, the CRISPR gene-editing system for the treatment of DDD comprises one or more sgRNAs targeting exon 1 of fTNFRSF1B. In some embodiments, the CRISPR gene-editing system for the treatment of DDD comprises one or more sgRNAs targeting exon 2 of fTNFRSF1B. In some embodiments, the CRISPR gene-editing system for the treatment of DDD comprises one or more sgRNAs targeting exon 3 of fTNFRSF1B. In some embodiments, the CRISPR gene-editing system for the treatment of DDD comprises one or more sgRNAs targeting exon 4 of fTNFRSF1B. In some embodiments, the CRISPR gene-editing system for the treatment of DDD comprises one or more sgRNAs targeting exon 5 of fTNFRSF1B. In some embodiments, the CRISPR gene-editing system for the treatment of DDD comprises one or more sgRNAs targeting exon 6 of fTNFRSF1B. In some embodiments, the CRISPR gene-editing system for the treatment of DDD comprises one or more sgRNAs targeting exon 7 of fTNFRSF1B. In some embodiments, the CRISPR gene-editing system for the treatment of DDD comprises one or more sgRNAs targeting exon 8 of fTNFRSF1B. In some embodiments, the CRISPR gene-editing system for the treatment of DDD comprises one or more sgRNAs targeting exon 9 of fTNFRSF1B. In some embodiments, the CRISPR gene-editing system for the treatment of DDD comprises one or more sgRNAs targeting exon 10 of fTNFRSF1B.

[00444] In some embodiments, the CRISPR gene-editing system for the treatment of DDD comprises one or more sgRNAs targeting TNFRSF3. In some embodiments, the CRISPR gene-editing system for the treatment of DDD comprises one or more sgRNAs targeting hTNFRSF3. In some embodiments, the CRISPR gene-editing system for the treatment of DDD comprises one or more sgRNAs targeting cTNFRSF3. In some embodiments, the CRISPR gene-editing system for the treatment of DDD comprises one or more sgRNAs targeting eTNFRSF3. In some embodiments, the CRISPR gene-editing system for the treatment of DDD comprises one or more sgRNAs targeting fTNFRSF3.

[00445] In some embodiments, the CRISPR gene-editing system for the treatment of DDD comprises one or more sgRNAs targeting exon 1 of hTNFRSF3. In some embodiments, the CRISPR gene-editing system for the treatment of DDD comprises one or more sgRNAs

targeting exon 2 of hTNFRSF3. In some embodiments, the CRISPR gene-editing system for the treatment of DDD comprises one or more sgRNAs targeting exon 3 of hTNFRSF3. In some embodiments, the CRISPR gene-editing system for the treatment of DDD comprises one or more sgRNAs targeting exon 4 of hTNFRSF3. In some embodiments, the CRISPR gene-editing system for the treatment of DDD comprises one or more sgRNAs targeting exon 5 of hTNFRSF3. In some embodiments, the CRISPR gene-editing system for the treatment of DDD comprises one or more sgRNAs targeting exon 6 of hTNFRSF3. In some embodiments, the CRISPR gene-editing system for the treatment of DDD comprises one or more sgRNAs targeting exon 7 of hTNFRSF3. In some embodiments, the CRISPR gene-editing system for the treatment of DDD comprises one or more sgRNAs targeting exon 8 of hTNFRSF3. In some embodiments, the CRISPR gene-editing system for the treatment of DDD comprises one or more sgRNAs targeting exon 9 of hTNFRSF3. In some embodiments, the CRISPR gene-editing system for the treatment of DDD comprises one or more sgRNAs targeting exon 10 of hTNFRSF3. In some embodiments, the CRISPR gene-editing system for the treatment of DDD comprises one or more sgRNAs targeting exon 11 of hTNFRSF3. In some embodiments, the CRISPR gene-editing system for the treatment of DDD comprises one or more sgRNAs targeting exon 12 of hTNFRSF3.

[00446] In some embodiments, the CRISPR gene-editing system for the treatment of DDD comprises one or more sgRNAs targeting exon 1 of cTNFRSF3. In some embodiments, the CRISPR gene-editing system for the treatment of DDD comprises one or more sgRNAs targeting exon 2 of cTNFRSF3. In some embodiments, the CRISPR gene-editing system for the treatment of DDD comprises one or more sgRNAs targeting exon 3 of cTNFRSF3. In some embodiments, the CRISPR gene-editing system for the treatment of DDD comprises one or more sgRNAs targeting exon 4 of cTNFRSF3. In some embodiments, the CRISPR gene-editing system for the treatment of DDD comprises one or more sgRNAs targeting exon 5 of cTNFRSF3. In some embodiments, the CRISPR gene-editing system for the treatment of DDD comprises one or more sgRNAs targeting exon 6 of cTNFRSF3. In some embodiments, the CRISPR gene-editing system for the treatment of DDD comprises one or more sgRNAs targeting exon 7 of cTNFRSF3. In some embodiments, the CRISPR gene-editing system for the treatment of DDD comprises one or more sgRNAs targeting exon 8 of cTNFRSF3. In some embodiments, the CRISPR gene-editing system for the treatment of DDD comprises one or more sgRNAs targeting exon 9 of cTNFRSF3. In some

embodiments, the CRISPR gene-editing system for the treatment of DDD comprises one or more sgRNAs targeting exon 10 of cTNFRSF3.

[00447] In some embodiments, the CRISPR gene-editing system for the treatment of DDD comprises one or more sgRNAs targeting exon 1 of eTNFRSF3. In some embodiments, the CRISPR gene-editing system for the treatment of DDD comprises one or more sgRNAs targeting exon 2 of eTNFRSF3. In some embodiments, the CRISPR gene-editing system for the treatment of DDD comprises one or more sgRNAs targeting exon 3 of eTNFRSF3. In some embodiments, the CRISPR gene-editing system for the treatment of DDD comprises one or more sgRNAs targeting exon 4 of eTNFRSF3. In some embodiments, the CRISPR gene-editing system for the treatment of DDD comprises one or more sgRNAs targeting exon 5 of eTNFRSF3. In some embodiments, the CRISPR gene-editing system for the treatment of DDD comprises one or more sgRNAs targeting exon 6 of eTNFRSF3. In some embodiments, the CRISPR gene-editing system for the treatment of DDD comprises one or more sgRNAs targeting exon 7 of eTNFRSF3. In some embodiments, the CRISPR gene-editing system for the treatment of DDD comprises one or more sgRNAs targeting exon 8 of eTNFRSF3. In some embodiments, the CRISPR gene-editing system for the treatment of DDD comprises one or more sgRNAs targeting exon 9 of eTNFRSF3. In some embodiments, the CRISPR gene-editing system for the treatment of DDD comprises one or more sgRNAs targeting exon 10 of eTNFRSF3.

[00448] In some embodiments, the CRISPR gene-editing system for the treatment of DDD comprises one or more sgRNAs targeting exon 1 of fTNFRSF3. In some embodiments, the CRISPR gene-editing system for the treatment of DDD comprises one or more sgRNAs targeting exon 2 of fTNFRSF3. In some embodiments, the CRISPR gene-editing system for the treatment of DDD comprises one or more sgRNAs targeting exon 3 of fTNFRSF3. In some embodiments, the CRISPR gene-editing system for the treatment of DDD comprises one or more sgRNAs targeting exon 4 of fTNFRSF3. In some embodiments, the CRISPR gene-editing system for the treatment of DDD comprises one or more sgRNAs targeting exon 5 of fTNFRSF3. In some embodiments, the CRISPR gene-editing system for the treatment of DDD comprises one or more sgRNAs targeting exon 6 of fTNFRSF3. In some embodiments, the CRISPR gene-editing system for the treatment of DDD comprises one or more sgRNAs targeting exon 7 of fTNFRSF3. In some embodiments, the CRISPR gene-editing system for the treatment of DDD comprises one or more sgRNAs targeting exon 8 of fTNFRSF3. In some embodiments, the CRISPR gene-editing system for the treatment of DDD comprises

one or more sgRNAs targeting exon 9 of fTNFRSF3. In some embodiments, the CRISPR gene-editing system for the treatment of DDD comprises one or more sgRNAs targeting exon 10 of fTNFRSF3.

[00449] In some embodiments, the CRISPR gene-editing system for the treatment of DDD comprises one or more sgRNAs targeting TNFRSF4. In some embodiments, the CRISPR gene-editing system for the treatment of DDD comprises one or more sgRNAs targeting hTNFRSF4. In some embodiments, the CRISPR gene-editing system for the treatment of DDD comprises one or more sgRNAs targeting cTNFRSF4. In some embodiments, the CRISPR gene-editing system for the treatment of DDD comprises one or more sgRNAs targeting eTNFRSF4. In some embodiments, the CRISPR gene-editing system for the treatment of DDD comprises one or more sgRNAs targeting fTNFRSF4.

[00450] In some embodiments, the CRISPR gene-editing system for the treatment of DDD comprises one or more sgRNAs targeting exon 1 of hTNFRSF4. In some embodiments, the CRISPR gene-editing system for the treatment of DDD comprises one or more sgRNAs targeting exon 2 of hTNFRSF4. In some embodiments, the CRISPR gene-editing system for the treatment of DDD comprises one or more sgRNAs targeting exon 3 of hTNFRSF4. In some embodiments, the CRISPR gene-editing system for the treatment of DDD comprises one or more sgRNAs targeting exon 4 of hTNFRSF4. In some embodiments, the CRISPR gene-editing system for the treatment of DDD comprises one or more sgRNAs targeting exon 5 of hTNFRSF4. In some embodiments, the CRISPR gene-editing system for the treatment of DDD comprises one or more sgRNAs targeting exon 6 of hTNFRSF4.

[00451] In some embodiments, the CRISPR gene-editing system for the treatment of DDD comprises one or more sgRNAs targeting exon 1 of cTNFRSF4. In some embodiments, the CRISPR gene-editing system for the treatment of DDD comprises one or more sgRNAs targeting exon 2 of cTNFRSF4. In some embodiments, the CRISPR gene-editing system for the treatment of DDD comprises one or more sgRNAs targeting exon 3 of cTNFRSF4. In some embodiments, the CRISPR gene-editing system for the treatment of DDD comprises one or more sgRNAs targeting exon 4 of cTNFRSF4. In some embodiments, the CRISPR gene-editing system for the treatment of DDD comprises one or more sgRNAs targeting exon 5 of cTNFRSF4. In some embodiments, the CRISPR gene-editing system for the treatment of DDD comprises one or more sgRNAs targeting exon 6 of cTNFRSF4. In some embodiments, the CRISPR gene-editing system for the treatment of DDD comprises one or more sgRNAs targeting exon 7 of cTNFRSF4.

[00452] In some embodiments, the CRISPR gene-editing system for the treatment of DDD comprises one or more sgRNAs targeting exon 1 of eTNFRSF4. In some embodiments, the CRISPR gene-editing system for the treatment of DDD comprises one or more sgRNAs targeting exon 2 of eTNFRSF4. In some embodiments, the CRISPR gene-editing system for the treatment of DDD comprises one or more sgRNAs targeting exon 3 of eTNFRSF4. In some embodiments, the CRISPR gene-editing system for the treatment of DDD comprises one or more sgRNAs targeting exon 4 of eTNFRSF4. In some embodiments, the CRISPR gene-editing system for the treatment of DDD comprises one or more sgRNAs targeting exon 5 of eTNFRSF4. In some embodiments, the CRISPR gene-editing system for the treatment of DDD comprises one or more sgRNAs targeting exon 6 of eTNFRSF4. In some embodiments, the CRISPR gene-editing system for the treatment of DDD comprises one or more sgRNAs targeting exon 7 of eTNFRSF4.

[00453] In some embodiments, the CRISPR gene-editing system for the treatment of DDD comprises one or more sgRNAs targeting exon 1 of fTNFRSF4. In some embodiments, the CRISPR gene-editing system for the treatment of DDD comprises one or more sgRNAs targeting exon 2 of fTNFRSF4. In some embodiments, the CRISPR gene-editing system for the treatment of DDD comprises one or more sgRNAs targeting exon 3 of fTNFRSF4. In some embodiments, the CRISPR gene-editing system for the treatment of DDD comprises one or more sgRNAs targeting exon 4 of fTNFRSF4. In some embodiments, the CRISPR gene-editing system for the treatment of DDD comprises one or more sgRNAs targeting exon 5 of fTNFRSF4. In some embodiments, the CRISPR gene-editing system for the treatment of DDD comprises one or more sgRNAs targeting exon 6 of fTNFRSF4. In some embodiments, the CRISPR gene-editing system for the treatment of DDD comprises one or more sgRNAs targeting exon 7 of fTNFRSF4.

[00454] In some embodiments, the CRISPR gene-editing system for the treatment of DDD comprises one or more sgRNAs targeting TNFRSF11A. In some embodiments, the CRISPR gene-editing system for the treatment of DDD comprises one or more sgRNAs targeting hTNFRSF11A. In some embodiments, the CRISPR gene-editing system for the treatment of DDD comprises one or more sgRNAs targeting cTNFRSF11A. In some embodiments, the CRISPR gene-editing system for the treatment of DDD comprises one or more sgRNAs targeting eTNFRSF11A. In some embodiments, the CRISPR gene-editing system for the treatment of DDD comprises one or more sgRNAs targeting fTNFRSF11A.

[00455] In some embodiments, the CRISPR gene-editing system for the treatment of DDD comprises one or more sgRNAs targeting exon 1 of hTNFRSF11A. In some embodiments, the CRISPR gene-editing system for the treatment of DDD comprises one or more sgRNAs targeting exon 2 of hTNFRSF11A. In some embodiments, the CRISPR gene-editing system for the treatment of DDD comprises one or more sgRNAs targeting exon 3 of hTNFRSF11A. In some embodiments, the CRISPR gene-editing system for the treatment of DDD comprises one or more sgRNAs targeting exon 4 of hTNFRSF11A. In some embodiments, the CRISPR gene-editing system for the treatment of DDD comprises one or more sgRNAs targeting exon 5 of hTNFRSF11A. In some embodiments, the CRISPR gene-editing system for the treatment of DDD comprises one or more sgRNAs targeting exon 6 of hTNFRSF11A. In some embodiments, the CRISPR gene-editing system for the treatment of DDD comprises one or more sgRNAs targeting exon 7 of hTNFRSF11A. In some embodiments, the CRISPR gene-editing system for the treatment of DDD comprises one or more sgRNAs targeting exon 8 of hTNFRSF11A. In some embodiments, the CRISPR gene-editing system for the treatment of DDD comprises one or more sgRNAs targeting exon 9 of hTNFRSF11A. In some embodiments, the CRISPR gene-editing system for the treatment of DDD comprises one or more sgRNAs targeting exon 10 of hTNFRSF11A. In some embodiments, the CRISPR gene-editing system for the treatment of DDD comprises one or more sgRNAs targeting exon 11 of hTNFRSF11A. In some embodiments, the CRISPR gene-editing system for the treatment of DDD comprises one or more sgRNAs targeting exon 12 of hTNFRSF11A.

[00456] In some embodiments, the CRISPR gene-editing system for the treatment of DDD comprises one or more sgRNAs targeting exon 1 of cTNFRSF11A. In some embodiments, the CRISPR gene-editing system for the treatment of DDD comprises one or more sgRNAs targeting exon 2 of cTNFRSF11A. In some embodiments, the CRISPR gene-editing system for the treatment of DDD comprises one or more sgRNAs targeting exon 3 of cTNFRSF11A. In some embodiments, the CRISPR gene-editing system for the treatment of DDD comprises one or more sgRNAs targeting exon 4 of cTNFRSF11A. In some embodiments, the CRISPR gene-editing system for the treatment of DDD comprises one or more sgRNAs targeting exon 5 of cTNFRSF11A. In some embodiments, the CRISPR gene-editing system for the treatment of DDD comprises one or more sgRNAs targeting exon 6 of cTNFRSF11A. In some embodiments, the CRISPR gene-editing system for the treatment of DDD comprises one or more sgRNAs targeting exon 7 of cTNFRSF11A. In some embodiments, the CRISPR

gene-editing system for the treatment of DDD comprises one or more sgRNAs targeting exon 8 of cTNFRSF11A. In some embodiments, the CRISPR gene-editing system for the treatment of DDD comprises one or more sgRNAs targeting exon 9 of cTNFRSF11A. In some embodiments, the CRISPR gene-editing system for the treatment of DDD comprises one or more sgRNAs targeting exon 10 of cTNFRSF11A. In some embodiments, the CRISPR gene-editing system for the treatment of DDD comprises one or more sgRNAs targeting exon 11 of cTNFRSF11A.

[00457] In some embodiments, the CRISPR gene-editing system for the treatment of DDD comprises one or more sgRNAs targeting exon 1 of eTNFRSF11A. In some embodiments, the CRISPR gene-editing system for the treatment of DDD comprises one or more sgRNAs targeting exon 2 of eTNFRSF11A. In some embodiments, the CRISPR gene-editing system for the treatment of DDD comprises one or more sgRNAs targeting exon 3 of eTNFRSF11A. In some embodiments, the CRISPR gene-editing system for the treatment of DDD comprises one or more sgRNAs targeting exon 4 of eTNFRSF11A. In some embodiments, the CRISPR gene-editing system for the treatment of DDD comprises one or more sgRNAs targeting exon 5 of eTNFRSF11A. In some embodiments, the CRISPR gene-editing system for the treatment of DDD comprises one or more sgRNAs targeting exon 6 of eTNFRSF11A. In some embodiments, the CRISPR gene-editing system for the treatment of DDD comprises one or more sgRNAs targeting exon 7 of eTNFRSF11A. In some embodiments, the CRISPR gene-editing system for the treatment of DDD comprises one or more sgRNAs targeting exon 8 of eTNFRSF11A. In some embodiments, the CRISPR gene-editing system for the treatment of DDD comprises one or more sgRNAs targeting exon 9 of eTNFRSF11A. In some embodiments, the CRISPR gene-editing system for the treatment of DDD comprises one or more sgRNAs targeting exon 10 of eTNFRSF11A.

[00458] In some embodiments, the CRISPR gene-editing system for the treatment of DDD comprises one or more sgRNAs targeting exon 1 of fTNFRSF11A. In some embodiments, the CRISPR gene-editing system for the treatment of DDD comprises one or more sgRNAs targeting exon 2 of fTNFRSF11A. In some embodiments, the CRISPR gene-editing system for the treatment of DDD comprises one or more sgRNAs targeting exon 3 of fTNFRSF11A. In some embodiments, the CRISPR gene-editing system for the treatment of DDD comprises one or more sgRNAs targeting exon 4 of fTNFRSF11A. In some embodiments, the CRISPR gene-editing system for the treatment of DDD comprises one or more sgRNAs targeting exon 5 of fTNFRSF11A. In some embodiments, the CRISPR gene-editing system for the

treatment of DDD comprises one or more sgRNAs targeting exon 6 of fTNFRSF11A. In some embodiments, the CRISPR gene-editing system for the treatment of DDD comprises one or more sgRNAs targeting exon 7 of fTNFRSF11A. In some embodiments, the CRISPR gene-editing system for the treatment of DDD comprises one or more sgRNAs targeting exon 8 of fTNFRSF11A. In some embodiments, the CRISPR gene-editing system for the treatment of DDD comprises one or more sgRNAs targeting exon 9 of fTNFRSF11A. In some embodiments, the CRISPR gene-editing system for the treatment of DDD comprises one or more sgRNAs targeting exon 10 of fTNFRSF11A. In some embodiments, the CRISPR gene-editing system for the treatment of DDD comprises one or more sgRNAs targeting exon 11 of fTNFRSF11A.

D. IDD

[00459] In one aspect, the present disclosure encompasses treatments for internal disc disruption (IDD). In some embodiments, the IDD treatment comprises a therapeutically effective amount of a Clustered Regularly Interspaced Short Palindromic Repeats (CRISPR) gene-editing system, the system comprising: (i) a CRISPR Associated (Cas) protein; and (ii) at least one guide RNA targeting IL1R1. In some embodiments, the IDD treatment comprises a CRISPR gene-editing system targeting hIL1R1. In some embodiments, the IDD treatment comprises a CRISPR gene-editing system targeting cIL1R1. In some embodiments, the IDD treatment comprises a CRISP gene-editing system R targeting eIL1R1. In some embodiments, the IDD treatment comprises a CRISPR gene-editing system targeting fIL1R1.

[00460] In some embodiments, the CRISPR gene-editing system for the treatment of IDD comprises one or more sgRNAs targeting exon 1 of hIL1R1. In some embodiments, the CRISPR gene-editing system for the treatment of IDD comprises one or more sgRNAs targeting exon 2 of hIL1R1. In some embodiments, the CRISPR gene-editing system for the treatment of IDD comprises one or more sgRNAs targeting exon 3 of hIL1R1. In some embodiments, the CRISPR gene-editing system for the treatment of IDD comprises one or more sgRNAs targeting exon 4 of hIL1R1. In some embodiments, the CRISPR gene-editing system for the treatment of IDD comprises one or more sgRNAs targeting exon 5 of hIL1R1. In some embodiments, the CRISPR gene-editing system for the treatment of IDD comprises one or more sgRNAs targeting exon 6 of hIL1R1. In some embodiments, the CRISPR gene-editing system for the treatment of IDD comprises one or more sgRNAs targeting exon 7 of hIL1R1. In some embodiments, the CRISPR gene-editing system for the treatment of IDD

comprises one or more sgRNAs targeting exon 8 of hIL1R1. In some embodiments, the CRISPR gene-editing system for the treatment of IDD comprises one or more sgRNAs targeting exon 9 of hIL1R1. In some embodiments, the CRISPR gene-editing system for the treatment of IDD comprises one or more sgRNAs targeting exon 10 of hIL1R1. In some embodiments, the CRISPR gene-editing system for the treatment of IDD comprises one or more sgRNAs targeting exon 11 of hIL1R1. In some embodiments, the CRISPR gene-editing system for the treatment of IDD comprises one or more sgRNAs targeting exon 12 of hIL1R1. In some embodiments, the CRISPR gene-editing system for the treatment of IDD comprises one or more sgRNAs targeting exon 13 of hIL1R1. In some embodiments, the CRISPR gene-editing system for the treatment of IDD comprises one or more sgRNAs targeting exon 14 of hIL1R1. In some embodiments, the CRISPR gene-editing system for the treatment of IDD comprises one or more sgRNAs targeting exon 15 of hIL1R1. In some embodiments, the CRISPR gene-editing system for the treatment of IDD comprises one or more sgRNAs targeting exon 16 of hIL1R1. In some embodiments, the CRISPR gene-editing system for the treatment of IDD comprises one or more sgRNAs targeting exon 17 of hIL1R1. In some embodiments, the CRISPR gene-editing system for the treatment of IDD comprises one or more sgRNAs targeting exon 18 of hIL1R1. In some embodiments, the CRISPR gene-editing system for the treatment of IDD comprises one or more sgRNAs targeting exon 19 of hIL1R1. In some embodiments, the CRISPR gene-editing system for the treatment of IDD comprises one or more sgRNAs targeting exon 20 of hIL1R1. In some embodiments, the CRISPR gene-editing system for the treatment of IDD comprises one or more sgRNAs targeting exon 21 of hIL1R1.

[00461] In some embodiments, the CRISPR gene-editing system for the treatment of IDD comprises one or more sgRNAs targeting exon 1 of cIL1R1. In some embodiments, the CRISPR gene-editing system for the treatment of IDD comprises one or more sgRNAs targeting exon 2 of cIL1R1. In some embodiments, the CRISPR gene-editing system for the treatment of IDD comprises one or more sgRNAs targeting exon 3 of cIL1R1. In some embodiments, the CRISPR gene-editing system for the treatment of IDD comprises one or more sgRNAs targeting exon 4 of cIL1R1. In some embodiments, the CRISPR gene-editing system for the treatment of IDD comprises one or more sgRNAs targeting exon 5 of cIL1R1. In some embodiments, the CRISPR gene-editing system for the treatment of IDD comprises one or more sgRNAs targeting exon 6 of cIL1R1. In some embodiments, the CRISPR gene-editing system for the treatment of IDD comprises one or more sgRNAs targeting exon 7 of

cIL1R1. In some embodiments, the CRISPR gene-editing system for the treatment of IDD comprises one or more sgRNAs targeting exon 8 of cIL1R1. In some embodiments, the CRISPR gene-editing system for the treatment of IDD comprises one or more sgRNAs targeting exon 9 of cIL1R1. In some embodiments, the CRISPR gene-editing system for the treatment of IDD comprises one or more sgRNAs targeting exon 10 of cIL1R1. In some embodiments, the CRISPR gene-editing system for the treatment of IDD comprises one or more sgRNAs targeting exon 11 of cIL1R1. In some embodiments, the CRISPR gene-editing system for the treatment of IDD comprises one or more sgRNAs targeting exon 12 of cIL1R1. In some embodiments, the CRISPR gene-editing system for the treatment of IDD comprises one or more sgRNAs targeting exon 13 of cIL1R1. In some embodiments, the CRISPR gene-editing system for the treatment of IDD comprises one or more sgRNAs targeting exon 14 of cIL1R1. In some embodiments, the CRISPR gene-editing system for the treatment of IDD comprises one or more sgRNAs targeting exon 15 of cIL1R1. In some embodiments, the CRISPR gene-editing system for the treatment of IDD comprises one or more sgRNAs targeting exon 16 of cIL1R1.

[00462] In some embodiments, the CRISPR gene-editing system for the treatment of IDD comprises one or more sgRNAs targeting exon 1 of eIL1R1. In some embodiments, the CRISPR gene-editing system for the treatment of IDD comprises one or more sgRNAs targeting exon 2 of eIL1R1. In some embodiments, the CRISPR gene-editing system for the treatment of IDD comprises one or more sgRNAs targeting exon 3 of eIL1R1. In some embodiments, the CRISPR gene-editing system for the treatment of IDD comprises one or more sgRNAs targeting exon 4 of eIL1R1. In some embodiments, the CRISPR gene-editing system for the treatment of IDD comprises one or more sgRNAs targeting exon 5 of eIL1R1. In some embodiments, the CRISPR gene-editing system for the treatment of IDD comprises one or more sgRNAs targeting exon 6 of eIL1R1. In some embodiments, the CRISPR gene-editing system for the treatment of IDD comprises one or more sgRNAs targeting exon 7 of eIL1R1. In some embodiments, the CRISPR gene-editing system for the treatment of IDD comprises one or more sgRNAs targeting exon 8 of eIL1R1. In some embodiments, the CRISPR gene-editing system for the treatment of IDD comprises one or more sgRNAs targeting exon 9 of eIL1R1. In some embodiments, the CRISPR gene-editing system for the treatment of IDD comprises one or more sgRNAs targeting exon 10 of eIL1R1. In some embodiments, the CRISPR gene-editing system for the treatment of IDD comprises one or more sgRNAs targeting exon 11 of eIL1R1. In some embodiments, the CRISPR gene-editing

system for the treatment of IDD comprises one or more sgRNAs targeting exon 12 of eIL1R1. In some embodiments, the CRISPR gene-editing system for the treatment of IDD comprises one or more sgRNAs targeting exon 13 of eIL1R1. In some embodiments, the CRISPR gene-editing system for the treatment of IDD comprises one or more sgRNAs targeting exon 14 of eIL1R1. In some embodiments, the CRISPR gene-editing system for the treatment of IDD comprises one or more sgRNAs targeting exon 15 of eIL1R1.

[00463] In some embodiments, the CRISPR gene-editing system for the treatment of IDD comprises one or more sgRNAs targeting exon 1 of fIL1R1. In some embodiments, the CRISPR gene-editing system for the treatment of IDD comprises one or more sgRNAs targeting exon 2 of fIL1R1. In some embodiments, the CRISPR gene-editing system for the treatment of IDD comprises one or more sgRNAs targeting exon 3 of fIL1R1. In some embodiments, the CRISPR gene-editing system for the treatment of IDD comprises one or more sgRNAs targeting exon 4 of fIL1R1. In some embodiments, the CRISPR gene-editing system for the treatment of IDD comprises one or more sgRNAs targeting exon 5 of fIL1R1. In some embodiments, the CRISPR gene-editing system for the treatment of IDD comprises one or more sgRNAs targeting exon 6 of fIL1R1. In some embodiments, the CRISPR gene-editing system for the treatment of IDD comprises one or more sgRNAs targeting exon 7 of fIL1R1. In some embodiments, the CRISPR gene-editing system for the treatment of IDD comprises one or more sgRNAs targeting exon 8 of fIL1R1. In some embodiments, the CRISPR gene-editing system for the treatment of IDD comprises one or more sgRNAs targeting exon 9 of fIL1R1. In some embodiments, the CRISPR gene-editing system for the treatment of IDD comprises one or more sgRNAs targeting exon 10 of fIL1R1. In some embodiments, the CRISPR gene-editing system for the treatment of IDD comprises one or more sgRNAs targeting exon 11 of fIL1R1. In some embodiments, the CRISPR gene-editing system for the treatment of IDD comprises one or more sgRNAs targeting exon 12 of fIL1R1. In some embodiments, the CRISPR gene-editing system for the treatment of IDD comprises one or more sgRNAs targeting exon 13 of fIL1R1. In some embodiments, the CRISPR gene-editing system for the treatment of IDD comprises one or more sgRNAs targeting exon 14 of fIL1R1. In some embodiments, the CRISPR gene-editing system for the treatment of IDD comprises one or more sgRNAs targeting exon 15 of fIL1R1. In some embodiments, the CRISPR gene-editing system for the treatment of IDD comprises one or more sgRNAs targeting exon 16 of fIL1R1. In some embodiments, the CRISPR gene-editing system for the treatment of IDD comprises one or more sgRNAs targeting exon 17 of fIL1R1. In some

embodiments, the CRISPR gene-editing system for the treatment of IDD comprises one or more sgRNAs targeting exon 18 of fIL1R1.

[00464] In some embodiments, the CRISPR gene-editing system for the treatment of IDD comprises one or more sgRNAs targeting IL1RAP. In some embodiments, the CRISPR gene-editing system for the treatment of IDD comprises one or more sgRNAs targeting hIL1RAP. In some embodiments, the CRISPR gene-editing system for the treatment of IDD comprises one or more sgRNAs targeting cIL1RAP. In some embodiments, the CRISPR gene-editing system for the treatment of IDD comprises one or more sgRNAs targeting eIL1RAP. In some embodiments, the CRISPR gene-editing system for the treatment of IDD comprises one or more sgRNAs targeting fIL1RAP.

[00465] In some embodiments, the CRISPR gene-editing system for the treatment of IDD comprises one or more sgRNAs targeting exon 1 of hIL1RAP. In some embodiments, the CRISPR gene-editing system for the treatment of IDD comprises one or more sgRNAs targeting exon 2 of hIL1RAP. In some embodiments, the CRISPR gene-editing system for the treatment of IDD comprises one or more sgRNAs targeting exon 3 of hIL1RAP. In some embodiments, the CRISPR gene-editing system for the treatment of IDD comprises one or more sgRNAs targeting exon 4 of hIL1RAP. In some embodiments, the CRISPR gene-editing system for the treatment of IDD comprises one or more sgRNAs targeting exon 5 of hIL1RAP. In some embodiments, the CRISPR gene-editing system for the treatment of IDD comprises one or more sgRNAs targeting exon 6 of hIL1RAP. In some embodiments, the CRISPR gene-editing system for the treatment of IDD comprises one or more sgRNAs targeting exon 7 of hIL1RAP. In some embodiments, the CRISPR gene-editing system for the treatment of IDD comprises one or more sgRNAs targeting exon 8 of hIL1RAP. In some embodiments, the CRISPR gene-editing system for the treatment of IDD comprises one or more sgRNAs targeting exon 9 of hIL1RAP. In some embodiments, the CRISPR gene-editing system for the treatment of IDD comprises one or more sgRNAs targeting exon 10 of hIL1RAP. In some embodiments, the CRISPR gene-editing system for the treatment of IDD comprises one or more sgRNAs targeting exon 11 of hIL1RAP. In some embodiments, the CRISPR gene-editing system for the treatment of IDD comprises one or more sgRNAs targeting exon 12 of hIL1RAP. In some embodiments, the CRISPR gene-editing system for the treatment of IDD comprises one or more sgRNAs targeting exon 13 of hIL1RAP. In some embodiments, the CRISPR gene-editing system for the treatment of IDD comprises one or more sgRNAs targeting exon 14 of hIL1RAP. In some embodiments, the CRISPR gene-

editing system for the treatment of IDD comprises one or more sgRNAs targeting exon 15 of hIL1RAP. In some embodiments, the CRISPR gene-editing system for the treatment of IDD comprises one or more sgRNAs targeting exon 16 of hIL1RAP. In some embodiments, the CRISPR gene-editing system for the treatment of IDD comprises one or more sgRNAs targeting exon 17 of hIL1RAP.

[00466] In some embodiments, the CRISPR gene-editing system for the treatment of IDD comprises one or more sgRNAs targeting exon 1 of cIL1RAP. In some embodiments, the CRISPR gene-editing system for the treatment of IDD comprises one or more sgRNAs targeting exon 2 of cIL1RAP. In some embodiments, the CRISPR gene-editing system for the treatment of IDD comprises one or more sgRNAs targeting exon 3 of cIL1RAP. In some embodiments, the CRISPR gene-editing system for the treatment of IDD comprises one or more sgRNAs targeting exon 4 of cIL1RAP. In some embodiments, the CRISPR gene-editing system for the treatment of IDD comprises one or more sgRNAs targeting exon 5 of cIL1RAP. In some embodiments, the CRISPR gene-editing system for the treatment of IDD comprises one or more sgRNAs targeting exon 6 of cIL1RAP. In some embodiments, the CRISPR gene-editing system for the treatment of IDD comprises one or more sgRNAs targeting exon 7 of cIL1RAP. In some embodiments, the CRISPR gene-editing system for the treatment of IDD comprises one or more sgRNAs targeting exon 8 of cIL1RAP. In some embodiments, the CRISPR gene-editing system for the treatment of IDD comprises one or more sgRNAs targeting exon 9 of cIL1RAP. In some embodiments, the CRISPR gene-editing system for the treatment of IDD comprises one or more sgRNAs targeting exon 10 of cIL1RAP. In some embodiments, the CRISPR gene-editing system for the treatment of IDD comprises one or more sgRNAs targeting exon 11 of cIL1RAP. In some embodiments, the CRISPR gene-editing system for the treatment of IDD comprises one or more sgRNAs targeting exon 12 of cIL1RAP. In some embodiments, the CRISPR gene-editing system for the treatment of IDD comprises one or more sgRNAs targeting exon 13 of cIL1RAP. In some embodiments, the CRISPR gene-editing system for the treatment of IDD comprises one or more sgRNAs targeting exon 14 of cIL1RAP. In some embodiments, the CRISPR gene-editing system for the treatment of IDD comprises one or more sgRNAs targeting exon 15 of cIL1RAP. In some embodiments, the CRISPR gene-editing system for the treatment of IDD comprises one or more sgRNAs targeting exon 16 of cIL1RAP.

[00467] In some embodiments, the CRISPR gene-editing system for the treatment of IDD comprises one or more sgRNAs targeting exon 1 of eIL1RAP. In some embodiments, the

CRISPR gene-editing system for the treatment of IDD comprises one or more sgRNAs targeting exon 2 of eIL1RAP. In some embodiments, the CRISPR gene-editing system for the treatment of IDD comprises one or more sgRNAs targeting exon 3 of eIL1RAP. In some embodiments, the CRISPR gene-editing system for the treatment of IDD comprises one or more sgRNAs targeting exon 4 of eIL1RAP. In some embodiments, the CRISPR gene-editing system for the treatment of IDD comprises one or more sgRNAs targeting exon 5 of eIL1RAP. In some embodiments, the CRISPR gene-editing system for the treatment of IDD comprises one or more sgRNAs targeting exon 6 of eIL1RAP. In some embodiments, the CRISPR gene-editing system for the treatment of IDD comprises one or more sgRNAs targeting exon 7 of eIL1RAP. In some embodiments, the CRISPR gene-editing system for the treatment of IDD comprises one or more sgRNAs targeting exon 8 of eIL1RAP. In some embodiments, the CRISPR gene-editing system for the treatment of IDD comprises one or more sgRNAs targeting exon 9 of eIL1RAP. In some embodiments, the CRISPR gene-editing system for the treatment of IDD comprises one or more sgRNAs targeting exon 10 of eIL1RAP. In some embodiments, the CRISPR gene-editing system for the treatment of IDD comprises one or more sgRNAs targeting exon 11 of eIL1RAP. In some embodiments, the CRISPR gene-editing system for the treatment of IDD comprises one or more sgRNAs targeting exon 12 of eIL1RAP. In some embodiments, the CRISPR gene-editing system for the treatment of IDD comprises one or more sgRNAs targeting exon 13 of eIL1RAP.

[00468] In some embodiments, the CRISPR gene-editing system for the treatment of IDD comprises one or more sgRNAs targeting exon 1 of fIL1RAP. In some embodiments, the CRISPR gene-editing system for the treatment of IDD comprises one or more sgRNAs targeting exon 2 of fIL1RAP. In some embodiments, the CRISPR gene-editing system for the treatment of IDD comprises one or more sgRNAs targeting exon 3 of fIL1RAP. In some embodiments, the CRISPR gene-editing system for the treatment of IDD comprises one or more sgRNAs targeting exon 4 of fIL1RAP. In some embodiments, the CRISPR gene-editing system for the treatment of IDD comprises one or more sgRNAs targeting exon 5 of fIL1RAP. In some embodiments, the CRISPR gene-editing system for the treatment of IDD comprises one or more sgRNAs targeting exon 6 of fIL1RAP. In some embodiments, the CRISPR gene-editing system for the treatment of IDD comprises one or more sgRNAs targeting exon 7 of fIL1RAP. In some embodiments, the CRISPR gene-editing system for the treatment of IDD comprises one or more sgRNAs targeting exon 8 of fIL1RAP. In some embodiments, the CRISPR gene-editing system for the treatment of IDD comprises one or

more sgRNAs targeting exon 9 of flL1RAP. In some embodiments, the CRISPR gene-editing system for the treatment of IDD comprises one or more sgRNAs targeting exon 10 of flL1RAP. In some embodiments, the CRISPR gene-editing system for the treatment of IDD comprises one or more sgRNAs targeting exon 11 of flL1RAP. In some embodiments, the CRISPR gene-editing system for the treatment of IDD comprises one or more sgRNAs targeting exon 12 of flL1RAP. In some embodiments, the CRISPR gene-editing system for the treatment of IDD comprises one or more sgRNAs targeting exon 13 of flL1RAP. In some embodiments, the CRISPR gene-editing system for the treatment of IDD comprises one or more sgRNAs targeting exon 14 of flL1RAP.

[00469] In some embodiments, the CRISPR gene-editing system for the treatment of IDD comprises one or more sgRNAs targeting TGFBR1. In some embodiments, the CRISPR gene-editing system for the treatment of IDD comprises one or more sgRNAs targeting hTGFBR1. In some embodiments, the CRISPR gene-editing system for the treatment of IDD comprises one or more sgRNAs targeting cTGFBR1. In some embodiments, the CRISPR gene-editing system for the treatment of IDD comprises one or more sgRNAs targeting e TGFBR1. In some embodiments, the CRISPR gene-editing system for the treatment of IDD comprises one or more sgRNAs targeting fTGFBR1.

[00470] In some embodiments, the CRISPR gene-editing system for the treatment of IDD comprises one or more sgRNAs targeting exon 1 of hTGFBR1. In some embodiments, the CRISPR gene-editing system for the treatment of IDD comprises one or more sgRNAs targeting exon 2 of hTGFBR1. In some embodiments, the CRISPR gene-editing system for the treatment of IDD comprises one or more sgRNAs targeting exon 3 of hTGFBR1. In some embodiments, the CRISPR gene-editing system for the treatment of IDD comprises one or more sgRNAs targeting exon 4 of hTGFBR1. In some embodiments, the CRISPR gene-editing system for the treatment of IDD comprises one or more sgRNAs targeting exon 5 of hTGFBR1. In some embodiments, the CRISPR gene-editing system for the treatment of IDD comprises one or more sgRNAs targeting exon 6 of hTGFBR1. In some embodiments, the CRISPR gene-editing system for the treatment of IDD comprises one or more sgRNAs targeting exon 7 of hTGFBR1. In some embodiments, the CRISPR gene-editing system for the treatment of IDD comprises one or more sgRNAs targeting exon 8 of hTGFBR1. In some embodiments, the CRISPR gene-editing system for the treatment of IDD comprises one or more sgRNAs targeting exon 9 of hTGFBR1. In some embodiments, the CRISPR gene-editing system for the treatment of IDD comprises one or more sgRNAs targeting exon 10 of

hTGFBR1. In some embodiments, the CRISPR gene-editing system for the treatment of IDD comprises one or more sgRNAs targeting exon 11 of hTGFBR1.

[00471] In some embodiments, the CRISPR gene-editing system for the treatment of IDD comprises one or more sgRNAs targeting exon 1 of cTGFBR1. In some embodiments, the CRISPR gene-editing system for the treatment of IDD comprises one or more sgRNAs targeting exon 2 of cTGFBR1. In some embodiments, the CRISPR gene-editing system for the treatment of IDD comprises one or more sgRNAs targeting exon 3 of cTGFBR1. In some embodiments, the CRISPR gene-editing system for the treatment of IDD comprises one or more sgRNAs targeting exon 4 of cTGFBR1. In some embodiments, the CRISPR gene-editing system for the treatment of IDD comprises one or more sgRNAs targeting exon 5 of cTGFBR1. In some embodiments, the CRISPR gene-editing system for the treatment of IDD comprises one or more sgRNAs targeting exon 6 of cTGFBR1. In some embodiments, the CRISPR gene-editing system for the treatment of IDD comprises one or more sgRNAs targeting exon 7 of cTGFBR1. In some embodiments, the CRISPR gene-editing system for the treatment of IDD comprises one or more sgRNAs targeting exon 8 of cTGFBR1. In some embodiments, the CRISPR gene-editing system for the treatment of IDD comprises one or more sgRNAs targeting exon 9 of cTGFBR1.

[00472] In some embodiments, the CRISPR gene-editing system for the treatment of IDD comprises one or more sgRNAs targeting exon 1 of eTGFBR1. In some embodiments, the CRISPR gene-editing system for the treatment of IDD comprises one or more sgRNAs targeting exon 2 of eTGFBR1. In some embodiments, the CRISPR gene-editing system for the treatment of IDD comprises one or more sgRNAs targeting exon 3 of eTGFBR1. In some embodiments, the CRISPR gene-editing system for the treatment of IDD comprises one or more sgRNAs targeting exon 4 of eTGFBR1. In some embodiments, the CRISPR gene-editing system for the treatment of IDD comprises one or more sgRNAs targeting exon 5 of eTGFBR1. In some embodiments, the CRISPR gene-editing system for the treatment of IDD comprises one or more sgRNAs targeting exon 6 of eTGFBR1. In some embodiments, the CRISPR gene-editing system for the treatment of IDD comprises one or more sgRNAs targeting exon 7 of eTGFBR1. In some embodiments, the CRISPR gene-editing system for the treatment of IDD comprises one or more sgRNAs targeting exon 8 of eTGFBR1. In some embodiments, the CRISPR gene-editing system for the treatment of IDD comprises one or more sgRNAs targeting exon 9 of eTGFBR1. In some embodiments, the CRISPR gene-editing system for the treatment of IDD comprises one or more sgRNAs targeting exon 10 of

eTGFBR1. In some embodiments, the CRISPR gene-editing system for the treatment of IDD comprises one or more sgRNAs targeting exon 11 of eTGFBR1. In some embodiments, the CRISPR gene-editing system for the treatment of IDD comprises one or more sgRNAs targeting exon 12 of eTGFBR1.

[00473] In some embodiments, the CRISPR gene-editing system for the treatment of IDD comprises one or more sgRNAs targeting exon 1 of fTGFBR1. In some embodiments, the CRISPR gene-editing system for the treatment of IDD comprises one or more sgRNAs targeting exon 2 of fTGFBR1. In some embodiments, the CRISPR gene-editing system for the treatment of IDD comprises one or more sgRNAs targeting exon 3 of fTGFBR1. In some embodiments, the CRISPR gene-editing system for the treatment of IDD comprises one or more sgRNAs targeting exon 4 of fTGFBR1. In some embodiments, the CRISPR gene-editing system for the treatment of IDD comprises one or more sgRNAs targeting exon 5 of fTGFBR1. In some embodiments, the CRISPR gene-editing system for the treatment of IDD comprises one or more sgRNAs targeting exon 6 of fTGFBR1. In some embodiments, the CRISPR gene-editing system for the treatment of IDD comprises one or more sgRNAs targeting exon 7 of fTGFBR1. In some embodiments, the CRISPR gene-editing system for the treatment of IDD comprises one or more sgRNAs targeting exon 8 of fTGFBR1. In some embodiments, the CRISPR gene-editing system for the treatment of IDD comprises one or more sgRNAs targeting exon 9 of fTGFBR1. In some embodiments, the CRISPR gene-editing system for the treatment of IDD comprises one or more sgRNAs targeting exon 10 of fTGFBR1. In some embodiments, the CRISPR gene-editing system for the treatment of IDD comprises one or more sgRNAs targeting exon 11 of fTGFBR1.

[00474] In some embodiments, the CRISPR gene-editing system for the treatment of IDD comprises one or more sgRNAs targeting TGFBR2. In some embodiments, the CRISPR gene-editing system for the treatment of IDD comprises one or more sgRNAs targeting hTGFBR2. In some embodiments, the CRISPR gene-editing system for the treatment of IDD comprises one or more sgRNAs targeting cTGFBR2. In some embodiments, the CRISPR gene-editing system for the treatment of IDD comprises one or more sgRNAs targeting eTGFBR2. In some embodiments, the CRISPR gene-editing system for the treatment of IDD comprises one or more sgRNAs targeting fTGFBR2.

[00475] In some embodiments, the CRISPR gene-editing system for the treatment of IDD comprises one or more sgRNAs targeting exon 1 of hTGFBR2. In some embodiments, the CRISPR gene-editing system for the treatment of IDD comprises one or more sgRNAs

targeting exon 2 of hTGFBR2. In some embodiments, the CRISPR gene-editing system for the treatment of IDD comprises one or more sgRNAs targeting exon 3 of hTGFBR2. In some embodiments, the CRISPR gene-editing system for the treatment of IDD comprises one or more sgRNAs targeting exon 4 of hTGFBR2. In some embodiments, the CRISPR gene-editing system for the treatment of IDD comprises one or more sgRNAs targeting exon 5 of hTGFBR2. In some embodiments, the CRISPR gene-editing system for the treatment of IDD comprises one or more sgRNAs targeting exon 6 of hTGFBR2. In some embodiments, the CRISPR gene-editing system for the treatment of IDD comprises one or more sgRNAs targeting exon 7 of hTGFBR2. In some embodiments, the CRISPR gene-editing system for the treatment of IDD comprises one or more sgRNAs targeting exon 8 of hTGFBR2. In some embodiments, the CRISPR gene-editing system for the treatment of IDD comprises one or more sgRNAs targeting exon 9 of hTGFBR2.

[00476] In some embodiments, the CRISPR gene-editing system for the treatment of IDD comprises one or more sgRNAs targeting exon 1 of cTGFBR2. In some embodiments, the CRISPR gene-editing system for the treatment of IDD comprises one or more sgRNAs targeting exon 2 of cTGFBR2. In some embodiments, the CRISPR gene-editing system for the treatment of IDD comprises one or more sgRNAs targeting exon 3 of cTGFBR2. In some embodiments, the CRISPR gene-editing system for the treatment of IDD comprises one or more sgRNAs targeting exon 4 of cTGFBR2. In some embodiments, the CRISPR gene-editing system for the treatment of IDD comprises one or more sgRNAs targeting exon 5 of cTGFBR2. In some embodiments, the CRISPR gene-editing system for the treatment of IDD comprises one or more sgRNAs targeting exon 6 of cTGFBR2. In some embodiments, the CRISPR gene-editing system for the treatment of IDD comprises one or more sgRNAs targeting exon 7 of cTGFBR2. In some embodiments, the CRISPR gene-editing system for the treatment of IDD comprises one or more sgRNAs targeting exon 8 of cTGFBR2.

[00477] In some embodiments, the CRISPR gene-editing system for the treatment of IDD comprises one or more sgRNAs targeting exon 1 of eTGFBR2. In some embodiments, the CRISPR gene-editing system for the treatment of IDD comprises one or more sgRNAs targeting exon 2 of eTGFBR2. In some embodiments, the CRISPR gene-editing system for the treatment of IDD comprises one or more sgRNAs targeting exon 3 of eTGFBR2. In some embodiments, the CRISPR gene-editing system for the treatment of IDD comprises one or more sgRNAs targeting exon 4 of eTGFBR2. In some embodiments, the CRISPR gene-editing system for the treatment of IDD comprises one or more sgRNAs targeting exon 5 of

eTGFBR2. In some embodiments, the CRISPR gene-editing system for the treatment of IDD comprises one or more sgRNAs targeting exon 6 of eTGFBR2. In some embodiments, the CRISPR gene-editing system for the treatment of IDD comprises one or more sgRNAs targeting exon 7 of eTGFBR2. In some embodiments, the CRISPR gene-editing system for the treatment of IDD comprises one or more sgRNAs targeting exon 8 of eTGFBR2. In some embodiments, the CRISPR gene-editing system for the treatment of IDD comprises one or more sgRNAs targeting exon 9 of eTGFBR2. In some embodiments, the CRISPR gene-editing system for the treatment of IDD comprises one or more sgRNAs targeting exon 10 of eTGFBR2.

[00478] In some embodiments, the CRISPR gene-editing system for the treatment of IDD comprises one or more sgRNAs targeting exon 1 of fTGFBR2. In some embodiments, the CRISPR gene-editing system for the treatment of IDD comprises one or more sgRNAs targeting exon 2 of fTGFBR2. In some embodiments, the CRISPR gene-editing system for the treatment of IDD comprises one or more sgRNAs targeting exon 3 of fTGFBR2. In some embodiments, the CRISPR gene-editing system for the treatment of IDD comprises one or more sgRNAs targeting exon 4 of fTGFBR2. In some embodiments, the CRISPR gene-editing system for the treatment of IDD comprises one or more sgRNAs targeting exon 5 of fTGFBR2. In some embodiments, the CRISPR gene-editing system for the treatment of IDD comprises one or more sgRNAs targeting exon 6 of fTGFBR2. In some embodiments, the CRISPR gene-editing system for the treatment of IDD comprises one or more sgRNAs targeting exon 7 of fTGFBR2. In some embodiments, the CRISPR gene-editing system for the treatment of IDD comprises one or more sgRNAs targeting exon 8 of fTGFBR2.

[00479] In some embodiments, the CRISPR gene-editing system for the treatment of IDD comprises one or more sgRNAs targeting IL6R. In some embodiments, the CRISPR gene-editing system for the treatment of IDD comprises one or more sgRNAs targeting hIL6R. In some embodiments, the CRISPR gene-editing system for the treatment of IDD comprises one or more sgRNAs targeting cIL6R. In some embodiments, the CRISPR gene-editing system for the treatment of IDD comprises one or more sgRNAs targeting eIL6R. In some embodiments, the CRISPR gene-editing system for the treatment of IDD comprises one or more sgRNAs targeting fIL6R.

[00480] In some embodiments, the CRISPR gene-editing system for the treatment of IDD comprises one or more sgRNAs targeting exon 1 of hIL6R. In some embodiments, the CRISPR gene-editing system for the treatment of IDD comprises one or more sgRNAs

targeting exon 2 of hIL6R. In some embodiments, the CRISPR gene-editing system for the treatment of IDD comprises one or more sgRNAs targeting exon 3 of hIL6R. In some embodiments, the CRISPR gene-editing system for the treatment of IDD comprises one or more sgRNAs targeting exon 4 of hIL6R. In some embodiments, the CRISPR gene-editing system for the treatment of IDD comprises one or more sgRNAs targeting exon 5 of hIL6R. In some embodiments, the CRISPR gene-editing system for the treatment of IDD comprises one or more sgRNAs targeting exon 6 of hIL6R. In some embodiments, the CRISPR gene-editing system for the treatment of IDD comprises one or more sgRNAs targeting exon 7 of hIL6R. In some embodiments, the CRISPR gene-editing system for the treatment of IDD comprises one or more sgRNAs targeting exon 8 of hIL6R. In some embodiments, the CRISPR gene-editing system for the treatment of IDD comprises one or more sgRNAs targeting exon 9 of hIL6R. In some embodiments, the CRISPR gene-editing system for the treatment of IDD comprises one or more sgRNAs targeting exon 10 of hIL6R. In some embodiments, the CRISPR gene-editing system for the treatment of IDD comprises one or more sgRNAs targeting exon 11 of hIL6R In some embodiments, the CRISPR gene-editing system for the treatment of IDD comprises one or more sgRNAs targeting exon 12 of hIL6R. In some embodiments, the CRISPR gene-editing system for the treatment of IDD comprises one or more sgRNAs targeting exon 13 of hIL6R. In some embodiments, the CRISPR gene-editing system for the treatment of IDD comprises one or more sgRNAs targeting exon 14 of hIL6R. In some embodiments, the CRISPR gene-editing system for the treatment of IDD comprises one or more sgRNAs targeting exon 15 of hIL6R.

[00481] In some embodiments, the CRISPR gene-editing system for the treatment of IDD comprises one or more sgRNAs targeting exon 1 of cIL6R. In some embodiments, the CRISPR gene-editing system for the treatment of IDD comprises one or more sgRNAs targeting exon 2 of cIL6R. In some embodiments, the CRISPR gene-editing system for the treatment of IDD comprises one or more sgRNAs targeting exon 3 of cIL6R. In some embodiments, the CRISPR gene-editing system for the treatment of IDD comprises one or more sgRNAs targeting exon 4 of cIL6R. In some embodiments, the CRISPR gene-editing system for the treatment of IDD comprises one or more sgRNAs targeting exon 5 of cIL6R. In some embodiments, the CRISPR gene-editing system for the treatment of IDD comprises one or more sgRNAs targeting exon 6 of cIL6R. In some embodiments, the CRISPR gene-editing system for the treatment of IDD comprises one or more sgRNAs targeting exon 7 of cIL6R. In some embodiments, the CRISPR gene-editing system for the treatment of IDD

comprises one or more sgRNAs targeting exon 8 of cIL6R. In some embodiments, the CRISPR gene-editing system for the treatment of IDD comprises one or more sgRNAs targeting exon 9 of cIL6R. In some embodiments, the CRISPR gene-editing system for the treatment of IDD comprises one or more sgRNAs targeting exon 10 of cIL6R. In some embodiments, the CRISPR gene-editing system for the treatment of IDD comprises one or more sgRNAs targeting exon 11 of cIL6R. In some embodiments, the CRISPR gene-editing system for the treatment of IDD comprises one or more sgRNAs targeting exon 12 of cIL6R. In some embodiments, the CRISPR gene-editing system for the treatment of IDD comprises one or more sgRNAs targeting exon 13 of cIL6R.

[00482] In some embodiments, the CRISPR gene-editing system for the treatment of IDD comprises one or more sgRNAs targeting exon 1 of eIL6R. In some embodiments, the CRISPR gene-editing system for the treatment of IDD comprises one or more sgRNAs targeting exon 2 of eIL6R. In some embodiments, the CRISPR gene-editing system for the treatment of IDD comprises one or more sgRNAs targeting exon 3 of eIL6R. In some embodiments, the CRISPR gene-editing system for the treatment of IDD comprises one or more sgRNAs targeting exon 4 of eIL6R. In some embodiments, the CRISPR gene-editing system for the treatment of IDD comprises one or more sgRNAs targeting exon 5 of eIL6R. In some embodiments, the CRISPR gene-editing system for the treatment of IDD comprises one or more sgRNAs targeting exon 6 of eIL6R. In some embodiments, the CRISPR gene-editing system for the treatment of IDD comprises one or more sgRNAs targeting exon 7 of eIL6R. In some embodiments, the CRISPR gene-editing system for the treatment of IDD comprises one or more sgRNAs targeting exon 8 of eIL6R. In some embodiments, the CRISPR gene-editing system for the treatment of IDD comprises one or more sgRNAs targeting exon 9 of eIL6R. In some embodiments, the CRISPR gene-editing system for the treatment of IDD comprises one or more sgRNAs targeting exon 10 of eIL6R. In some embodiments, the CRISPR gene-editing system for the treatment of IDD comprises one or more sgRNAs targeting exon 11 of eIL6R.

[00483] In some embodiments, the CRISPR gene-editing system for the treatment of IDD comprises one or more sgRNAs targeting exon 1 of fIL6R. In some embodiments, the CRISPR gene-editing system for the treatment of IDD comprises one or more sgRNAs targeting exon 2 of fIL6R. In some embodiments, the CRISPR gene-editing system for the treatment of IDD comprises one or more sgRNAs targeting exon 3 of fIL6R. In some embodiments, the CRISPR gene-editing system for the treatment of IDD comprises one or

more sgRNAs targeting exon 4 of fIL6R. In some embodiments, the CRISPR gene-editing system for the treatment of IDD comprises one or more sgRNAs targeting exon 5 of fIL6R. In some embodiments, the CRISPR gene-editing system for the treatment of IDD comprises one or more sgRNAs targeting exon 6 of fIL6R. In some embodiments, the CRISPR gene-editing system for the treatment of IDD comprises one or more sgRNAs targeting exon 7 of fIL6R. In some embodiments, the CRISPR gene-editing system for the treatment of IDD comprises one or more sgRNAs targeting exon 8 of fIL6R. In some embodiments, the CRISPR gene-editing system for the treatment of IDD comprises one or more sgRNAs targeting exon 9 of fIL6R. In some embodiments, the CRISPR gene-editing system for the treatment of IDD comprises one or more sgRNAs targeting exon 10 of fIL6R.

[00484] In some embodiments, the CRISPR gene-editing system for the treatment of IDD comprises one or more sgRNAs targeting IL6ST. In some embodiments, the CRISPR gene-editing system for the treatment of IDD comprises one or more sgRNAs targeting hIL6ST. In some embodiments, the CRISPR gene-editing system for the treatment of IDD comprises one or more sgRNAs targeting cIL6ST. In some embodiments, the CRISPR gene-editing system for the treatment of IDD comprises one or more sgRNAs targeting eIL6ST. In some embodiments, the CRISPR gene-editing system for the treatment of IDD comprises one or more sgRNAs targeting fIL6ST.

[00485] In some embodiments, the CRISPR gene-editing system for the treatment of IDD comprises one or more sgRNAs targeting exon 1 of hIL6ST. In some embodiments, the CRISPR gene-editing system for the treatment of IDD comprises one or more sgRNAs targeting exon 2 of hIL6ST. In some embodiments, the CRISPR gene-editing system for the treatment of IDD comprises one or more sgRNAs targeting exon 3 of hIL6ST. In some embodiments, the CRISPR gene-editing system for the treatment of IDD comprises one or more sgRNAs targeting exon 4 of hIL6ST. In some embodiments, the CRISPR gene-editing system for the treatment of IDD comprises one or more sgRNAs targeting exon 5 of hIL6ST. In some embodiments, the CRISPR gene-editing system for the treatment of IDD comprises one or more sgRNAs targeting exon 6 of hIL6ST. In some embodiments, the CRISPR gene-editing system for the treatment of IDD comprises one or more sgRNAs targeting exon 7 of hIL6ST. In some embodiments, the CRISPR gene-editing system for the treatment of IDD comprises one or more sgRNAs targeting exon 8 of hIL6ST. In some embodiments, the CRISPR gene-editing system for the treatment of IDD comprises one or more sgRNAs targeting exon 9 of hIL6ST. In some embodiments, the CRISPR gene-editing system for the

treatment of IDD comprises one or more sgRNAs targeting exon 10 of hIL6ST. In some embodiments, the CRISPR gene-editing system for the treatment of IDD comprises one or more sgRNAs targeting exon 11 of hIL6ST. In some embodiments, the CRISPR gene-editing system for the treatment of IDD comprises one or more sgRNAs targeting exon 12 of hIL6ST. In some embodiments, the CRISPR gene-editing system for the treatment of IDD comprises one or more sgRNAs targeting exon 13 of hIL6ST. In some embodiments, the CRISPR gene-editing system for the treatment of IDD comprises one or more sgRNAs targeting exon 14 of hIL6ST. In some embodiments, the CRISPR gene-editing system for the treatment of IDD comprises one or more sgRNAs targeting exon 15 of hIL6ST. In some embodiments, the CRISPR gene-editing system for the treatment of IDD comprises one or more sgRNAs targeting exon 16 of hIL6ST. In some embodiments, the CRISPR gene-editing system for the treatment of IDD comprises one or more sgRNAs targeting exon 17 of hIL6ST. In some embodiments, the CRISPR gene-editing system for the treatment of IDD comprises one or more sgRNAs targeting exon 18 of hIL6ST. In some embodiments, the CRISPR gene-editing system for the treatment of IDD comprises one or more sgRNAs targeting exon 19 of hIL6ST.

[00486] In some embodiments, the CRISPR gene-editing system for the treatment of IDD comprises one or more sgRNAs targeting exon 1 of cIL6ST. In some embodiments, the CRISPR gene-editing system for the treatment of IDD comprises one or more sgRNAs targeting exon 2 of cIL6ST. In some embodiments, the CRISPR gene-editing system for the treatment of IDD comprises one or more sgRNAs targeting exon 3 of cIL6ST. In some embodiments, the CRISPR gene-editing system for the treatment of IDD comprises one or more sgRNAs targeting exon 4 of cIL6ST. In some embodiments, the CRISPR gene-editing system for the treatment of IDD comprises one or more sgRNAs targeting exon 5 of cIL6ST. In some embodiments, the CRISPR gene-editing system for the treatment of IDD comprises one or more sgRNAs targeting exon 6 of cIL6ST. In some embodiments, the CRISPR gene-editing system for the treatment of IDD comprises one or more sgRNAs targeting exon 7 of cIL6ST. In some embodiments, the CRISPR gene-editing system for the treatment of IDD comprises one or more sgRNAs targeting exon 8 of cIL6ST. In some embodiments, the CRISPR gene-editing system for the treatment of IDD comprises one or more sgRNAs targeting exon 9 of cIL6ST. In some embodiments, the CRISPR gene-editing system for the treatment of IDD comprises one or more sgRNAs targeting exon 10 of cIL6ST. In some embodiments, the CRISPR gene-editing system for the treatment of IDD comprises one or

more sgRNAs targeting exon 11 of cIL6ST In some embodiments, the CRISPR gene-editing system for the treatment of IDD comprises one or more sgRNAs targeting exon 12 of cIL6ST. In some embodiments, the CRISPR gene-editing system for the treatment of IDD comprises one or more sgRNAs targeting exon 13 of cIL6ST. In some embodiments, the CRISPR gene-editing system for the treatment of IDD comprises one or more sgRNAs targeting exon 14 of cIL6ST. In some embodiments, the CRISPR gene-editing system for the treatment of IDD comprises one or more sgRNAs targeting exon 15 of cIL6ST. In some embodiments, the CRISPR gene-editing system for the treatment of IDD comprises one or more sgRNAs targeting exon 16 of cIL6ST. In some embodiments, the CRISPR gene-editing system for the treatment of IDD comprises one or more sgRNAs targeting exon 17 of cIL6ST. In some embodiments, the CRISPR gene-editing system for the treatment of IDD comprises one or more sgRNAs targeting exon 18 of cIL6ST.

[00487] In some embodiments, the CRISPR gene-editing system for the treatment of IDD comprises one or more sgRNAs targeting exon 1 of eIL6ST. In some embodiments, the CRISPR gene-editing system for the treatment of IDD comprises one or more sgRNAs targeting exon 2 of eIL6ST. In some embodiments, the CRISPR gene-editing system for the treatment of IDD comprises one or more sgRNAs targeting exon 3 of eIL6ST. In some embodiments, the CRISPR gene-editing system for the treatment of IDD comprises one or more sgRNAs targeting exon 4 of eIL6ST. In some embodiments, the CRISPR gene-editing system for the treatment of IDD comprises one or more sgRNAs targeting exon 5 of eIL6ST. In some embodiments, the CRISPR gene-editing system for the treatment of IDD comprises one or more sgRNAs targeting exon 6 of eIL6ST. In some embodiments, the CRISPR gene-editing system for the treatment of IDD comprises one or more sgRNAs targeting exon 7 of eIL6ST. In some embodiments, the CRISPR gene-editing system for the treatment of IDD comprises one or more sgRNAs targeting exon 8 of eIL6ST. In some embodiments, the CRISPR gene-editing system for the treatment of IDD comprises one or more sgRNAs targeting exon 9 of eIL6ST. In some embodiments, the CRISPR gene-editing system for the treatment of IDD comprises one or more sgRNAs targeting exon 10 of eIL6ST. In some embodiments, the CRISPR gene-editing system for the treatment of IDD comprises one or more sgRNAs targeting exon 11 of eIL6ST In some embodiments, the CRISPR gene-editing system for the treatment of IDD comprises one or more sgRNAs targeting exon 12 of eIL6ST. In some embodiments, the CRISPR gene-editing system for the treatment of IDD comprises one or more sgRNAs targeting exon 13 of eIL6ST. In some embodiments, the

CRISPR gene-editing system for the treatment of IDD comprises one or more sgRNAs targeting exon 14 of eIL6ST. In some embodiments, the CRISPR gene-editing system for the treatment of IDD comprises one or more sgRNAs targeting exon 15 of eIL6ST. In some embodiments, the CRISPR gene-editing system for the treatment of IDD comprises one or more sgRNAs targeting exon 16 of eIL6ST. In some embodiments, the CRISPR gene-editing system for the treatment of IDD comprises one or more sgRNAs targeting exon 17 of eIL6ST. In some embodiments, the CRISPR gene-editing system for the treatment of IDD comprises one or more sgRNAs targeting exon 18 of eIL6ST.

[00488] In some embodiments, the CRISPR gene-editing system for the treatment of IDD comprises one or more sgRNAs targeting exon 1 of fIL6ST. In some embodiments, the CRISPR gene-editing system for the treatment of IDD comprises one or more sgRNAs targeting exon 2 of fIL6ST. In some embodiments, the CRISPR gene-editing system for the treatment of IDD comprises one or more sgRNAs targeting exon 3 of fIL6ST. In some embodiments, the CRISPR gene-editing system for the treatment of IDD comprises one or more sgRNAs targeting exon 4 of fIL6ST. In some embodiments, the CRISPR gene-editing system for the treatment of IDD comprises one or more sgRNAs targeting exon 5 of fIL6ST. In some embodiments, the CRISPR gene-editing system for the treatment of IDD comprises one or more sgRNAs targeting exon 6 of fIL6ST. In some embodiments, the CRISPR gene-editing system for the treatment of IDD comprises one or more sgRNAs targeting exon 7 of fIL6ST. In some embodiments, the CRISPR gene-editing system for the treatment of IDD comprises one or more sgRNAs targeting exon 8 of fIL6ST. In some embodiments, the CRISPR gene-editing system for the treatment of IDD comprises one or more sgRNAs targeting exon 9 of fIL6ST. In some embodiments, the CRISPR gene-editing system for the treatment of IDD comprises one or more sgRNAs targeting exon 10 of fIL6ST. In some embodiments, the CRISPR gene-editing system for the treatment of IDD comprises one or more sgRNAs targeting exon 11 of fIL6ST In some embodiments, the CRISPR gene-editing system for the treatment of IDD comprises one or more sgRNAs targeting exon 12 of fIL6ST. In some embodiments, the CRISPR gene-editing system for the treatment of IDD comprises one or more sgRNAs targeting exon 13 of fIL6ST. In some embodiments, the CRISPR gene-editing system for the treatment of IDD comprises one or more sgRNAs targeting exon 14 of fIL6ST. In some embodiments, the CRISPR gene-editing system for the treatment of IDD comprises one or more sgRNAs targeting exon 15 of fIL6ST. In some embodiments, the CRISPR gene-editing system for the treatment of IDD comprises one or more sgRNAs

targeting exon 16 of flL6ST. In some embodiments, the CRISPR gene-editing system for the treatment of IDD comprises one or more sgRNAs targeting exon 17 of flL6ST. In some embodiments, the CRISPR gene-editing system for the treatment of IDD comprises one or more sgRNAs targeting exon 18 of flL6ST. In some embodiments, the CRISPR gene-editing system for the treatment of IDD comprises one or more sgRNAs targeting exon 19 of flL6ST. In some embodiments, the CRISPR gene-editing system for the treatment of IDD comprises one or more sgRNAs targeting exon 20 of flL6ST.

[00489] In some embodiments, the CRISPR gene-editing system for the treatment of IDD comprises one or more sgRNAs targeting TNFRSF1A. In some embodiments, the CRISPR gene-editing system for the treatment of IDD comprises one or more sgRNAs targeting hTNFRSF1A. In some embodiments, the CRISPR gene-editing system for the treatment of IDD comprises one or more sgRNAs targeting cTNFRSF1A. In some embodiments, the CRISPR gene-editing system for the treatment of IDD comprises one or more sgRNAs targeting eTNFRSF1A. In some embodiments, the CRISPR gene-editing system for the treatment of IDD comprises one or more sgRNAs targeting fTNFRSF1A.

[00490] In some embodiments, the CRISPR gene-editing system for the treatment of IDD comprises one or more sgRNAs targeting exon 1 of hTNFRSF1A. In some embodiments, the CRISPR gene-editing system for the treatment of IDD comprises one or more sgRNAs targeting exon 2 of hTNFRSF1A. In some embodiments, the CRISPR gene-editing system for the treatment of IDD comprises one or more sgRNAs targeting exon 3 of hTNFRSF1A. In some embodiments, the CRISPR gene-editing system for the treatment of IDD comprises one or more sgRNAs targeting exon 4 of hTNFRSF1A. In some embodiments, the CRISPR gene-editing system for the treatment of IDD comprises one or more sgRNAs targeting exon 5 of hTNFRSF1A. In some embodiments, the CRISPR gene-editing system for the treatment of IDD comprises one or more sgRNAs targeting exon 6 of hTNFRSF1A. In some embodiments, the CRISPR gene-editing system for the treatment of IDD comprises one or more sgRNAs targeting exon 7 of hTNFRSF1A. In some embodiments, the CRISPR gene-editing system for the treatment of IDD comprises one or more sgRNAs targeting exon 8 of hTNFRSF1A. In some embodiments, the CRISPR gene-editing system for the treatment of IDD comprises one or more sgRNAs targeting exon 9 of hTNFRSF1A. In some embodiments, the CRISPR gene-editing system for the treatment of IDD comprises one or more sgRNAs targeting exon 10 of hTNFRSF1A. In some embodiments, the CRISPR gene-

editing system for the treatment of IDD comprises one or more sgRNAs targeting exon 11 of hTNFRSF1A.

[00491] In some embodiments, the CRISPR gene-editing system for the treatment of IDD comprises one or more sgRNAs targeting exon 1 of cTNFRSF1A. In some embodiments, the CRISPR gene-editing system for the treatment of IDD comprises one or more sgRNAs targeting exon 2 of cTNFRSF1A. In some embodiments, the CRISPR gene-editing system for the treatment of IDD comprises one or more sgRNAs targeting exon 3 of cTNFRSF1A. In some embodiments, the CRISPR gene-editing system for the treatment of IDD comprises one or more sgRNAs targeting exon 4 of cTNFRSF1A. In some embodiments, the CRISPR gene-editing system for the treatment of IDD comprises one or more sgRNAs targeting exon 5 of cTNFRSF1A. In some embodiments, the CRISPR gene-editing system for the treatment of IDD comprises one or more sgRNAs targeting exon 6 of cTNFRSF1A. In some embodiments, the CRISPR gene-editing system for the treatment of IDD comprises one or more sgRNAs targeting exon 7 of cTNFRSF1A. In some embodiments, the CRISPR gene-editing system for the treatment of IDD comprises one or more sgRNAs targeting exon 8 of cTNFRSF1A. In some embodiments, the CRISPR gene-editing system for the treatment of IDD comprises one or more sgRNAs targeting exon 9 of cTNFRSF1A. In some embodiments, the CRISPR gene-editing system for the treatment of IDD comprises one or more sgRNAs targeting exon 10 of cTNFRSF1A. In some embodiments, the CRISPR gene-editing system for the treatment of IDD comprises one or more sgRNAs targeting exon 11 of cTNFRSF1A.

[00492] In some embodiments, the CRISPR gene-editing system for the treatment of IDD comprises one or more sgRNAs targeting exon 1 of eTNFRSF1A. In some embodiments, the CRISPR gene-editing system for the treatment of IDD comprises one or more sgRNAs targeting exon 2 of eTNFRSF1A. In some embodiments, the CRISPR gene-editing system for the treatment of IDD comprises one or more sgRNAs targeting exon 3 of eTNFRSF1A. In some embodiments, the CRISPR gene-editing system for the treatment of IDD comprises one or more sgRNAs targeting exon 4 of eTNFRSF1A. In some embodiments, the CRISPR gene-editing system for the treatment of IDD comprises one or more sgRNAs targeting exon 5 of eTNFRSF1A. In some embodiments, the CRISPR gene-editing system for the treatment of IDD comprises one or more sgRNAs targeting exon 6 of eTNFRSF1A. In some embodiments, the CRISPR gene-editing system for the treatment of IDD comprises one or more sgRNAs targeting exon 7 of eTNFRSF1A. In some embodiments, the CRISPR gene-

editing system for the treatment of IDD comprises one or more sgRNAs targeting exon 8 of eTNFRSF1A. In some embodiments, the CRISPR gene-editing system for the treatment of IDD comprises one or more sgRNAs targeting exon 9 of eTNFRSF1A. In some embodiments, the CRISPR gene-editing system for the treatment of IDD comprises one or more sgRNAs targeting exon 10 of eTNFRSF1A.

[00493] In some embodiments, the CRISPR gene-editing system for the treatment of IDD comprises one or more sgRNAs targeting exon 1 of fTNFRSF1A. In some embodiments, the CRISPR gene-editing system for the treatment of IDD comprises one or more sgRNAs targeting exon 2 of fTNFRSF1A. In some embodiments, the CRISPR gene-editing system for the treatment of IDD comprises one or more sgRNAs targeting exon 3 of fTNFRSF1A. In some embodiments, the CRISPR gene-editing system for the treatment of IDD comprises one or more sgRNAs targeting exon 4 of fTNFRSF1A. In some embodiments, the CRISPR gene-editing system for the treatment of IDD comprises one or more sgRNAs targeting exon 5 of fTNFRSF1A. In some embodiments, the CRISPR gene-editing system for the treatment of IDD comprises one or more sgRNAs targeting exon 6 of fTNFRSF1A. In some embodiments, the CRISPR gene-editing system for the treatment of IDD comprises one or more sgRNAs targeting exon 7 of fTNFRSF1A. In some embodiments, the CRISPR gene-editing system for the treatment of IDD comprises one or more sgRNAs targeting exon 8 of fTNFRSF1A. In some embodiments, the CRISPR gene-editing system for the treatment of IDD comprises one or more sgRNAs targeting exon 9 of fTNFRSF1A. In some embodiments, the CRISPR gene-editing system for the treatment of IDD comprises one or more sgRNAs targeting exon 10 of fTNFRSF1A.

[00494] In some embodiments, the CRISPR gene-editing system for the treatment of IDD comprises one or more sgRNAs targeting TNFRSF1B. In some embodiments, the CRISPR gene-editing system for the treatment of IDD comprises one or more sgRNAs targeting hTNFRSF1B. In some embodiments, the CRISPR gene-editing system for the treatment of IDD comprises one or more sgRNAs targeting cTNFRSF1B. In some embodiments, the CRISPR gene-editing system for the treatment of IDD comprises one or more sgRNAs targeting eTNFRSF1B. In some embodiments, the CRISPR gene-editing system for the treatment of IDD comprises one or more sgRNAs targeting fTNFRSF1B.

[00495] In some embodiments, the CRISPR gene-editing system for the treatment of IDD comprises one or more sgRNAs targeting exon 1 of hTNFRSF1B. In some embodiments, the CRISPR gene-editing system for the treatment of IDD comprises one or more sgRNAs

targeting exon 2 of hTNFRSF1B. In some embodiments, the CRISPR gene-editing system for the treatment of IDD comprises one or more sgRNAs targeting exon 3 of hTNFRSF1B. In some embodiments, the CRISPR gene-editing system for the treatment of IDD comprises one or more sgRNAs targeting exon 4 of hTNFRSF1B. In some embodiments, the CRISPR gene-editing system for the treatment of IDD comprises one or more sgRNAs targeting exon 5 of hTNFRSF1B. In some embodiments, the CRISPR gene-editing system for the treatment of IDD comprises one or more sgRNAs targeting exon 6 of hTNFRSF1B. In some embodiments, the CRISPR gene-editing system for the treatment of IDD comprises one or more sgRNAs targeting exon 7 of hTNFRSF1B. In some embodiments, the CRISPR gene-editing system for the treatment of IDD comprises one or more sgRNAs targeting exon 8 of hTNFRSF1B. In some embodiments, the CRISPR gene-editing system for the treatment of IDD comprises one or more sgRNAs targeting exon 9 of hTNFRSF1B. In some embodiments, the CRISPR gene-editing system for the treatment of IDD comprises one or more sgRNAs targeting exon 10 of hTNFRSF1B. In some embodiments, the CRISPR gene-editing system for the treatment of IDD comprises one or more sgRNAs targeting exon 11 of hTNFRSF1B In some embodiments, the CRISPR gene-editing system for the treatment of IDD comprises one or more sgRNAs targeting exon 12 of hTNFRSF1B. In some embodiments, the CRISPR gene-editing system for the treatment of IDD comprises one or more sgRNAs targeting exon 13 of hTNFRSF1B.

[00496] In some embodiments, the CRISPR gene-editing system for the treatment of IDD comprises one or more sgRNAs targeting exon 1 of cTNFRSF1B. In some embodiments, the CRISPR gene-editing system for the treatment of IDD comprises one or more sgRNAs targeting exon 2 of cTNFRSF1B. In some embodiments, the CRISPR gene-editing system for the treatment of IDD comprises one or more sgRNAs targeting exon 3 of cTNFRSF1B. In some embodiments, the CRISPR gene-editing system for the treatment of IDD comprises one or more sgRNAs targeting exon 4 of cTNFRSF1B. In some embodiments, the CRISPR gene-editing system for the treatment of IDD comprises one or more sgRNAs targeting exon 5 of cTNFRSF1B. In some embodiments, the CRISPR gene-editing system for the treatment of IDD comprises one or more sgRNAs targeting exon 6 of cTNFRSF1B. In some embodiments, the CRISPR gene-editing system for the treatment of IDD comprises one or more sgRNAs targeting exon 7 of cTNFRSF1B. In some embodiments, the CRISPR gene-editing system for the treatment of IDD comprises one or more sgRNAs targeting exon 8 of cTNFRSF1B. In some embodiments, the CRISPR gene-editing system for the treatment of

IDD comprises one or more sgRNAs targeting exon 9 of cTNFRSF1B. In some embodiments, the CRISPR gene-editing system for the treatment of IDD comprises one or more sgRNAs targeting exon 10 of cTNFRSF1B. In some embodiments, the CRISPR gene-editing system for the treatment of IDD comprises one or more sgRNAs targeting exon 11 of cTNFRSF1B.

[00497] In some embodiments, the CRISPR gene-editing system for the treatment of IDD comprises one or more sgRNAs targeting exon 1 of eTNFRSF1B. In some embodiments, the CRISPR gene-editing system for the treatment of IDD comprises one or more sgRNAs targeting exon 2 of eTNFRSF1B. In some embodiments, the CRISPR gene-editing system for the treatment of IDD comprises one or more sgRNAs targeting exon 3 of eTNFRSF1B. In some embodiments, the CRISPR gene-editing system for the treatment of IDD comprises one or more sgRNAs targeting exon 4 of eTNFRSF1B. In some embodiments, the CRISPR gene-editing system for the treatment of IDD comprises one or more sgRNAs targeting exon 5 of eTNFRSF1B. In some embodiments, the CRISPR gene-editing system for the treatment of IDD comprises one or more sgRNAs targeting exon 6 of eTNFRSF1B. In some embodiments, the CRISPR gene-editing system for the treatment of IDD comprises one or more sgRNAs targeting exon 7 of eTNFRSF1B. In some embodiments, the CRISPR gene-editing system for the treatment of IDD comprises one or more sgRNAs targeting exon 8 of eTNFRSF1B. In some embodiments, the CRISPR gene-editing system for the treatment of IDD comprises one or more sgRNAs targeting exon 9 of eTNFRSF1B. In some embodiments, the CRISPR gene-editing system for the treatment of IDD comprises one or more sgRNAs targeting exon 10 of eTNFRSF1B. In some embodiments, the CRISPR gene-editing system for the treatment of IDD comprises one or more sgRNAs targeting exon 11 of eTNFRSF1B.

[00498] In some embodiments, the CRISPR gene-editing system for the treatment of IDD comprises one or more sgRNAs targeting exon 1 of fTNFRSF1B. In some embodiments, the CRISPR gene-editing system for the treatment of IDD comprises one or more sgRNAs targeting exon 2 of fTNFRSF1B. In some embodiments, the CRISPR gene-editing system for the treatment of IDD comprises one or more sgRNAs targeting exon 3 of fTNFRSF1B. In some embodiments, the CRISPR gene-editing system for the treatment of IDD comprises one or more sgRNAs targeting exon 4 of fTNFRSF1B. In some embodiments, the CRISPR gene-editing system for the treatment of IDD comprises one or more sgRNAs targeting exon 5 of fTNFRSF1B. In some embodiments, the CRISPR gene-editing system for the treatment

of IDD comprises one or more sgRNAs targeting exon 6 of fTNFRSF1B. In some embodiments, the CRISPR gene-editing system for the treatment of IDD comprises one or more sgRNAs targeting exon 7 of fTNFRSF1B. In some embodiments, the CRISPR gene-editing system for the treatment of IDD comprises one or more sgRNAs targeting exon 8 of fTNFRSF1B. In some embodiments, the CRISPR gene-editing system for the treatment of IDD comprises one or more sgRNAs targeting exon 9 of fTNFRSF1B. In some embodiments, the CRISPR gene-editing system for the treatment of IDD comprises one or more sgRNAs targeting exon 10 of fTNFRSF1B.

[00499] In some embodiments, the CRISPR gene-editing system for the treatment of IDD comprises one or more sgRNAs targeting TNFRSF3. In some embodiments, the CRISPR gene-editing system for the treatment of IDD comprises one or more sgRNAs targeting hTNFRSF3. In some embodiments, the CRISPR gene-editing system for the treatment of IDD comprises one or more sgRNAs targeting cTNFRSF3. In some embodiments, the CRISPR gene-editing system for the treatment of IDD comprises one or more sgRNAs targeting eTNFRSF3. In some embodiments, the CRISPR gene-editing system for the treatment of IDD comprises one or more sgRNAs targeting fTNFRSF3.

[00500] In some embodiments, the CRISPR gene-editing system for the treatment of IDD comprises one or more sgRNAs targeting exon 1 of hTNFRSF3. In some embodiments, the CRISPR gene-editing system for the treatment of IDD comprises one or more sgRNAs targeting exon 2 of hTNFRSF3. In some embodiments, the CRISPR gene-editing system for the treatment of IDD comprises one or more sgRNAs targeting exon 3 of hTNFRSF3. In some embodiments, the CRISPR gene-editing system for the treatment of IDD comprises one or more sgRNAs targeting exon 4 of hTNFRSF3. In some embodiments, the CRISPR gene-editing system for the treatment of IDD comprises one or more sgRNAs targeting exon 5 of hTNFRSF3. In some embodiments, the CRISPR gene-editing system for the treatment of IDD comprises one or more sgRNAs targeting exon 6 of hTNFRSF3. In some embodiments, the CRISPR gene-editing system for the treatment of IDD comprises one or more sgRNAs targeting exon 7 of hTNFRSF3. In some embodiments, the CRISPR gene-editing system for the treatment of IDD comprises one or more sgRNAs targeting exon 8 of hTNFRSF3. In some embodiments, the CRISPR gene-editing system for the treatment of IDD comprises one or more sgRNAs targeting exon 9 of hTNFRSF3. In some embodiments, the CRISPR gene-editing system for the treatment of IDD comprises one or more sgRNAs targeting exon 10 of hTNFRSF3. In some embodiments, the CRISPR gene-editing system for the treatment of

IDD comprises one or more sgRNAs targeting exon 11 of hTNFRSF3. In some embodiments, the CRISPR gene-editing system for the treatment of IDD comprises one or more sgRNAs targeting exon 12 of hTNFRSF3.

[00501] In some embodiments, the CRISPR gene-editing system for the treatment of IDD comprises one or more sgRNAs targeting exon 1 of cTNFRSF3. In some embodiments, the CRISPR gene-editing system for the treatment of IDD comprises one or more sgRNAs targeting exon 2 of cTNFRSF3. In some embodiments, the CRISPR gene-editing system for the treatment of IDD comprises one or more sgRNAs targeting exon 3 of cTNFRSF3. In some embodiments, the CRISPR gene-editing system for the treatment of IDD comprises one or more sgRNAs targeting exon 4 of cTNFRSF3. In some embodiments, the CRISPR gene-editing system for the treatment of IDD comprises one or more sgRNAs targeting exon 5 of cTNFRSF3. In some embodiments, the CRISPR gene-editing system for the treatment of IDD comprises one or more sgRNAs targeting exon 6 of cTNFRSF3. In some embodiments, the CRISPR gene-editing system for the treatment of IDD comprises one or more sgRNAs targeting exon 7 of cTNFRSF3. In some embodiments, the CRISPR gene-editing system for the treatment of IDD comprises one or more sgRNAs targeting exon 8 of cTNFRSF3. In some embodiments, the CRISPR gene-editing system for the treatment of IDD comprises one or more sgRNAs targeting exon 9 of cTNFRSF3. In some embodiments, the CRISPR gene-editing system for the treatment of IDD comprises one or more sgRNAs targeting exon 10 of cTNFRSF3.

[00502] In some embodiments, the CRISPR gene-editing system for the treatment of IDD comprises one or more sgRNAs targeting exon 1 of eTNFRSF3. In some embodiments, the CRISPR gene-editing system for the treatment of IDD comprises one or more sgRNAs targeting exon 2 of eTNFRSF3. In some embodiments, the CRISPR gene-editing system for the treatment of IDD comprises one or more sgRNAs targeting exon 3 of eTNFRSF3. In some embodiments, the CRISPR gene-editing system for the treatment of IDD comprises one or more sgRNAs targeting exon 4 of eTNFRSF3. In some embodiments, the CRISPR gene-editing system for the treatment of IDD comprises one or more sgRNAs targeting exon 5 of eTNFRSF3. In some embodiments, the CRISPR gene-editing system for the treatment of IDD comprises one or more sgRNAs targeting exon 6 of eTNFRSF3. In some embodiments, the CRISPR gene-editing system for the treatment of IDD comprises one or more sgRNAs targeting exon 7 of eTNFRSF3. In some embodiments, the CRISPR gene-editing system for the treatment of IDD comprises one or more sgRNAs targeting exon 8 of eTNFRSF3. In

some embodiments, the CRISPR gene-editing system for the treatment of IDD comprises one or more sgRNAs targeting exon 9 of eTNFRSF3. In some embodiments, the CRISPR gene-editing system for the treatment of IDD comprises one or more sgRNAs targeting exon 10 of eTNFRSF3.

[00503] In some embodiments, the CRISPR gene-editing system for the treatment of IDD comprises one or more sgRNAs targeting exon 1 of fTNFRSF3. In some embodiments, the CRISPR gene-editing system for the treatment of IDD comprises one or more sgRNAs targeting exon 2 of fTNFRSF3. In some embodiments, the CRISPR gene-editing system for the treatment of IDD comprises one or more sgRNAs targeting exon 3 of fTNFRSF3. In some embodiments, the CRISPR gene-editing system for the treatment of IDD comprises one or more sgRNAs targeting exon 4 of fTNFRSF3. In some embodiments, the CRISPR gene-editing system for the treatment of IDD comprises one or more sgRNAs targeting exon 5 of fTNFRSF3. In some embodiments, the CRISPR gene-editing system for the treatment of IDD comprises one or more sgRNAs targeting exon 6 of fTNFRSF3. In some embodiments, the CRISPR gene-editing system for the treatment of IDD comprises one or more sgRNAs targeting exon 7 of fTNFRSF3. In some embodiments, the CRISPR gene-editing system for the treatment of IDD comprises one or more sgRNAs targeting exon 8 of fTNFRSF3. In some embodiments, the CRISPR gene-editing system for the treatment of IDD comprises one or more sgRNAs targeting exon 9 of fTNFRSF3. In some embodiments, the CRISPR gene-editing system for the treatment of IDD comprises one or more sgRNAs targeting exon 10 of fTNFRSF3.

[00504] In some embodiments, the CRISPR gene-editing system for the treatment of IDD comprises one or more sgRNAs targeting TNFRSF4. In some embodiments, the CRISPR gene-editing system for the treatment of IDD comprises one or more sgRNAs targeting hTNFRSF4. In some embodiments, the CRISPR gene-editing system for the treatment of IDD comprises one or more sgRNAs targeting cTNFRSF4. In some embodiments, the CRISPR gene-editing system for the treatment of IDD comprises one or more sgRNAs targeting eTNFRSF4. In some embodiments, the CRISPR gene-editing system for the treatment of IDD comprises one or more sgRNAs targeting fTNFRSF4.

[00505] In some embodiments, the CRISPR gene-editing system for the treatment of IDD comprises one or more sgRNAs targeting exon 1 of hTNFRSF4. In some embodiments, the CRISPR gene-editing system for the treatment of IDD comprises one or more sgRNAs targeting exon 2 of hTNFRSF4. In some embodiments, the CRISPR gene-editing system for

the treatment of IDD comprises one or more sgRNAs targeting exon 3 of hTNFRSF4. In some embodiments, the CRISPR gene-editing system for the treatment of IDD comprises one or more sgRNAs targeting exon 4 of hTNFRSF4. In some embodiments, the CRISPR gene-editing system for the treatment of IDD comprises one or more sgRNAs targeting exon 5 of hTNFRSF4. In some embodiments, the CRISPR gene-editing system for the treatment of IDD comprises one or more sgRNAs targeting exon 6 of hTNFRSF4.

[00506] In some embodiments, the CRISPR gene-editing system for the treatment of IDD comprises one or more sgRNAs targeting exon 1 of cTNFRSF4. In some embodiments, the CRISPR gene-editing system for the treatment of IDD comprises one or more sgRNAs targeting exon 2 of cTNFRSF4. In some embodiments, the CRISPR gene-editing system for the treatment of IDD comprises one or more sgRNAs targeting exon 3 of cTNFRSF4. In some embodiments, the CRISPR gene-editing system for the treatment of IDD comprises one or more sgRNAs targeting exon 4 of cTNFRSF4. In some embodiments, the CRISPR gene-editing system for the treatment of IDD comprises one or more sgRNAs targeting exon 5 of cTNFRSF4. In some embodiments, the CRISPR gene-editing system for the treatment of IDD comprises one or more sgRNAs targeting exon 6 of cTNFRSF4. In some embodiments, the CRISPR gene-editing system for the treatment of IDD comprises one or more sgRNAs targeting exon 7 of cTNFRSF4.

[00507] In some embodiments, the CRISPR gene-editing system for the treatment of IDD comprises one or more sgRNAs targeting exon 1 of eTNFRSF4. In some embodiments, the CRISPR gene-editing system for the treatment of IDD comprises one or more sgRNAs targeting exon 2 of eTNFRSF4. In some embodiments, the CRISPR gene-editing system for the treatment of IDD comprises one or more sgRNAs targeting exon 3 of eTNFRSF4. In some embodiments, the CRISPR gene-editing system for the treatment of IDD comprises one or more sgRNAs targeting exon 4 of eTNFRSF4. In some embodiments, the CRISPR gene-editing system for the treatment of IDD comprises one or more sgRNAs targeting exon 5 of eTNFRSF4. In some embodiments, the CRISPR gene-editing system for the treatment of IDD comprises one or more sgRNAs targeting exon 6 of eTNFRSF4. In some embodiments, the CRISPR gene-editing system for the treatment of IDD comprises one or more sgRNAs targeting exon 7 of eTNFRSF4.

[00508] In some embodiments, the CRISPR gene-editing system for the treatment of IDD comprises one or more sgRNAs targeting exon 1 of fTNFRSF4. In some embodiments, the CRISPR gene-editing system for the treatment of IDD comprises one or more sgRNAs

targeting exon 2 of fTNFRSF4. In some embodiments, the CRISPR gene-editing system for the treatment of IDD comprises one or more sgRNAs targeting exon 3 of fTNFRSF4. In some embodiments, the CRISPR gene-editing system for the treatment of IDD comprises one or more sgRNAs targeting exon 4 of fTNFRSF4. In some embodiments, the CRISPR gene-editing system for the treatment of IDD comprises one or more sgRNAs targeting exon 5 of fTNFRSF4. In some embodiments, the CRISPR gene-editing system for the treatment of IDD comprises one or more sgRNAs targeting exon 6 of fTNFRSF4. In some embodiments, the CRISPR gene-editing system for the treatment of IDD comprises one or more sgRNAs targeting exon 7 of fTNFRSF4.

[00509] In some embodiments, the CRISPR gene-editing system for the treatment of IDD comprises one or more sgRNAs targeting TNFRSF11A. In some embodiments, the CRISPR gene-editing system for the treatment of IDD comprises one or more sgRNAs targeting hTNFRSF11A. In some embodiments, the CRISPR gene-editing system for the treatment of IDD comprises one or more sgRNAs targeting cTNFRSF11A. In some embodiments, the CRISPR gene-editing system for the treatment of IDD comprises one or more sgRNAs targeting eTNFRSF11A. In some embodiments, the CRISPR gene-editing system for the treatment of IDD comprises one or more sgRNAs targeting fTNFRSF11A.

[00510] In some embodiments, the CRISPR gene-editing system for the treatment of IDD comprises one or more sgRNAs targeting exon 1 of hTNFRSF11A. In some embodiments, the CRISPR gene-editing system for the treatment of IDD comprises one or more sgRNAs targeting exon 2 of hTNFRSF11A. In some embodiments, the CRISPR gene-editing system for the treatment of IDD comprises one or more sgRNAs targeting exon 3 of hTNFRSF11A. In some embodiments, the CRISPR gene-editing system for the treatment of IDD comprises one or more sgRNAs targeting exon 4 of hTNFRSF11A. In some embodiments, the CRISPR gene-editing system for the treatment of IDD comprises one or more sgRNAs targeting exon 5 of hTNFRSF11A. In some embodiments, the CRISPR gene-editing system for the treatment of IDD comprises one or more sgRNAs targeting exon 6 of hTNFRSF11A. In some embodiments, the CRISPR gene-editing system for the treatment of IDD comprises one or more sgRNAs targeting exon 7 of hTNFRSF11A. In some embodiments, the CRISPR gene-editing system for the treatment of IDD comprises one or more sgRNAs targeting exon 8 of hTNFRSF11A. In some embodiments, the CRISPR gene-editing system for the treatment of IDD comprises one or more sgRNAs targeting exon 9 of hTNFRSF11A. In some embodiments, the CRISPR gene-editing system for the treatment of IDD comprises one

or more sgRNAs targeting exon 10 of hTNFRSF11A. In some embodiments, the CRISPR gene-editing system for the treatment of IDD comprises one or more sgRNAs targeting exon 11 of hTNFRSF11A. In some embodiments, the CRISPR gene-editing system for the treatment of IDD comprises one or more sgRNAs targeting exon 12 of hTNFRSF11A.

[00511] In some embodiments, the CRISPR gene-editing system for the treatment of IDD comprises one or more sgRNAs targeting exon 1 of cTNFRSF11A. In some embodiments, the CRISPR gene-editing system for the treatment of IDD comprises one or more sgRNAs targeting exon 2 of cTNFRSF11A. In some embodiments, the CRISPR gene-editing system for the treatment of IDD comprises one or more sgRNAs targeting exon 3 of cTNFRSF11A. In some embodiments, the CRISPR gene-editing system for the treatment of IDD comprises one or more sgRNAs targeting exon 4 of cTNFRSF11A. In some embodiments, the CRISPR gene-editing system for the treatment of IDD comprises one or more sgRNAs targeting exon 5 of cTNFRSF11A. In some embodiments, the CRISPR gene-editing system for the treatment of IDD comprises one or more sgRNAs targeting exon 6 of cTNFRSF11A. In some embodiments, the CRISPR gene-editing system for the treatment of IDD comprises one or more sgRNAs targeting exon 7 of cTNFRSF11A. In some embodiments, the CRISPR gene-editing system for the treatment of IDD comprises one or more sgRNAs targeting exon 8 of cTNFRSF11A. In some embodiments, the CRISPR gene-editing system for the treatment of IDD comprises one or more sgRNAs targeting exon 9 of cTNFRSF11A. In some embodiments, the CRISPR gene-editing system for the treatment of IDD comprises one or more sgRNAs targeting exon 10 of cTNFRSF11A. In some embodiments, the CRISPR gene-editing system for the treatment of IDD comprises one or more sgRNAs targeting exon 11 of cTNFRSF11A.

[00512] In some embodiments, the CRISPR gene-editing system for the treatment of IDD comprises one or more sgRNAs targeting exon 1 of eTNFRSF11A. In some embodiments, the CRISPR gene-editing system for the treatment of IDD comprises one or more sgRNAs targeting exon 2 of eTNFRSF11A. In some embodiments, the CRISPR gene-editing system for the treatment of IDD comprises one or more sgRNAs targeting exon 3 of eTNFRSF11A. In some embodiments, the CRISPR gene-editing system for the treatment of IDD comprises one or more sgRNAs targeting exon 4 of eTNFRSF11A. In some embodiments, the CRISPR gene-editing system for the treatment of IDD comprises one or more sgRNAs targeting exon 5 of eTNFRSF11A. In some embodiments, the CRISPR gene-editing system for the treatment of IDD comprises one or more sgRNAs targeting exon 6 of eTNFRSF11A. In

some embodiments, the CRISPR gene-editing system for the treatment of IDD comprises one or more sgRNAs targeting exon 7 of eTNFRSF11A. In some embodiments, the CRISPR gene-editing system for the treatment of IDD comprises one or more sgRNAs targeting exon 8 of eTNFRSF11A. In some embodiments, the CRISPR gene-editing system for the treatment of IDD comprises one or more sgRNAs targeting exon 9 of eTNFRSF11A. In some embodiments, the CRISPR gene-editing system for the treatment of IDD comprises one or more sgRNAs targeting exon 10 of eTNFRSF11A.

[00513] In some embodiments, the CRISPR gene-editing system for the treatment of IDD comprises one or more sgRNAs targeting exon 1 of fTNFRSF11A. In some embodiments, the CRISPR gene-editing system for the treatment of IDD comprises one or more sgRNAs targeting exon 2 of fTNFRSF11A. In some embodiments, the CRISPR gene-editing system for the treatment of IDD comprises one or more sgRNAs targeting exon 3 of fTNFRSF11A. In some embodiments, the CRISPR gene-editing system for the treatment of IDD comprises one or more sgRNAs targeting exon 4 of fTNFRSF11A. In some embodiments, the CRISPR gene-editing system for the treatment of IDD comprises one or more sgRNAs targeting exon 5 of fTNFRSF11A. In some embodiments, the CRISPR gene-editing system for the treatment of IDD comprises one or more sgRNAs targeting exon 6 of fTNFRSF11A. In some embodiments, the CRISPR gene-editing system for the treatment of IDD comprises one or more sgRNAs targeting exon 7 of fTNFRSF11A. In some embodiments, the CRISPR gene-editing system for the treatment of IDD comprises one or more sgRNAs targeting exon 8 of fTNFRSF11A. In some embodiments, the CRISPR gene-editing system for the treatment of IDD comprises one or more sgRNAs targeting exon 9 of fTNFRSF11A. In some embodiments, the CRISPR gene-editing system for the treatment of IDD comprises one or more sgRNAs targeting exon 10 of fTNFRSF11A. In some embodiments, the CRISPR gene-editing system for the treatment of IDD comprises one or more sgRNAs targeting exon 11 of fTNFRSF11A.

VI. Delivery

A. Viral vectors

[00514] In one aspect, the present disclosure encompasses methods of delivery of a CRISPR gene-editing system targeting a gene selected from IL1R1, IL1R2, IL1RAP, IL1RL1, TGFBR1, TGFBR2, IL6R, IL6ST, TNFRSF1A, TNFRSF1B, TNFRSF3, TNFRSF4, TNFRSF11A and combinations thereof using one or more recombinant viral particle. In

some embodiments, the one of more viral vectors comprise a recombinant virus selected from a retrovirus, an adenovirus, an adeno-associated virus, a lentivirus, and a herpes simplex virus-1. In some embodiments, the one of more viral vectors comprise a recombinant adeno-associated virus (AAV). In some embodiments, the recombinant AAV is of serotype 5 (AAV5). In some embodiments, the recombinant AAV is of serotype 6 (AAV6). In some embodiments, the one or more viral vectors comprise: a first viral vector comprising a first nucleic acid, in the one or more nucleic acids, encoding the Cas protein; and a second viral vector comprising a second nucleic acid, in the one or more nucleic acids, encoding the at least one guide RNA. In some embodiments, the one or more viral vectors comprise a viral vector comprising a single nucleic acid, wherein the single nucleic acid encodes the Cas9 protein and the at least one guide RNA.

1. Adeno-associated virus (AAV)

[00515] A viral vector system useful for delivery of nucleic acids is the adeno-associated virus (AAV). Adeno-associated virus is a naturally occurring defective virus that requires another virus, such as an adenovirus or a herpes virus, as a helper virus for efficient replication and a productive life cycle. For a review see Muzyczka et al., Curr. Topics in Micro. and Immunol. 158:97-129 (1992). It is also one of the few viruses that may integrate its DNA into non-dividing cells, and exhibits a high frequency of stable integration (see for example Flotte et al., Am. J. Respir. Cell. Mol. Biol. 7:349-356 (1992); Samulski et al., J. Virol. 63:3822-3828 (1989); and McLaughlin et al., J. Virol. 62:1963-1973 (1989). Vectors containing as little as 300 base pairs of AAV can be packaged and can integrate. Space for exogenous DNA is limited to about 4.5 kb. An AAV vector such as that described in Tratschin et al., Mol. Cell. Biol. 5:3251-3260 (1985) can be used to introduce DNA into cells. A variety of nucleic acids have been introduced into different cell types using AAV vectors (see for example Hermonat et al., Proc. Natl. Acad. Sci. USA 81:6466-6470 (1984); Tratschin et al., Mol. Cell. Biol. 4:2072-2081 (1985); Wondisford et al., Mol. Endocrinol. 2:32-39 (1988); Tratschin et al., J. Virol. 51:611-619 (1984); and Flotte et al., J. Biol. Chem. 268:3781-3790 (1993). The identification of Staphylococcus aureus (SaCas9) and other smaller Cas9 enzymes that can be packaged into adeno-associated viral (AAV) vectors that are highly stable and effective in vivo, easily produced, approved by FDA, and tested in multiple clinical trials, paves new avenues for therapeutic gene editing.

[00516] According to particular embodiments, a CRISPR gene-editing system targeting a gene selected from IL1R1, IL1R2, IL1RAP, IL1RL1, TGFBR1, TGFBR2, IL6R, IL6ST, TNFRSF1A, TNFRSF1B, TNFRSF3, TNFRSF4, TNFRSF11A, and combinations thereof further comprise a recombinant AAV vector. In some embodiments, the CRISPR gene-editing system is encoded by a nucleic acid, wherein the nucleic acid is a recombinant AAV genome. In some embodiments, the AAV vector is selected from an AAV1 vector, an AAV2 vector, an AAV3 vector, an AAV4 vector, an AAV5 vector, an AAV6 vector, an AAV7 vector, an AAV8 vector, an AAV9 vector, and an AAV10 vector.

[00517] In some aspects, the AAV vector comprises a serotype selected from the group consisting of: AAV1, AAV1(Y705+731F+T492V), AAV2(Y444+500+730F+T491V), AAV3(Y705+731F), AAV4, AAV5, AAV5(Y436+693+719F), AAV6, AAV6 (VP3 variant Y705F/Y731F/T492V), AAV-7m8, AAV8, AAV8(Y733F), AAV9, AAV9 (VP3 variant Y731F), AAV10(Y733F), AAV-ShH10, and AAV-DJ/8. In some aspects, the AAV vector comprises a serotype selected from the group consisting of: AAV1, AAV5, AAV6, AAV6 (Y705F/Y731F/T492V), AAV8, AAV9, and AAV9 (Y731F).

[00518] In some embodiments, use of the CRISPR gene-editing system further comprising one or more LNPs to target a gene selected from IL1R1, IL1RAP, TGFBR1, TGFBR2, IL6R, IL6ST, TNFRSF1A, TNFRSF1B, TNFRSF3, TNFRSF4, TNFRSF11A, and combinations thereof is therapeutic.

[00519] In one aspect, use of the CRISPR gene-editing system further comprising one or more AAV vectors to target TGFBR1 and/or TGFBR2 is therapeutic. In some embodiments, use of the system treats one or more joint disease or illness or one or more back or spine conditions or disorders. In some embodiments, use of the system treats one or more musculoskeletal diseases, conditions, and illnesses, including, but not limited to, Loeys-Dietz Syndrome, osteoarthritis, Marfan syndrome, aortic aneurysm (e.g., familial thoracic 3 aortic aneurysm), craniofacial abnormalities, and combinations thereof. In other embodiments, use of the system treats neoplastic diseases, conditions, and illnesses, including, but not limited to, pancreatic cancer, multiple self-healing squamous epithelioma (Ferguson-Smith disease), gastrointestinal stromal tumors (GIST), hereditary nonpolyposis colorectal cancer (Lynch Syndrome), metastatic colorectal carcinoma, bone neoplasms, anaplastic carcinoma, spindle-cell carcinoma, lung neoplasms, brain neoplasms, and combinations thereof.

[00520] In some embodiments, the CRISPR gene-editing system further comprising one or more AAV vectors to target IL1R1 and/or IL1RAP is therapeutic. In some embodiments, use of the system treats one or more joint disease or illness or one or more back or spine conditions or disorders. In some embodiments, use of the system treats one or more musculoskeletal diseases, conditions, and illnesses, including, but not limited to, rheumatoid arthritis, gout, osteoarthritis, immune-mediated arthritis or polyarthritis, osteoporosis, intervertebral disc disease (IVDD), psoriatic arthritis, arthritis, polymyositis, acute or chronic inflammatory synovitis, proliferative synovitis, bone neoplasms, sarcoid myopathy, cortex bone disorders, idiopathic scoliosis, tendinopathy, myofibrillar myopathy, enthesis-related arthritis, ankylosing spondylitis, degenerative polyarthritis, arthopathy, osteitis deformans, prolapsed lumbar disc, polymyositis ossificans, idiopathic polymyositis, Luft Disease, adult-onset Still's Disease, osteoarthritis deformans, Bachet's Disease, and combinations thereof. In other embodiments, use of the system treats one or more neoplastic diseases, conditions, and illnesses, including, but not limited to, osteosarcoma, multiple myeloma, lymphoma(e.g., B-cell or cutaneous T-cell lymphoma), leukemia, thyroid carcinoma, glioma, renal cell carcinoma, chondrosarcoma, glioblastoma, melanoma, neuroblastoma, polycystic ovary syndrome, Kaposi sarcoma, squamous cell carcinoma, leiomyosarcoma, malignant peripheral nerve sheath tumor, Ewing's sarcoma, esophageal neoplasms, colon cancer, lung cancer, breast cancer, pancreatic cancer, stomach cancer, epithelial ovarian cancer, cholectoral cancer, liver cancer, skin cancer, prostate cancer, cervical cancer, ovarian cancer, bladder cancer, oral cavity cancer, and combinations thereof. In other embodiments, use of the system treats one or more inflammatory diseases, conditions, and illnesses, including, but not limited to, autoinflammatory disease (AID), cryopyrin-associated periodic syndrome (CAPS), systemic lupus erythematosus (SLE), inflammatory bowel disease (IBD) and combinations thereof. In some embodiments, use of the system treats one or more cardiac diseases, conditions, and illnesses, including, but not limited to, myocardial infarction, heart failure (e.g., refractory or acute decompensated heart failure), arrthymias, pericarditis (e.g., refractory idiopathic pericarditis), myocarditis, sepsis-induced cardiomyopathy, atherosclerosis, coronary artery disease and combinations thereof. In some embodiments, use of the system treats one or more neurological diseases, conditions, and illnesses, including, but not limited to, acute thrombotic stroke, epilepsy, multiple sclerosis, Alzheimer's Disease and combinations thereof. In some embodiments, use of the system treats one or more opthalmic diseases, conditions, and illnesses, including, but not limited to, uveitis, scleritis, Sjogren asthenia, dry eye and combinations thereof. In some embodiments, use of the system

treats one or more diseases, conditions, and illnesses, including, but not limited to, chronic kidney disease, Type 2 diabetes, gastroesophageal reflux disease (GERD), non-HP-associated peptic ulcer disease, and pulmonary fibrosis.

2. Lentivirus

[00521] In some aspects, the viral vector is a lentivirus. In an aspect, the lentivirus is selected from the group consisting of: human immunodeficiency-1 (HIV-1), human immunodeficiency-2 (HIV-2), simian immunodeficiency virus (SIV), feline immunodeficiency virus (FIV), bovine immunodeficiency virus (BIV), Jembrana Disease Virus (JDV), equine infectious anemia virus (EIAV), and caprine arthritis encephalitis virus (CAEV).

[00522] Lentiviral transduction systems are known in the art and are described, e.g., in Levine, et al., Proc. Nat'l Acad. Sci. 2006, 103, 17372-77; Zufferey, et al., Nat. Biotechnol. 1997, 15, 871-75; Dull, et al., J. Virology 1998, 72, 8463-71, and U.S. Patent No. 6,627,442, the disclosures of each of which are incorporated by reference herein.

[00523] In one aspect, use of the CRISPR gene-editing system further comprising one or more lentiviral vectors to target TGFBR1 and/or TGFBR2 is therapeutic. In some embodiments, use of the system treats one or more joint disease or illness, fibrosis and/or scarring, or one or more back or spine conditions or disorders. In some embodiments, use of the system treats one or more musculoskeletal diseases, conditions, and illnesses, including, but not limited to, Loeys-Dietz Syndrome, osteoarthritis, Marfan syndrome, aortic aneurysm (e.g., familial thoracic 3 aortic aneurysm), craniofacial abnormalities, and combinations thereof. In other embodiments, use of the system treats neoplastic diseases, conditions, and illnesses, including, but not limited to, pancreatic cancer, multiple self-healing squamous epithelioma (Ferguson-Smith disease), gastrointestinal stromal tumors (GIST), hereditary nonpolyposis colorectal cancer (Lynch Syndrome), metastatic colorectal carcinoma, bone neoplasms, anaplastic carcinoma, spindle-cell carcinoma, lung neoplasms, brain neoplasms, and combinations thereof.

[00524] In some embodiments, the CRISPR gene-editing system further comprising one or more lentiviral vectors to target IL1R1 and/or IL1RAP is therapeutic. In some embodiments, use of the system treats one or more joint disease or illness, fibrosis and/or scarring, or one or more back or spine conditions or disorders. In some embodiments, use of the system treats one or more musculoskeletal diseases, conditions, and illnesses, including, but not limited to,

rheumatoid arthritis, gout, osteoarthritis, osteoporosis, intervertebral disc disease (IVDD), psoriatic arthritis, arthritis, polymyositis, proliferative synovitis, bone neoplasms, sarcoid myopathy, cortex bone disorders, idiopathic scoliosis, tendinopathy, myofibrillar myopathy, enthesis-related arthritis, ankylosing spondylitis, degenerative polyarthritis, arthropathy, osteitis deformans, prolapsed lumbar disc, polymyositis ossificans, idiopathic polymyositis, Luft Disease, adult-onset Still's Disease, osteoarthritis deformans, Bachet's Disease, and combinations thereof. In other embodiments, use of the system treats one or more neoplastic diseases, conditions, and illnesses, including, but not limited to, osteosarcoma, multiple myeloma, lymphoma(e.g., B-cell or cutaneous T-cell lymphoma), leukemia, thyroid carcinoma, glioma, renal cell carcinoma, chondrosarcoma, glioblastoma, melanoma, neuroblastoma, polycystic ovary syndrome, Kaposi sarcoma, squamous cell carcinoma, leiomyosarcoma, malignant peripheral nerve sheath tumor, Ewing's sarcoma, esophageal neoplasms, colon cancer, lung cancer, breast cancer, pancreatic cancer, stomach cancer, epithelial ovarian cancer, cholectoral cancer, liver cancer, skin cancer, prostate cancer, cervical cancer, ovarian cancer, bladder cancer, oral cavity cancer, and combinations thereof. In other embodiments, use of the system treats one or more inflammatory diseases, conditions, and illnesses, including, but not limited to, autoinflammatory disease (AID), cryopyrin-associated periodic syndrome (CAPS), systemic lupus erythematosus (SLE), inflammatory bowel disease (IBD) and combinations thereof. In some embodiments, use of the system treats one or more cardiac diseases, conditions, and illnesses, including, but not limited to, myocardial infarction, heart failure (e.g., refractory or acute decompensated heart failure), arrythmias, pericarditis (e.g., refractory idiopathic pericarditis), myocarditis, sepsis-induced cardiomyopathy, atherosclerosis, coronary artery disease and combinations thereof. In some embodiments, use of the system treats one or more neurological diseases, conditions, and illnesses, including, but not limited to, acute thrombotic stroke, epilepsy, multiple sclerosis, Alzheimer's Disease and combinations thereof. In some embodiments, use of the system treats one or more ophthalmic diseases, conditions, and illnesses, including, but not limited to, uveitis, scleritis, Sjogren asthenia, dry eye and combinations thereof. In some embodiments, use of the system treats one or more diseases, conditions, and illnesses, including, but not limited to, chronic kidney disease, Type 2 diabetes, gastroesophageal reflux disease (GERD), non-HP-associated peptic ulcer disease, and pulmonary fibrosis.

B. Lipid nanoparticles (LNP)

[00525] In some embodiments, a CRISPR gene-editing system is delivered by a nanoparticle. Without wishing to be bound by any particular theory, in certain embodiments, nucleic acids, when present in the nanoparticle, are resistant in aqueous solution to degradation with a nuclease. In other embodiments, proteins are protected from protease degradation. In some embodiments, proteins and nucleic acids encapsulated by nanoparticles are capable of penetrating the cellular plasma membrane.

[00526] Lipid nanoparticles comprising nucleic acids and their method of preparation is disclosed in at least WO2017/019935, WO2017/049074, WO2017/201346, WO2017/218704, WO2018/006052, WO2018/013525, WO2018/089540, WO2018/119115, WO2018/126084, WO2018/157009, WO2018/170336, WO2018/222890, WO2019/046809, WO2019/089828, WO2020/061284, WO2020/061317, WO2020/081938, WO2020/097511, WO2020/097520, WO2020/097540, WO2020/097548, WO2020/214946, WO2020/219941, WO2020/232276, WO2020/227615, WO2020/061295, WO2021/007278, WO2021/016430, WO2021/021988, EP Patent No. EP 2 972 360, US20200155691, US20200237671, U.S. Patent Nos. 8,058,069, 8,492,359, 8,822,668, 9,364,435, 9,404,127, 9,504,651, 9,593,077, 9,738,593, 9,868,691, 9,868,692, 9,950,068, 10,138,213, 10,166,298, 10,221,127, 10,238,754, 10,266,485, 10,383,952, 10,730,924, 10,766,852, 11,079,379, 11,141,378 and 11,246,933, which are incorporated herein by reference in their entirety for all purposes.

[00527] Lipid Nanoparticle Compositions

[00528] In some embodiments, the largest dimension of a nanoparticle composition is 1 micrometer or shorter (e.g., 1 micrometer, 900 nm, 800 nm, 700 nm, 600 nm, 500 nm, 400 nm, 300 nm, 200 nm, 175 nm, 150 nm, 125 nm, 100 nm, 75 nm, 50 nm, or shorter), e.g., when measured by dynamic light scattering (DLS), transmission electron microscopy, scanning electron microscopy, or another method. Nanoparticle compositions include, for example, lipid nanoparticles (LNPs), liposomes, lipid vesicles, and lipoplexes. In some embodiments, nanoparticle compositions are vesicles including one or more lipid bilayers. In certain embodiments, a nanoparticle composition includes two or more concentric bilayers separated by aqueous compartments. Lipid bilayers may be functionalized and/or crosslinked to one another. Lipid bilayers may include one or more ligands, proteins, or channels. In various embodiments , lipid nanoparticles described herein have a mean diameter of from about 30 nm to about 150 nm, from about 40 nm to about 150 nm, from about 50 nm to about 150 nm, from about 60 nm to about 130 nm, from about 70 nm to about 110 nm, from about 70 nm to about 100 nm, from about 80 nm to about 100 nm, from about 90 nm to about 100

nm, from about 70 nm to about 90 nm, from about 80 nm to about 90 nm, from about 70 nm to about 80 nm, or about 30 nm, 35 nm, 40 nm, 45 nm, 50 nm, 55 nm, 60 nm, 65 nm, 70 nm, 75 nm, 80 nm, 85 nm, 90 nm, 95 nm, 100 nm, 105 nm, 110 nm, 115 nm, 120 nm, 125 nm, 130 nm, 135 nm, 140 nm, 145 nm, or 150 nm, and are substantially non-toxic.

[00529] In certain embodiments, the lipid nanoparticles described herein comprise one or more components, including a lipid component, , and (optionally) a structural component. The lipid component comprises lipids selected from ionizable and/or cationic lipids (i.e., lipids that may have a positive or partial positive charge at physiological pH), neutral lipids (e.g., phospholipids, or sphingolipids), and polymer-conjugated lipids (e.g., PEGylated lipids). In some embodiments, the lipid component comprises a single ionizable lipid. In other embodiments, the lipid component comprises 2, 3, 4, 5, 6, 7, 8, 9, 10, 15, or 20 ionizable lipids. In some embodiments, the lipid component comprises a single neutral lipid. In other embodiments, the lipid component comprises 2, 3, 4, 5, 6, 7, 8, 9, 10, 15, or 20 neutral lipids. In some embodiments, the lipid com-ponent comprises a single polymer-conjugated lipid. In other embodiments, the lipid component comprises 2, 3, 4, 5, 6, 7, 8, 9, 10, 15, or 20 polymer-conjugated lipids. In some embodiments, the structural component comprises a single structural lipid. In other embodiments, the structural component comprises 2, 3, 4, 5, 6, 7, 8, 9, 10, 15, or 20 structural lipids. In some embodiments, the lipid component comprises at least one cationic lipid, at least one neutral lipid, and at least one polymer-conjugated lipid. The present disclosure contemplates that the lipid component may comprise any combination of the foregoing constituents.

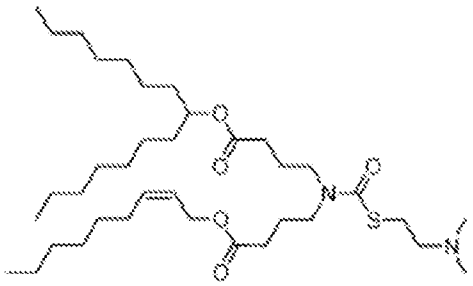
[00530] Ionizable/Cationic Lipids

[00531] In some embodiments, the lipid component comprises an ionizable lipid. In some embodiments, the ionizable lipid is anionic. In other embodiments, the ionizable lipid is a cationic lipid. In some embodiments, the lipid component comprises cationic lipids including, but not limited to, a cationic lipid selected from the group consisting of 3-(didodecylamino)-N1,N1,4-tridodecyl-1-piperazineethanamine (KL10), N1-[2-(didodecylamino)ethyl]-N1,N4,N4-tridodecyl-1,4-piperazinediethanamine (KL22), 14,25-ditridecyl-15,18,21,24-tetraaza-octatriacontane (KL25), 1,2-dilinoleyloxy-N,N-dimethylaminopropane (DLin-DMA), 2,2-dilinoleyl-4-dimethylaminomethyl-[1,3]-dioxolane (DLin-K-DMA), heptatriaconta-6,9,28,31-tetraen-19-yl 4-(dimethylamino)butanoate (DLin-MC3-DMA), 2,2-dilinoleyl-4-(2-dimethylaminoethyl)-[1,3]-dioxolane (DLin-KC2-DMA), 1,2-dioleyloxy-N,N-dimethylaminopropane (DODMA), 2-({8-[(3.beta.)-cholest-5-en-3-yloxy]octyl}oxy)-

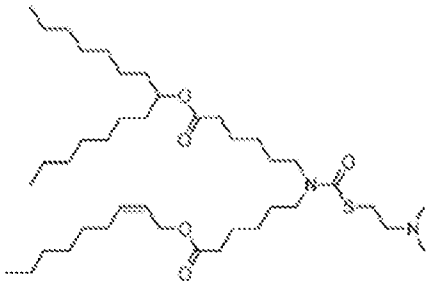
N,N-dimethyl-3-[(9Z,12Z)- -octadeca-9,12-dien-1-yloxy]propan-1-amine (Octyl-CLinDMA), (2R)-2-({8-[(3.beta.)-cholest-5-en-3-yloxy]octyl}oxy)-N,N-dimethyl-3-[(9Z- ,12Z)-octadeca-9,12-dien-1-yloxy]propan-1-amine (Octyl-CLinDMA (2R)), (2S)-2-({8-[(3.beta.)-cholest-5-en-3-yloxy]octyl}oxy)-N,N-dimethyl-3-[(9Z- ,12Z)-octadeca-9,12-dien-1-yloxy]propan-1-amine (Octyl-CLinDMA (2S)), a lipid including a cyclic amine group, and mixtures thereof.

[00532] Non-exhaustive and non-limiting examples of cationic lipids include:

[00533]

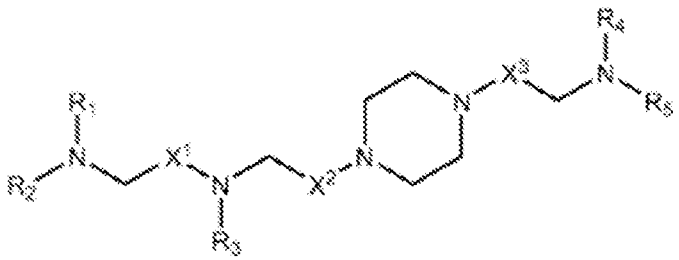


ATX-0081

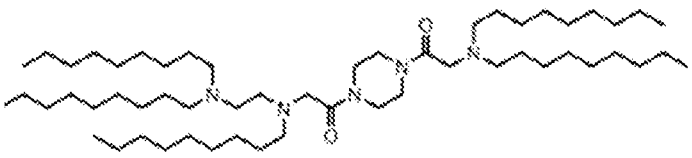


ATX-0095

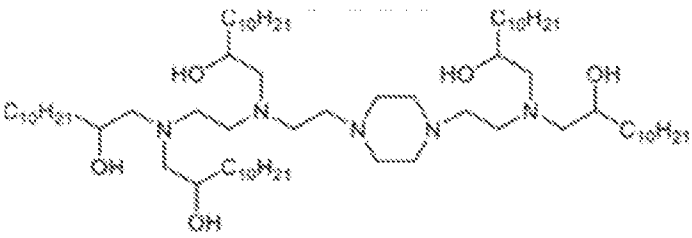
[00534]

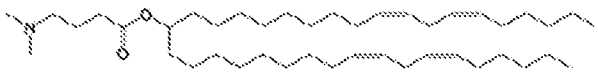


[00535]

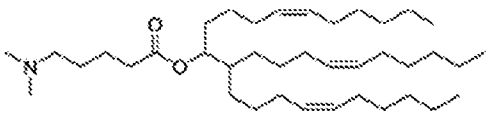


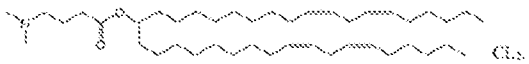
[00536]



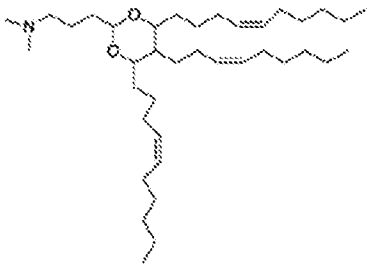


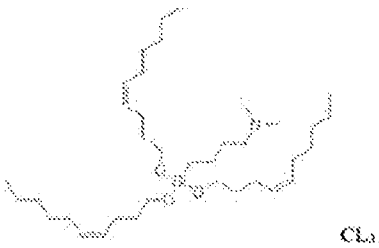
MC3





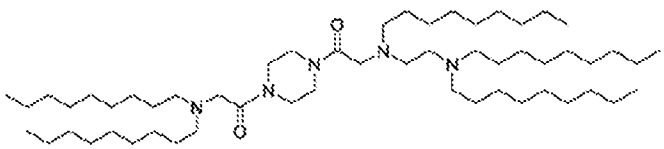
Genevant CL_1



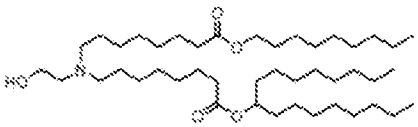


CL_3

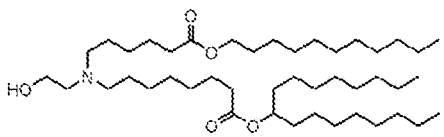
[00537]



Compound (A),

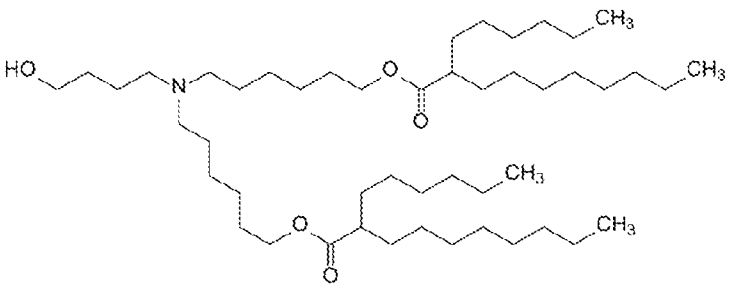


Moderna Lipid 5

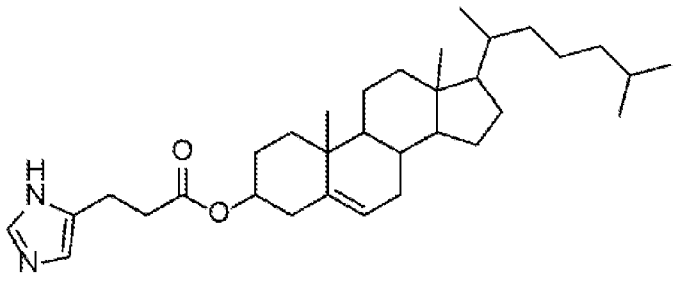


Moderna Lipid H

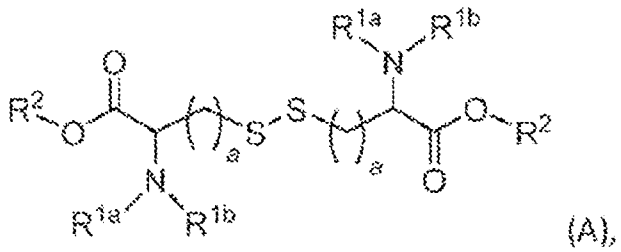
[00538]



[00539]

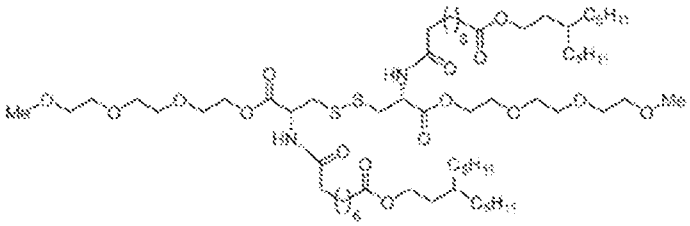


[00540]

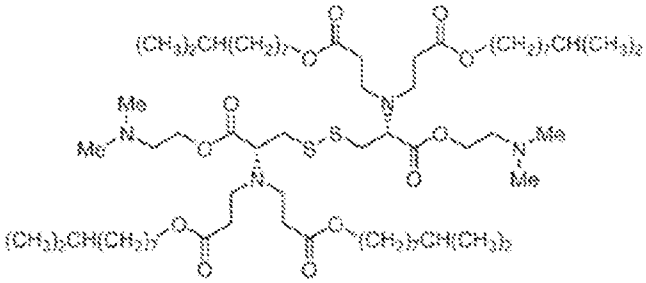


(A),

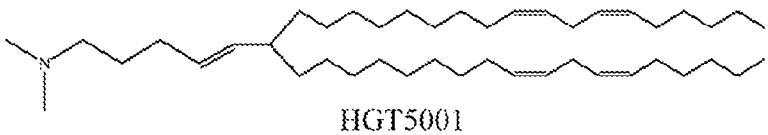
[00541]



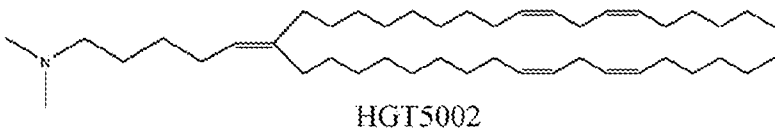
[00542]



[00543]

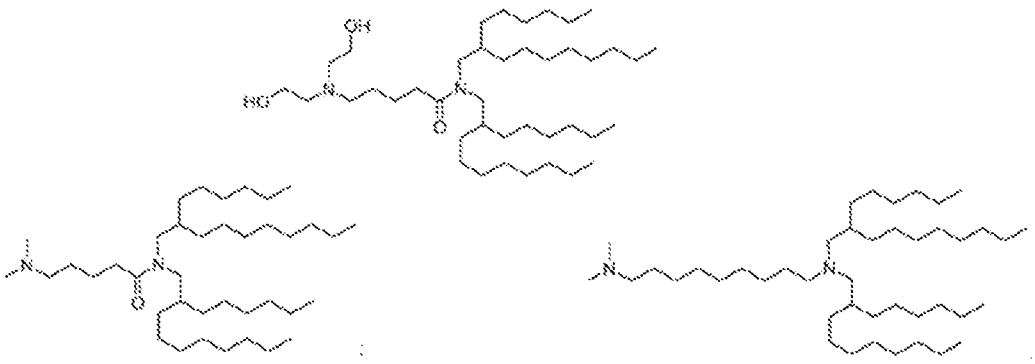


HGT5001

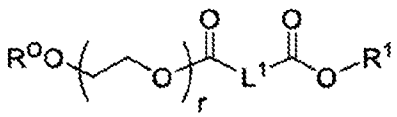


HGT5002

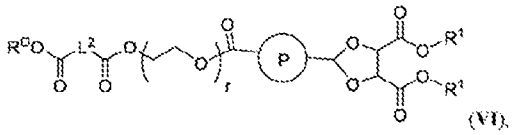
[00544]



[00545]

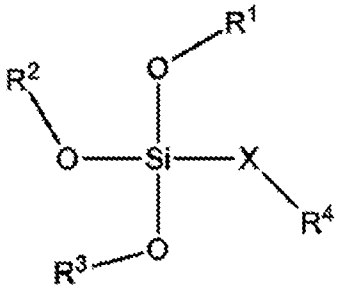


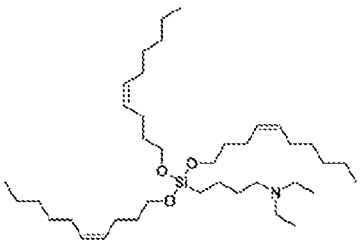
(I),



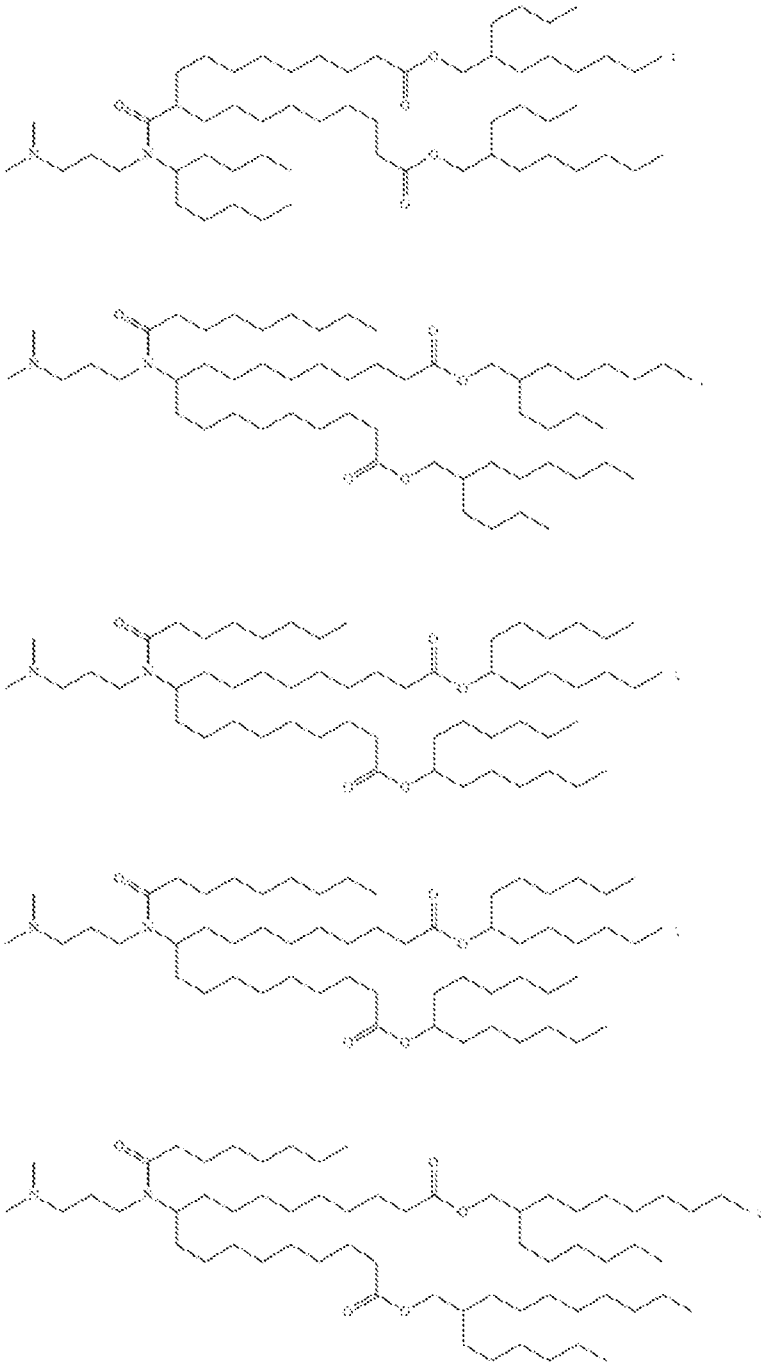
(VI).

[00546]





[00547]



[00548]

[00549] Neutral Lipids/Phospholipids

[00550] In some embodiments, the lipid component further comprises neutral lipids including, but not limited to, a phospholipid selected from the group consisting of 1,2-dilinoleoyl-sn-glycero-3-phosphocholine (DLPC), 1,2-dimyristoyl-sn-glycero-phosphocholine (DMPC), 1,2-dioleoyl-sn-glycero-3-phosphocholine (DOPC), 1,2-dipalmitoyl-sn-glycero-3-phosphocholine (DPPC), 1,2-distearoyl-sn-glycero-3-phosphocholine (DSPC), 1,2-diundecanoyl-sn-glycero-phosphocholine (DUPC), 1-palmitoyl-

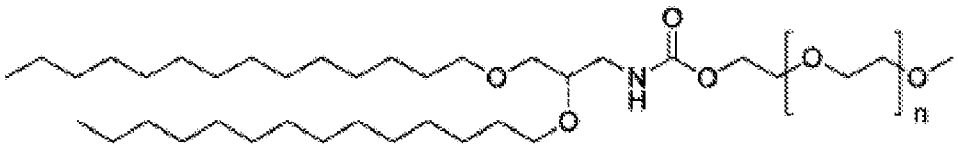
2-oleoyl-sn-glycero-3-phosphocholine (POPC), 1,2-di-O-octadecenyl-sn-glycero-3-phosphocholine (18:0 Diether PC), 1-oleoyl-2-cholesterylhemisuccinoyl-sn-glycero-3-phosphocholine (OChemsPC), 1-hexadecyl-sn-glycero-3-phosphocholine (C16 Lyso PC), 1,2-dilinolenoyl-sn-glycero-3-phosphocholine, 1,2-diarachidonoyl-sn-glycero-3-phosphocholine, 1,2-didocosahexaenoyl-sn-glycero-3-phosphocholine, 1,2-dioleoyl-sn-glycero-3-phosphoethanolamine (DOPE), 1,2-diphytanoyl-sn-glycero-3-phosphoethanolamine (ME 16.0 PE), 1,2-distearoyl-sn-glycero-3-phosphoethanolamine, 1,2-dilinoleoyl-sn-glycero-3-phosphoethanolamine, 1,2-dilinolenoyl-sn-glycero-3-phosphoethanolamine, 1,2-diarachidonoyl-sn-glycero-3-phosphoethanolamine, 1,2-didocosahexaenoyl-sn-glycero-3-phosphoethanolamine, 1,2-dioleoyl-sn-glycero-3-phospho-rac-(1-glycerol) sodium salt (DOPG), sphingomyelin (SM), and mixtures thereof.

[00551] Polymer-conjugated Lipids

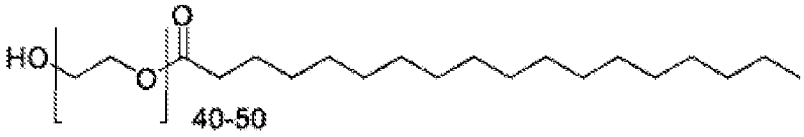
[00552] In some embodiments, the lipid component further comprises polymer-conjugated lipids, including, but not limited to, a PEGylated lipid selected from the group consisting of PEG-modified phosphatidylethanolamines, PEG-modified phosphatidic acids, PEG-modified ceramides, PEG-modified dialkylamines, PEG-modified diacylglycerols, PEG-modified dialkylglycerols, and mixtures thereof. For example, a PEG lipid may be PEG-c-DOMG, PEG-DMG, PEG_{2000}-c-DMG, PEG-DLPE, PEG-DMPE, PEG-DPPC, PEG-DMA or a PEG-DSPE lipid.

[00553] Non-exhaustive and non-limiting examples of PEG lipids include:

[00554]

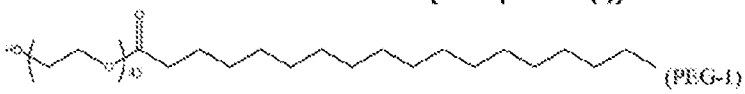


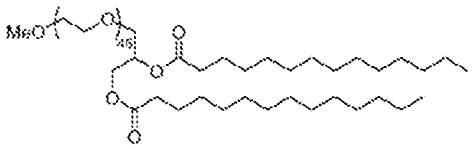
[00555] PEG-C-DMA

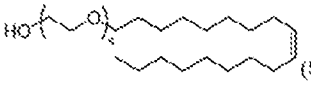


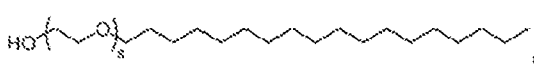
PEG Stearate (Compound (I))

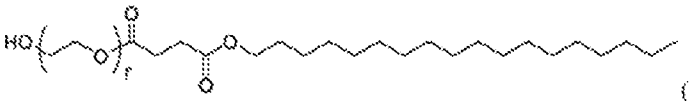
[00556]


(PEG-1)

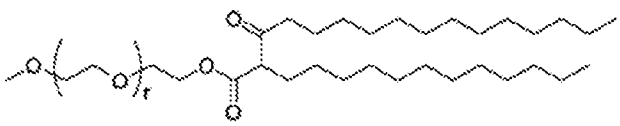

(PEG-2),


(S-1b),


(S-1a),


(L1),

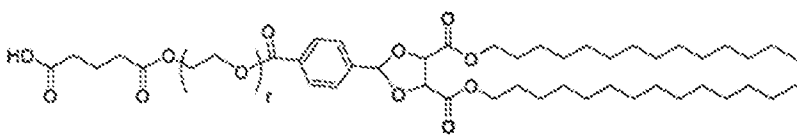

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(L20),

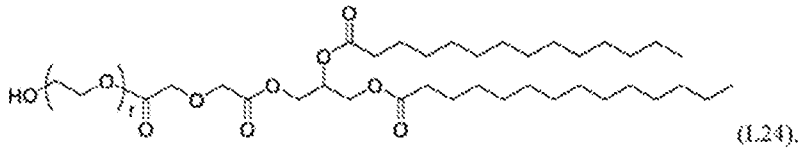
[00557]


(L35),


(L36),

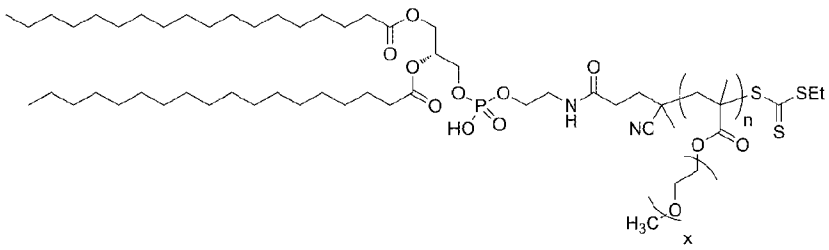

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[00558]

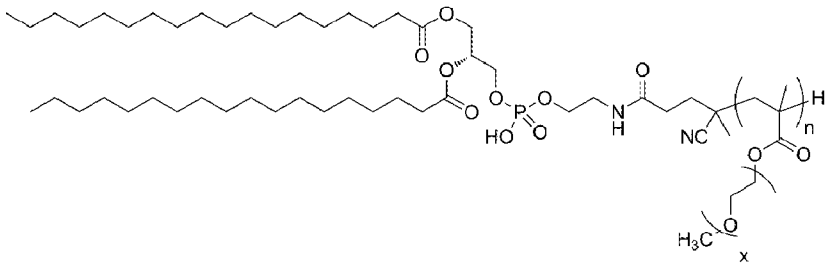


(I.24).

[00559]



(IIa),



(IIb),

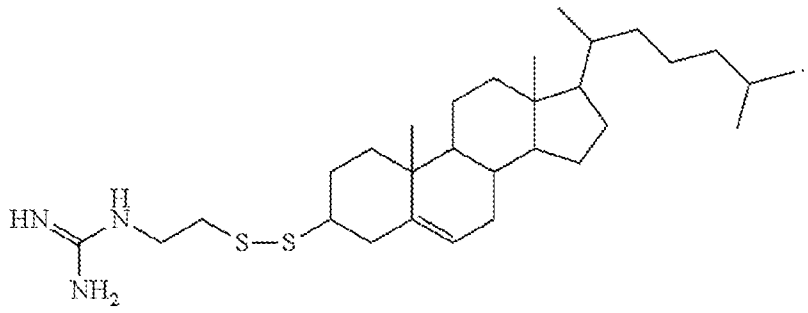
[00560]

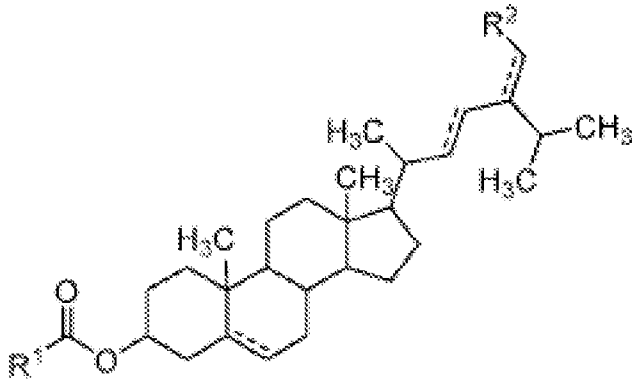
[00561] Structural Lipids/Sterols

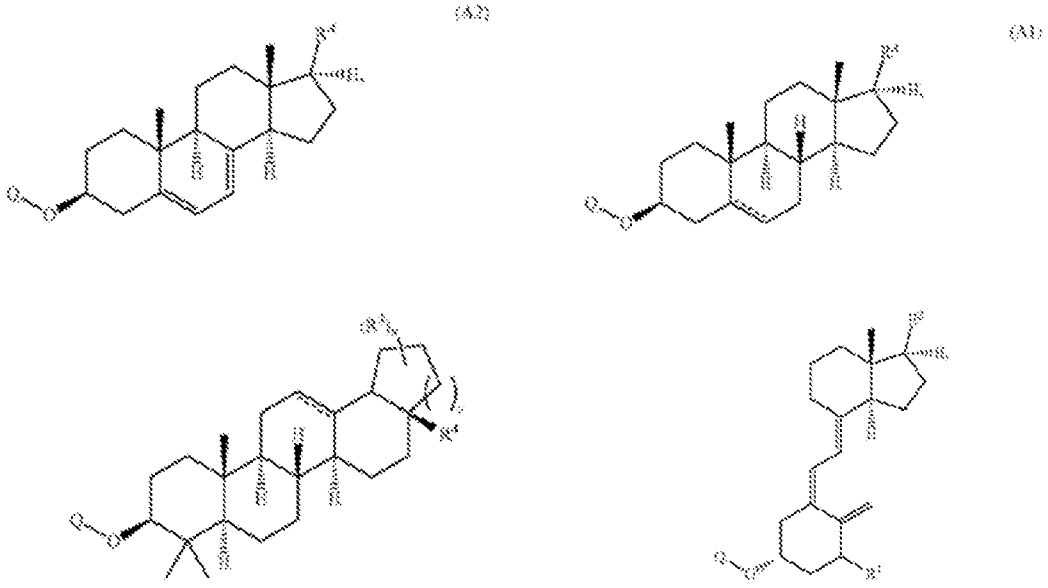
[00562] In some embodiments, the LNP further comprises a structural component. See generally Patel, S., et al. (2020). Nature Communications, 11(1), 1-13. In some embodiments, the structural component comprises a sterol including, but not limited to, a sterol selected from the group consisting of cholesterol, fecosterol, stigmasterol, stigmastanol, sitosterol, β-sitosterol, lupeol, betulin, ursolic acid, oleanolic acid, campesterol, fucosterol, brassicasterol, ergosterol, 9, 11-dehydroergosterol, tomatidine, tomatine, α-tocopherol, and mixtures thereof. In other embodiments, the structural lipid includes cholesterol and a corticosteroid (e.g., prednisolone, dexamethasone, prednisone, and hydrocortisone), or a combination thereof.

[00563] Non-exhaustive and non-limiting examples of structural lipids include:

(HGT4002)

[00564] 

[00565] 

[00566] 

[00567] Formulations

[00568] Nanoparticle compositions may include a lipid component and one or more additional components, such as a therapeutic and/or prophylactic. A nanoparticle composition may be designed for one or more specific applications or targets. The elements of a nanoparticle composition may be selected based on a particular application or target, and/or

based on the efficacy, toxicity, expense, ease of use, availability, or other feature of one or more elements. Similarly, the particular formulation of a nanoparticle composition may be selected for a particular application or target according to, for example, the efficacy and toxicity of particular combinations of elements.

[00569] The lipid component of a nanoparticle composition may include, for example, a cationic lipid, a phospholipid (such as an unsaturated lipid, e.g., DOPE or DSPC), a PEG lipid, and a structural lipid. The elements of the lipid component may be provided in specific fractions.

[00570] In some embodiments, the lipid component of a nanoparticle composition includes an ionizable lipid, a phospholipid, a PEG lipid, and a structural lipid. In certain embodiments, the lipid com-ponent of the nanoparticle composition includes about 30 mol % to about 60 mol % ionizable lipid, about 0 mol % to about 30 mol % phospholipid, about 0 mol % to about 10 mol % of PEG lipid, and about 17.5 mol % to about 50 mol % structural lipid, provided that the total mol % does not exceed 100%. In some embodiments, the lipid component of the nanoparticle composition includes about 35 mol % to about 55 mol % compound of ionizable lipid, about 5 mol % to about 25 mol % phospholipid, about 0 mol % to about 10 mol % of PEG lipid, and about 30 mol % to about 40 mol % structural lipid. In a particular embodiment, the lipid component includes about 50 mol % said compound, about 10 mol % phospholipid, about 38.5 mol % structural lipid, and about 1.5 mol % of PEG lipid. In another embodiment, the lipid component includes about 40 mol % said compound, about 20 mol % phospholipid, about 38.5 mol % structural lipid, and about 1.5 mol % of PEG lipid. In some embodiments, the phospholipid may be DOPE or DSPC. In other embodiments, the PEG lipid may be PEG-DMG and/or the structural lipid may be cholesterol.

[00571] In some embodiments, the ionizable lipids comprise between about 20 and about 60 mol % of the lipid component. In other embodiments, the ionizable lipids comprise between about 35 and about 55 mol % of the lipid component. In various embodiments, the ionizable lipids comprise about 20, 21, 22, 23, 24, 25, 26, 27, 28, 29, 30, 35, 40, 45, 50, 55, or 60 mol % of the lipid component.

[00572] In some embodiments, the neutral lipids comprise between about 0 and about 30 mol % of the lipid component. In other embodiments, the neutral lipids comprise between about 5 and about 25 mol % of the lipid component. In various embodiments, the neutral

lipids comprise about 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 25, or 30 mol % of the lipid component.

[00573] In some embodiments, the polymer-conjugated lipids comprise between about 0 and about 15 mol % of the lipid component. In other embodiments, the polymer-conjugated lipids comprise between about 0.5 and about 10 mol % of the lipid component. In various embodiments, the polymer-conjugated lipids comprise about 0.5, 1, 1.5, 2, 2.5, 3, 3.5, 4, 4.5, 5, 5.5, 6, 6.5, 7, 7.5, 8, 8.5 9, 9.5, 10, or 15 mol % of the lipid component.

[00574] In some embodiments, the structural component comprises about 17.5 mol % to about 50 mol % of the lipid component. In other embodiments, the structural component comprises about 30 to about 40 mol % of the lipid component. In various embodiments, the structural component comprises about 17.5, 20, 22.5, 25, 27.5, 30, 31, 32, 33, 34, 35, 36, 37, 38, 39, 40, 41, 42, 43, 44, 45, 46, 47, 48, 49, or 50 mol % of the lipid component.

[00575] The structural component may alternatively be expressed as a ratio relative to the lipid component. In some embodiments, the structural component is in a ratio of about 1:1 with the lipid component (sterol:lipids). In other embodiments, the structural component is in a ratio of about 1:5 with the lipid component (sterol:lipids). In various embodiments, the structural component is in a ratio of about 1:1, 1:2, 1:3, 1:4, 1:5, 1:6, 1:7, 1:8, 1:9, 1:10, 1:15, 1:20, or 1:25 with the lipid component (sterol:lipids).

[00576] Nanoparticle compositions may be designed for one or more specific applications or targets. For example, a nanoparticle composition may be designed to deliver a therapeutic and/or prophylactic such as an RNA to a particular cell, tissue, organ, or system or group thereof in a mammal's body. Physiochemical properties of nanoparticle compositions may be altered in order to increase selectivity for particular bodily targets. For instance, particle sizes may be adjusted based on the fenestration sizes of different organs. The therapeutic and/or prophylactic included in a nanoparticle composition may also be selected based on the desired delivery target or tar-gets. For example, a therapeutic and/or prophylactic may be selected for a particular indication, condition, disease, or disorder and/or for delivery to a particular cell, tissue, organ, or system or group thereof (e.g., localized or specific delivery). In certain embodiments, a nanoparticle com-position may include an mRNA encoding a polypeptide of interest capable of being translated within a cell to produce the polypeptide of interest. Such a composition may be designed to be specifically delivered to a particular

organ. In some embodiments, a composition may be de-signed to be specifically delivered to a mammalian joint.

[00577] The amount of a therapeutic and/or prophylactic in a nanoparticle composition may depend on the size, composition, desired target and/or application, or other properties of the nanoparticle composition as well as on the properties of the therapeutic and/or prophylactic. For example, the amount of an RNA useful in a nanoparticle composition may depend on the size, sequence, and other characteristics of the RNA. The relative amounts of a therapeutic and/or prophylactic and other elements (e.g., lipids) in a nanoparticle composition may also vary. In some embodiments, the wt/wt ratio of the lipid component to a therapeutic and/or prophylactic in a nanoparticle composition may be from about 5:1 to about 60:1, such as 5:1, 6:1, 7:1, 8:1, 9:1, 10:1, 11:1, 12:1, 13:1, 14:1, 15:1, 16:1, 17:1, 18:1, 19:1, 20:1, 25:1, 30:1, 35:1, 40:1, 45:1, 50:1, and 60:1. For example, the wt/wt ratio of the lipid component to a therapeutic and/or prophylactic may be from about 10:1 to about 40:1. In certain embodiments, the wt/wt ratio is about 20:1. The amount of a therapeutic and/or prophylactic in a nanoparticle composition may, for example, be measured using absorption spectroscopy (e.g., ultraviolet-visible spectroscopy).

[00578] In some embodiments, the therapeutic and/or prophylactic comprises a nucleic acid component. In some embodiments, the nucleic acid component comprises RNA including, but not limited to, RNA selected from the group consisting of messenger RNA (mRNA), CRISPR RNA (crRNA), tracrRNA, single-guide RNA (sgRNA), short interfering RNA (siRNA), antisense oligonucleotides (ASO), and mixtures thereof. In other embodiments, the nucleic acid component comprises DNA including, but not limited to, DNA selected from the group consisting of linear DNA, plasmid DNA, antisense oligonucleotide, and mixtures thereof.

[00579] In some embodiments, a nanoparticle composition includes one or more RNAs, and the one or more RNAs, lipids, and amounts thereof may be selected to provide a specific N:P ratio. The N:P ratio of the composition refers to the molar ratio of nitrogen atoms in one or more lipids to the number of phosphate groups in an RNA. In general, a lower N:P ratio is preferred. The one or more RNA, lipids, and amounts thereof may be selected to provide an N:P ratio from about 2:1 to about 30:1, such as 2:1, 3:1, 4:1, 5:1, 6:1, 7:1, 8:1, 9:1, 10:1, 12:1, 14:1, 16:1, 18:1, 20:1, 22:1, 24:1, 26:1, 28:1, or 30:1. In certain embodiments, the N:P ratio may be from about 2:1 to about 8:1. In other embodiments, the N:P ratio is from about 5:1 to

about 8:1. For example, the N:P ratio may be about 5.0:1, about 5.5:1, about 5.67:1, about 6.0:1, about 6.5:1, or about 7.0:1. For example, the N:P ratio may be about 5.67:1.

[00580] In some embodiments, the nucleic acid component is comprised of a modified nucleic acid. For example, an RNA may be a modified RNA. That is, an RNA may include one or more nucleobases, nucleosides, nucleotides, or linkers that are non-naturally occurring. A "modified" species may also be referred to herein as an "altered" species. Species may be modified or altered chemically, structurally, or functionally. For example, a modified nucleobase species may include one or more substitutions that are not naturally occurring.

[00581] In certain embodiments, the present disclosure comprises methods for treating back or spine conditions or disorders. In other embodiments, the present disclosure comprises methods for treating discogenic disorders. In some embodiments, the present disclosure comprises methods for treating localized nociception, inflammation, or morphological changes associated with back or spine conditions or disorders in a subject in need thereof, the method comprising administering a therapeutically effective amount of a CRISPR-Cas composition encapsulated within or associated with a lipid nanoparticle (LNP), wherein the composition comprises one or more non-naturally occurring polynucleotides encoding a Cas9 protein and at least one sgRNA. In some embodiments, LNPs are administered intradiscally. In other embodiments, LNPs are administered epidurally. In some embodiments, LNPs are administered peridiscally. In some embodiments, LNPs are administered perivertebrally.

[00582] Physical Properties

[00583] The characteristics of a nanoparticle composition may depend on the components thereof. For example, a nanoparticle composition including cholesterol as a structural lipid may have different characteristics than a nanoparticle composition that includes a different structural lipid. Similarly, the characteristics of a nanoparticle composition may depend on the absolute or relative amounts of its components. For instance, a nanoparticle composition including a higher molar fraction of a phospholipid may have different characteristics than a nanoparticle composition including a lower molar fraction of a phospholipid. Characteristics may also vary depending on the method and conditions of preparation of the nanoparticle composition.

[00584] Nanoparticle compositions may be characterized by a variety of methods. For example, microscopy (e.g., transmission electron microscopy or scanning electron

microscopy) may be used to examine the morphology and size distribution of a nanoparticle composition. Dynamic light scattering or potentiometry (e.g., potentiometric titrations) may be used to measure zeta potentials. Dynamic light scattering may also be utilized to determine particle sizes. Instruments such as the Zetasizer Nano ZS (Malvern Instruments Ltd, Malvern, Worcestershire, UK) may also be used to measure multiple characteristics of a nanoparticle composition, such as particle size, polydispersity index, and zeta potential.

[00585] The mean size of a nanoparticle composition may be between 10 nm and 1 micrometer, e.g., measured by dynamic light scattering (DLS). For example, the mean size may be from about 40 nm to about 150 nm, such as about 40 nm, 45 nm, 50 nm, 55 nm, 60 nm, 65 nm, 70 nm, 75 nm, 80 nm, 85 nm, 90 nm, 95 nm, 100 nm, 105 nm, 110 nm, 115 nm, 120 nm, 125 nm, 130 nm, 135 nm, 140 nm, 145 nm, or 150 nm. In some embodiments, the mean size of a nanoparticle composition may be from about 50 nm to about 100 nm, from about 50 nm to about 90 nm, from about 50 nm to about 80 nm, from about 50 nm to about 70 nm, from about 50 nm to about 60 nm, from about 60 nm to about 100 nm, from about 60 nm to about 90 nm, from about 60 nm to about 80 nm, from about 60 nm to about 70 nm, from about 70 nm to about 100 nm, from about 70 nm to about 90 nm, from about 70 nm to about 80 nm, from about 80 nm to about 100 nm, from about 80 nm to about 90 nm, or from about 90 nm to about 100 nm. In certain embodiments, the mean size of a nanoparticle composition may be from about 70 nm to about 100 nm. In a particular embodiment, the mean size may be about 80 nm. In other embodiments, the mean size may be about 100 nm.

[00586] A nanoparticle composition may be relatively homogenous. A polydispersity index may be used to indicate the homogeneity of a nanoparticle composition, e.g., the particle size distribution of the nanoparticle compositions. A small (e.g., less than 0.3) polydispersity index generally indicates a narrow particle size distribution. A nanoparticle composition may have a polydispersity index from about 0 to about 0.25, such as 0.01, 0.02, 0.03, 0.04, 0.05, 0.06, 0.07, 0.08, 0.09, 0.10, 0.11, 0.12, 0.13, 0.14, 0.15, 0.16, 0.17, 0.18, 0.19, 0.20, 0.21, 0.22, 0.23, 0.24, or 0.25. In some embodiments, the polydispersity index of a nanoparticle composition may be from about 0.10 to about 0.20.

[00587] The zeta potential of a nanoparticle composition may be used to indicate the electrokinetic potential of the composition. For example, the zeta potential may describe the surface charge of a nanoparticle composition. Nanoparticle compositions with relatively low charges, positive or negative, are generally desirable, as more highly charged species may interact undesirably with cells, tissues, and other elements in the body. In some embodiments,

the zeta potential of a nanoparticle composition may be from about -10 mV to about +20 mV, from about -10 mV to about +15 mV, from about -10 mV to about +10 mV, from about -10 mV to about +5 mV, from about -10 mV to about 0 mV, from about -10 mV to about -5 mV, from about -5 mV to about +20 mV, from about -5 mV to about +15 mV, from about -5 mV to about +10 mV, from about -5 mV to about +5 mV, from about -5 mV to about 0 mV, from about 0 mV to about +20 mV, from about 0 mV to about +15 mV, from about 0 mV to about +10 mV, from about 0 mV to about +5 mV, from about +5 mV to about +20 mV, from about +5 mV to about +15 mV, or from about +5 mV to about +10 mV.

[00588] The efficiency of encapsulation of a therapeutic and/or prophylactic describes the amount of therapeutic and/or prophylactic that is encapsulated or otherwise associated with a nanoparticle composition after preparation, relative to the initial amount provided. The encapsulation efficiency is desirably high (e.g., close to 100%). The encapsulation efficiency may be measured, for example, by comparing the amount of therapeutic and/or prophylactic in a solution containing the nanoparticle composition before and after breaking up the nanoparticle composition with one or more organic solvents or detergents. Fluorescence may be used to measure the amount of free therapeutic and/or prophylactic (e.g., RNA) in a solution. For the nanoparticle compositions described herein, the encapsulation efficiency of a therapeutic and/or prophylactic may be at least 50%, for example 50%, 55%, 60%, 65%, 70%, 75%, 80%, 85%, 9 0%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100%. In some embodiments, the encapsulation efficiency may be at least 80%. In certain embodiments, the encapsulation efficiency may be at least 90%.

[00589] A nanoparticle composition may optionally comprise one or more coatings. For example, a nanoparticle composition may be formulated in a capsule, film, or tablet having a coating. A capsule, film, or tablet including a composition described herein may have any useful size, tensile strength, hardness, or density.

[00590] Unless otherwise defined, all technical and scientific terms used herein have the same meaning as commonly understood by one of ordinary skill in the art to which this disclosure belongs. Although methods and materials similar or equivalent to those described herein may be used in the practice or testing of the present disclosure, suitable methods and materials are described below. All publications, patent applications, patents, and other references mentioned herein are incorporated by reference in their entirety. In addition, the materials, methods, and examples are illustrative only and not intended to be limiting.

[00591] In some embodiments, the CRISPR gene-editing system comprises one or more RNA-containing compositions. In some embodiments, the CRISPR gene-editing system further comprises one or more nanoparticles. In some embodiments, said one or more RNA-containing compositions comprises a guide RNA. In some embodiments, said one or more RNA-containing compositions comprises an mRNA. In some embodiments, said one or more RNA-containing compositions comprises an RNP (e.g., Cas9 and a guide RNA). In some embodiments, said one or more nanoparticles are lipid nanoparticles (LNP).

[00592] In some embodiments, the CRISPR gene-editing system comprises one or more LNPs collectively encapsulating (i) the RNA-guided nuclease or the nucleic acid encoding the RNA-guided nuclease and (ii) the at least one guide RNA or the nucleic acid encoding the at least one guide RNA. In some embodiments, the one or more LNPs comprises a first plurality of LNP encapsulating the RNA-guided nuclease or a nucleic acid encoding an RNA-guided nuclease and a second plurality of LNP encapsulating the at least one guide RNA or a nucleic acid encoding at least one guide RNA.

[00593] In some embodiments, the one or more LNP comprises a component selected from the group consisting of 3-(didodecylamino)-N1,N1,4-tridodecyl-1-piperazineethanamine (KL10), N1-[2-(didodecylamino)ethyl]-N1,N4,N4-tridodecyl-1,4-piperazinediethanamine (KL22), 14,25-ditridecyl-15,18,21,24-tetraaza-octatriacontane (KL25), 1,2-dilinoleyloxy-N,N-dimethylaminopropane (DLin-DMA), 2,2-dilinoleyl-4-dimethylaminomethyl-[1,3]-dioxolane (DLin-K-DMA), heptatriaconta-6,9,28,31-tetraen-19-yl 4-(dimethylamino)butanoate (DLin-MC3-DMA), 2,2-dilinoleyl-4-(2-dimethylaminoethyl)-[1,3]-dioxolane (DLin-KC2-DMA), 1,2-dioleyloxy-N,N-dimethylaminopropane (DODMA), 2-({8-[(3.beta.)-cholest-5-en-3-yloxy]octyl}oxy)-N,N-dimethyl-3-[(9Z,12Z)- -octadeca-9,12-dien-1-yloxy]propan-1-amine (Octyl-CLinDMA), (2R)-2-({8-[(3.beta.)-cholest-5-en-3-yloxy]octyl}oxy)-N,N-dimethyl-3-[(9Z- ,12Z)-octadeca-9,12-dien-1-yloxy]propan-1-amine (Octyl-CLinDMA (2R)), (2S)-2-({8-[(3.beta.)-cholest-5-en-3-yloxy]octyl}oxy)-N,N-dimethyl-3-[(9Z- ,12Z)-octadeca-9,12-dien-1-yloxy]propan-1-amine (Octyl-CLinDMA (2S)), a lipid including a cyclic amine group, and a mixture thereof.

[00594] In some embodiments, the one or more LNP comprises a component selected from the group consisting of 1,2-dilinoleoyl-sn-glycero-3-phosphocholine (DLPC), 1,2-dimyristoyl-sn-glycero-phosphocholine (DMPC), 1,2-dioleoyl-sn-glycero-3-phosphocholine (DOPC), 1,2-dipalmitoyl-sn-glycero-3-phosphocholine (DPPC), 1,2-distearoyl-sn-glycero-3-phosphocholine (DSPC), 1,2-diundecanoyl-sn-glycero-phosphocholine (DUPC), 1-palmitoyl-

2-oleoyl-sn-glycero-3-phosphocholine (POPC), 1,2-di-O-octadecenyl-sn-glycero-3-phosphocholine (18:0 Diether PC), 1-oleoyl-2-cholesterylhemisuccinoyl-sn-glycero-3-phosphocholine (OChemsPC), 1-hexadecyl-sn-glycero-3-phosphocholine (C16 Lyso PC), 1,2-dilinolenoyl-sn-glycero-3-phosphocholine, 1,2-diarachidonoyl-sn-glycero-3-phosphocholine, 1,2-didocosahexaenoyl-sn-glycero-3-phosphocholine, 1,2-dioleoyl-sn-glycero-3-phosphoethanolamine (DOPE), 1,2-diphytanoyl-sn-glycero-3-phosphoethanolamine (ME 16.0 PE), 1,2-distearoyl-sn-glycero-3-phosphoethanolamine, 1,2-dilinoleoyl-sn-glycero-3-phosphoethanolamine, 1,2-dilinolenoyl-sn-glycero-3-phosphoethanolamine, 1,2-diarachidonoyl-sn-glycero-3-phosphoethanolamine, 1,2-didocosahexaenoyl-sn-glycero-3-phosphoethanolamine, 1,2-dioleoyl-sn-glycero-3-phospho-rac-(1-glycerol) sodium salt (DOPG), sphingomyelin (SM), and a mixture thereof.

[00595] In some embodiments, the one or more LNP comprises a component selected from the group consisting of PEG-modified phosphatidylethanolamines, PEG-modified phosphatidic acids, PEG-modified ceramides, PEG-modified dialkylamines, PEG-modified diacylglycerols, PEG-modified dialkylglycerols, and mixtures thereof. For example, a PEG lipid may be PEG-c-DOMG, PEG-DMG, PEG-DLPE, PEG-DMPE, PEG-DPPC, PEG-DMA, a PEG-DSPE lipid, and a mixture thereof.

[00596] In some embodiments, the one or more LNP comprises a component selected from the group consisting of a cholesterol, fecosterol, stigmasterol, stigmastanol, sitosterol, β-sitosterol, lupeol, betulin, ursolic acid, oleanolic acid, campesterol, fucosterol, brassicasterol, ergosterol, 9, 11-dehydroergosterol, tomatidine, tomatine, α-tocopherol, and a mixture thereof.

[00597] In some embodiments, use of the CRISPR gene-editing system further comprising one or more LNPs to target a gene selected from IL1R1, IL1RAP, TGFBR1, TGFBR2, IL6R, IL6ST, TNFRSF1A, TNFRSF1B, TNFRSF3, TNFRSF4, TNFRSF11A, and combinations thereof is therapeutic.

[00598] In some aspect, use of the CRISPR gene-editing system further comprising one or more LNPs to target TGFBR1 and/or TGFBR2 is therapeutic. In some embodiments, use of the system treats one or more joint disease or illness or one or more back or spine conditions or disorders. In some embodiments, use of the system treats one or more musculoskeletal diseases, conditions, and illnesses, including, but not limited to, Loeys-Dietz Syndrome, osteoarthritis, Marfan syndrome, aortic aneurysm (e.g., familial thoracic 3 aortic aneurysm),

craniofacial abnormalities, and combinations thereof. In other embodiments, use of the system treats neoplastic diseases, conditions, and illnesses, including, but not limited to, pancreatic cancer, multiple self-healing squamous epithelioma (Ferguson-Smith disease), gastrointestinal stromal tumors (GIST), hereditary nonpolyposis colorectal cancer (Lynch Syndrome), metastatic colorectal carcinoma, bone neoplasms, anaplastic carcinoma, spindle-cell carcinoma, lung neoplasms, brain neoplasms, and combinations thereof.

[00599] In some embodiments, the CRISPR gene-editing system further comprising one or more LNPs to target IL1R1 and/or IL1RAP is therapeutic. In some embodiments, use of the system treats one or more joint disease or illness or one or more back or spine conditions or disorders. In some embodiments, use of the system treats one or more musculoskeletal diseases, conditions, and illnesses, including, but not limited to, rheumatoid arthritis, gout, osteoarthritis, osteoporosis, intervertebral disc disease (IVDD), psoriatic arthritis, arthritis, polymyositis, proliferative synovitis, bone neoplasms, sarcoid myopathy, cortex bone disorders, idiopathic scoliosis, tendinopathy, myofibrillar myopathy, enthesis-related arthritis, ankylosing spondylitis, degenerative polyarthritis, arthropathy, osteitis deformans, prolapsed lumbar disc, polymyositis ossificans, idiopathic polymyositis, Luft Disease, adult-onset Still's Disease, osteoarthritis deformans, Bachet's Disease, and combinations thereof. In other embodiments, use of the system treats one or more neoplastic diseases, conditions, and illnesses, including, but not limited to, osteosarcoma, multiple myeloma, lymphoma(e.g., B-cell or cutaneous T-cell lymphoma), leukemia, thyroid carcinoma, glioma, renal cell carcinoma, chondrosarcoma, glioblastoma, melanoma, neuroblastoma, polycystic ovary syndrome, Kaposi sarcoma, squamous cell carcinoma, leiomyosarcoma, malignant peripheral nerve sheath tumor, Ewing's sarcoma, esophageal neoplasms, colon cancer, lung cancer, breast cancer, pancreatic cancer, stomach cancer, epithelial ovarian cancer, cholectoral cancer, liver cancer, skin cancer, prostate cancer, cervical cancer, ovarian cancer, bladder cancer, oral cavity cancer, and combinations thereof. In other embodiments, use of the system treats one or more inflammatory diseases, conditions, and illnesses, including, but not limited to, autoinflammatory disease (AID), cryopyrin-associated periodic syndrome (CAPS), systemic lupus erythematosus (SLE), inflammatory bowel disease (IBD) and combinations thereof. In some embodiments, use of the system treats one or more cardiac diseases, conditions, and illnesses, including, but not limited to, myocardial infarction, heart failure (e.g., refractory or acute decompensated heart failure), arrythmias, pericarditis (e.g., refractory idiopathic pericarditis), myocarditis, sepsis-induced cardiomyopathy,

atherosclerosis, coronary artery disease and combinations thereof. In some embodiments, use of the system treats one or more neurological diseases, conditions, and illnesses, including, but not limited to, acute thrombotic stroke, epilepsy, multiple sclerosis, Alzheimer's Disease and combinations thereof. In some embodiments, use of the system treats one or more ophthalmic diseases, conditions, and illnesses, including, but not limited to, uveitis, scleritis, Sjogren asthenia, dry eye and combinations thereof. In some embodiments, use of the system treats one or more diseases, conditions, and illnesses, including, but not limited to, chronic kidney disease, Type 2 diabetes, gastroesophageal reflux disease (GERD), non-HP-associated peptic ulcer disease, and pulmonary fibrosis.

C. Virus-like particles

[00600] In one aspect, the present disclosure encompasses means for delivering a CRISPR gene-editing system to a mammalian cell via a virus-like particle (VLP). In some embodiments, a CRISPR gene-editing system is delivered by a VLP. Without wishing to be bound by any particular theory, in certain embodiments, nucleic acids, when present in the particle, are resistant in aqueous solution to degradation with a nuclease. In other embodiments, proteins are protected from protease degradation while present in the particle. In some embodiments, proteins and nucleic acids encapsulated by VLPs are capable of penetrating the cellular plasma membrane.

[00601] In some embodiments, the CRISPR gene-editing system comprises one or more RNA-containing compositions. In some embodiments, the CRISPR gene-editing system further comprises one or more VLPs. In some embodiments, said one or more RNA-containing compositions comprises a guide RNA. In some embodiments, said one or more RNA-containing compositions comprises an mRNA. In some embodiments, said one or more RNA-containing compositions comprises an RNP (e.g., Cas9 and a guide RNA).

[00602] In some embodiments, the CRISPR gene-editing system comprises one or more virus-like particles collectively encapsulating (i) the RNA-guided nuclease or the nucleic acid encoding the RNA-guided nuclease and (ii) the at least one guide RNA or the nucleic acid encoding the at least one guide RNA. In some embodiments, the one or more virus-like particles comprises a first plurality of virus-like particles encapsulating the RNA-guided nuclease or a nucleic acid encoding an RNA-guided nuclease and a second plurality of virus-

like particles encapsulating the at least one guide RNA or a nucleic acid encoding at least one guide RNA.

[00603] In some embodiments, use of the CRISPR gene-editing system further comprising one or more LNPs to target a gene selected from IL1R1, IL1RAP, TGFBR1, TGFBR2, IL6R, IL6ST, TNFRSF1A, TNFRSF1B, TNFRSF3, TNFRSF4, TNFRSF11A, and combinations thereof is therapeutic.

[00604] In one aspect, use of the CRISPR gene-editing system further comprising one or more VLPs to target TGFBR1 and/or TGFBR2 is therapeutic. In some embodiments, use of the system treats one or more joint disease or illness or one or more back or spine conditions or disorders. In some embodiments, use of the system treats one or more musculoskeletal diseases, conditions, and illnesses, including, but not limited to, Loeys-Dietz Syndrome, osteoarthritis, Marfan syndrome, aortic aneurysm (e.g., familial thoracic 3 aortic aneurysm), craniofacial abnormalities, and combinations thereof. In other embodiments, use of the system treats neoplastic diseases, conditions, and illnesses, including, but not limited to, pancreatic cancer, multiple self-healing squamous epithelioma (Ferguson-Smith disease), gastrointestinal stromal tumors (GIST), hereditary nonpolyposis colorectal cancer (Lynch Syndrome), metastatic colorectal carcinoma, bone neoplasms, anaplastic carcinoma, spindle-cell carcinoma, lung neoplasms, brain neoplasms, and combinations thereof.

[00605] In some embodiments, the CRISPR gene-editing system further comprising one or more VLPs to target IL1R1 and/or IL1RAP is therapeutic. In some embodiments, use of the system treats one or more joint disease or illness or one or more back or spine conditions or disorders. In some embodiments, use of the system treats one or more musculoskeletal diseases, conditions, and illnesses, including, but not limited to, rheumatoid arthritis, gout, osteoarthritis, osteoporosis, intervertebral disc disease (IVDD), psoriatic arthritis, arthritis, polymyositis, proliferative synovitis, bone neoplasms, sarcoid myopathy, cortex bone disorders, idiopathic scoliosis, tendinopathy, myofibrillar myopathy, enthesis-related arthritis, ankylosing spondylitis, degenerative polyarthritis, arthropathy, osteitis deformans, prolapsed lumbar disc, polymyositis ossificans, idiopathic polymyositis, Luft Disease, adult-onset Still's Disease, osteoarthritis deformans, Bachet's Disease, and combinations thereof. In other embodiments, use of the system treats one or more neoplastic diseases, conditions, and illnesses, including, but not limited to, osteosarcoma, multiple myeloma, lymphoma(e.g., B-cell or cutaneous T-cell lymphoma), leukemia, thyroid carcinoma, glioma, renal cell carcinoma, chondrosarcoma, glioblastoma, melanoma, neuroblastoma, polycystic ovary

syndrome, Kaposi sarcoma, squamous cell carcinoma, leiomyosarcoma, malignant peripheral nerve sheath tumor, Ewing's sarcoma, esophageal neoplasms, colon cancer, lung cancer, breast cancer, pancreatic cancer, stomach cancer, epithelial ovarian cancer, cholectoral cancer, liver cancer, skin cancer, prostate cancer, cervical cancer, ovarian cancer, bladder cancer, oral cavity cancer, and combinations thereof. In other embodiments, use of the system treats one or more inflammatory diseases, conditions, and illnesses, including, but not limited to, autoinflammatory disease (AID), cryopyrin-associated periodic syndrome (CAPS), systemic lupus erythematosus (SLE), inflammatory bowel disease (IBD) and combinations thereof. In some embodiments, use of the system treats one or more cardiac diseases, conditions, and illnesses, including, but not limited to, myocardial infarction, heart failure (e.g., refractory or acute decompensated heart failure), arrythmias, pericarditis (e.g., refractory idiopathic pericarditis), myocarditis, sepsis-induced cardiomyopathy, atherosclerosis, coronary artery disease and combinations thereof. In some embodiments, use of the system treats one or more neurological diseases, conditions, and illnesses, including, but not limited to, acute thrombotic stroke, epilepsy, multiple sclerosis, Alzheimer's Disease and combinations thereof. In some embodiments, use of the system treats one or more ophthalmic diseases, conditions, and illnesses, including, but not limited to, uveitis, scleritis, Sjogren asthenia, dry eye and combinations thereof. In some embodiments, use of the system treats one or more diseases, conditions, and illnesses, including, but not limited to, chronic kidney disease, Type 2 diabetes, gastroesophageal reflux disease (GERD), non-HP-associated peptic ulcer disease, and pulmonary fibrosis.

D. Miscellaneous modes of delivery

1. Liposomes

[00606] In some embodiments, nucleic acids encoding a CRISPR gene-editing system targeting a gene selected from IL1R1, IL1R2, IL1RAP, IL1RL1, TGFBR1, TGFBR2, IL6R, IL6ST, TNFRSF1A, TNFRSF1B, TNFRSF3, TNFRSF4, TNFRSF11A, and combinations thereof (e.g., Cas9 or gRNA) are entrapped in liposomes bearing positive charges on their surface (e.g., lipofectins), which can be tagged with antibodies against cell surface antigens of the target cells. These delivery vehicles can also be used to deliver Cas9 protein/gRNA complexes.

[00607] In some embodiments, the CRISPR gene-editing system comprises one or more RNA-containing compositions. In some embodiments, the CRISPR gene-editing system further comprises one or more liposomes. In some embodiments, said one or more RNA-containing compositions comprises a guide RNA. In some embodiments, said one or more RNA-containing compositions comprises an mRNA. In some embodiments, said one or more RNA-containing compositions comprises an RNP (e.g., Cas9 and a guide RNA).

[00608] In some embodiments, wherein the composition comprises one or more liposomes collectively encapsulating (i) the RNA-guided nuclease or the nucleic acid encoding the RNA-guided nuclease and (ii) the at least one guide RNA or the nucleic acid encoding the at least one guide RNA. In some embodiments, the one or more liposomes comprises a first plurality of liposomes encapsulating the RNA-guided nuclease or a nucleic acid encoding an RNA-guided nuclease and a second plurality of liposomes encapsulating the at least one guide RNA or a nucleic acid encoding at least one guide RNA.

[00609] In some embodiments, use of the CRISPR gene-editing system further comprising one or more LNPs to target a gene selected from IL1R1, IL1RAP, TGFBR1, TGFBR2, IL6R, IL6ST, TNFRSF1A, TNFRSF1B, TNFRSF3, TNFRSF4, TNFRSF11A, and combinations thereof is therapeutic.

[00610] In one aspect, use of the CRISPR gene-editing system further comprising one or more liposomes to target TGFBR1 and/or TGFBR2 is therapeutic. In some embodiments, use of the system treats one or more joint disease or illness or one or more back or spine conditions or disorders. In some embodiments, use of the system treats one or more musculoskeletal diseases, conditions, and illnesses, including, but not limited to, Loeys-Dietz Syndrome, osteoarthritis, Marfan syndrome, aortic aneurysm (e.g., familial thoracic 3 aortic aneurysm), craniofacial abnormalities, and combinations thereof. In other embodiments, use of the system treats neoplastic diseases, conditions, and illnesses, including, but not limited to, pancreatic cancer, multiple self-healing squamous epithelioma (Ferguson-Smith disease), gastrointestinal stromal tumors (GIST), hereditary nonpolyposis colorectal cancer (Lynch Syndrome), metastatic colorectal carcinoma, bone neoplasms, anaplastic carcinoma, spindle-cell carcinoma, lung neoplasms, brain neoplasms, and combinations thereof.

[00611] In some embodiments, the CRISPR gene-editing system further comprising one or more liposomes to target IL1R1 and/or IL1RAP is therapeutic. In some embodiments, use of the system treats one or more joint disease or illness or one or more back or spine conditions

or disorders. In some embodiments, use of the system treats one or more musculoskeletal diseases, conditions, and illnesses, including, but not limited to, rheumatoid arthritis, gout, osteoarthritis, osteoporosis, intervertebral disc disease (IVDD), psoriatic arthritis, arthritis, polymyositis, proliferative synovitis, bone neoplasms, sarcoid myopathy, cortex bone disorders, idiopathic scoliosis, tendinopathy, myofibrillar myopathy, enthesis-related arthritis, ankylosing spondylitis, degenerative polyarthritis, arthropathy, osteitis deformans, prolapsed lumbar disc, polymyositis ossificans, idiopathic polymyositis, Luft Disease, adult-onset Still's Disease, osteoarthritis deformans, Bachet's Disease, and combinations thereof. In other embodiments, use of the system treats one or more neoplastic diseases, conditions, and illnesses, including, but not limited to, osteosarcoma, multiple myeloma, lymphoma(e.g., B-cell or cutaneous T-cell lymphoma), leukemia, thyroid carcinoma, glioma, renal cell carcinoma, chondrosarcoma, glioblastoma, melanoma, neuroblastoma, polycystic ovary syndrome, Kaposi sarcoma, squamous cell carcinoma, leiomyosarcoma, malignant peripheral nerve sheath tumor, Ewing's sarcoma, esophageal neoplasms, colon cancer, lung cancer, breast cancer, pancreatic cancer, stomach cancer, epithelial ovarian cancer, cholectoral cancer, liver cancer, skin cancer, prostate cancer, cervical cancer, ovarian cancer, bladder cancer, oral cavity cancer, and combinations thereof. In other embodiments, use of the system treats one or more inflammatory diseases, conditions, and illnesses, including, but not limited to, autoinflammatory disease (AID), cryopyrin-associated periodic syndrome (CAPS), systemic lupus erythematosus (SLE), inflammatory bowel disease (IBD) and combinations thereof. In some embodiments, use of the system treats one or more cardiac diseases, conditions, and illnesses, including, but not limited to, myocardial infarction, heart failure (e.g., refractory or acute decompensated heart failure), arrythmias, pericarditis (e.g., refractory idiopathic pericarditis), myocarditis, sepsis-induced cardiomyopathy, atherosclerosis, coronary artery disease and combinations thereof. In some embodiments, use of the system treats one or more neurological diseases, conditions, and illnesses, including, but not limited to, acute thrombotic stroke, epilepsy, multiple sclerosis, Alzheimer's Disease and combinations thereof. In some embodiments, use of the system treats one or more ophthalmic diseases, conditions, and illnesses, including, but not limited to, uveitis, scleritis, Sjogren asthenia, dry eye and combinations thereof. In some embodiments, use of the system treats one or more diseases, conditions, and illnesses, including, but not limited to, chronic kidney disease, Type 2 diabetes, gastroesophageal reflux disease (GERD), non-HP-associated peptic ulcer disease, and pulmonary fibrosis.

2. Lipid nanocrystals (LNC)

[00612] In one aspect, the In one aspect, the present disclosure encompasses means for delivering a CRISPR gene-editing system to a mammalian cell via a lipid nanocrystal (LNC). In some embodiments, a CRISPR gene-editing system is delivered by a LNC. Without wishing to be bound by any particular theory, in certain embodiments, nucleic acids, when present in the nanocrystal, are resistant in aqueous solution to degradation with a nuclease. In other embodiments, proteins are protected from protease degradation while present in the nanocrystal. In some embodiments, proteins and nucleic acids encapsulated by nanocrystal are capable of penetrating the cellular plasma membrane.

[00613] In some embodiments, the CRISPR gene-editing system comprises one or more RNA-containing compositions. In some embodiments, the CRISPR gene-editing system further comprises one or more nanocrystals. In some embodiments, said one or more RNA-containing compositions comprises a guide RNA. In some embodiments, said one or more RNA-containing compositions comprises an mRNA. In some embodiments, said one or more RNA-containing compositions comprises an RNP (e.g., Cas9 and a guide RNA). In some embodiments, said one or more nanocrystals are lipid nanocrystals (LNC).

[00614] In some embodiments, the CRISPR gene-editing system comprises one or more LNCs collectively encapsulating (i) the RNA-guided nuclease or the nucleic acid encoding the RNA-guided nuclease and (ii) the at least one guide RNA or the nucleic acid encoding the at least one guide RNA. In some embodiments, the one or more LNCs comprises a first plurality of LNC encapsulating the RNA-guided nuclease or a nucleic acid encoding an RNA-guided nuclease and a second plurality of LNC encapsulating the at least one guide RNA or a nucleic acid encoding at least one guide RNA.

[00615] In some embodiments, use of the CRISPR gene-editing system further comprising one or more LNPs to target a gene selected from IL1R1, IL1RAP, TGFBR1, TGFBR2, IL6R, IL6ST, TNFRSF1A, TNFRSF1B, TNFRSF3, TNFRSF4, TNFRSF11A, and combinations thereof is therapeutic.

[00616] In one aspect, use of the CRISPR gene-editing system further comprising one or more LNCs to target TGFBR1 and/or TGFBR2 is therapeutic. In some embodiments, use of the system treats one or more joint disease or illness or one or more back or spine conditions or disorders. In some embodiments, use of the system treats one or more musculoskeletal diseases, conditions, and illnesses, including, but not limited to, Loeys-Dietz Syndrome,

osteoarthritis, Marfan syndrome, aortic aneurysm (e.g., familial thoracic 3 aortic aneurysm), craniofacial abnormalities, and combinations thereof. In other embodiments, use of the system treats neoplastic diseases, conditions, and illnesses, including, but not limited to, pancreatic cancer, multiple self-healing squamous epithelioma (Ferguson-Smith disease), gastrointestinal stromal tumors (GIST), hereditary nonpolyposis colorectal cancer (Lynch Syndrome), metastatic colorectal carcinoma, bone neoplasms, anaplastic carcinoma, spindle-cell carcinoma, lung neoplasms, brain neoplasms, and combinations thereof.

[00617] In some embodiments, the CRISPR gene-editing system further comprising one or more LNCs to target IL1R1 and/or IL1RAP is therapeutic. In some embodiments, use of the system treats one or more joint disease or illness or one or more back or spine conditions or disorders. In some embodiments, use of the system treats one or more musculoskeletal diseases, conditions, and illnesses, including, but not limited to, rheumatoid arthritis, gout, osteoarthritis, osteoporosis, intervertebral disc disease (IVDD), psoriatic arthritis, arthritis, polymyositis, proliferative synovitis, bone neoplasms, sarcoid myopathy, cortex bone disorders, idiopathic scoliosis, tendinopathy, myofibrillar myopathy, enthesis-related arthritis, ankylosing spondylitis, degenerative polyarthritis, arthropathy, osteitis deformans, prolapsed lumbar disc, polymyositis ossificans, idiopathic polymyositis, Luft Disease, adult-onset Still's Disease, osteoarthritis deformans, Bachet's Disease, and combinations thereof. In other embodiments, use of the system treats one or more neoplastic diseases, conditions, and illnesses, including, but not limited to, osteosarcoma, multiple myeloma, lymphoma(e.g., B-cell or cutaneous T-cell lymphoma), leukemia, thyroid carcinoma, glioma, renal cell carcinoma, chondrosarcoma, glioblastoma, melanoma, neuroblastoma, polycystic ovary syndrome, Kaposi sarcoma, squamous cell carcinoma, leiomyosarcoma, malignant peripheral nerve sheath tumor, Ewing's sarcoma, esophageal neoplasms, colon cancer, lung cancer, breast cancer, pancreatic cancer, stomach cancer, epithelial ovarian cancer, cholectoral cancer, liver cancer, skin cancer, prostate cancer, cervical cancer, ovarian cancer, bladder cancer, oral cavity cancer, and combinations thereof. In other embodiments, use of the system treats one or more inflammatory diseases, conditions, and illnesses, including, but not limited to, autoinflammatory disease (AID), cryopyrin-associated periodic syndrome (CAPS), systemic lupus erythematosus (SLE), inflammatory bowel disease (IBD) and combinations thereof. In some embodiments, use of the system treats one or more cardiac diseases, conditions, and illnesses, including, but not limited to, myocardial infarction, heart failure (e.g., refractory or acute decompensated heart failure), arrythmias, pericarditis (e.g.,

refractory idiopathic pericarditis), myocarditis, sepsis-induced cardiomyopathy, atherosclerosis, coronary artery disease and combinations thereof. In some embodiments, use of the system treats one or more neurological diseases, conditions, and illnesses, including, but not limited to, acute thrombotic stroke, epilepsy, multiple sclerosis, Alzheimer's Disease and combinations thereof. In some embodiments, use of the system treats one or more ophthalmic diseases, conditions, and illnesses, including, but not limited to, uveitis, scleritis, Sjogren asthenia, dry eye and combinations thereof. In some embodiments, use of the system treats one or more diseases, conditions, and illnesses, including, but not limited to, chronic kidney disease, Type 2 diabetes, gastroesophageal reflux disease (GERD), non-HP-associated peptic ulcer disease, and pulmonary fibrosis.

VII. Pharmaceutical compositions

[00618] In one aspect, the present disclosure encompasses pharmaceutical compositions comprising a CRISPR gene-editing system for treatment of a mammal in need thereof. In some embodiments, the CRISPR gene-editing system targets a gene selected from IL1R1, IL1R2, IL1RAP, IL1RL1, TGFBR1, TGFBR2, IL6R, IL6ST, TNFRSF1A, TNFRSF1B, TNFRSF3, TNFRSF4, TNFRSF11A, and combinations thereof. In some embodiments, the mammal is selected from a human, a dog, a horse, and a cat.

A. IL1R1

[00619] In some embodiments, the pharmaceutical composition comprising a CRISPR gene-editing system targets IL1R1. In some embodiments, the CRISPR gene-editing system targeting IL1R1 is delivered to a mammalian cell via viral vector. In some embodiments, the CRISPR gene-editing system targeting IL1R1 is delivered to a mammalian cell via an AAV vector. In some embodiments, the CRISPR gene-editing system targeting IL1R1 is delivered to a mammalian cell via a lentiviral vector. In some embodiments, the CRISPR gene-editing system targeting IL1R1 is delivered to a mammalian cell via a lipid nanoparticle. In some embodiments, the CRISPR gene-editing system targeting IL1R1 is delivered to a mammalian cell via a virus-like particle. In some embodiments, the CRISPR gene-editing system targeting IL1R1 is delivered to a mammalian cell via a liposome. In some embodiments, the CRISPR gene-editing system targeting IL1R1 is delivered to a mammalian cell via a lipid nanocrystal.

[00620] In various embodiments, the pharmaceutical composition comprising a CRISPR gene-editing system that targets the IL1R1 gene is used in a method of treating a mammal in need thereof. In some embodiments, the method treats one or more joint disease or illness or one or more back or spine conditions or disorders. In some embodiments, the method treats one or more musculoskeletal diseases, conditions, and illnesses, including, but not limited to, rheumatoid arthritis, gout, osteoarthritis, osteoporosis, intervertebral disc disease (IVDD), psoriatic arthritis, arthritis, polymyositis, proliferative synovitis, bone neoplasms, sarcoid myopathy, cortex bone disorders, idiopathic scoliosis, tendinopathy, myofibrillar myopathy, enthesis-related arthritis, ankylosing spondylitis, degenerative polyarthritis, arthropathy, osteitis deformans, prolapsed lumbar disc, polymyositis ossificans, idiopathic polymyositis, Luft Disease, adult-onset Still's Disease, osteoarthritis deformans, Bachet's Disease, and combinations thereof. In other embodiments, use of the system treats one or more neoplastic diseases, conditions, and illnesses, including, but not limited to, osteosarcoma, multiple myeloma, lymphoma(e.g., B-cell or cutaneous T-cell lymphoma), leukemia, thyroid carcinoma, glioma, renal cell carcinoma, chondrosarcoma, glioblastoma, melanoma, neuroblastoma, polycystic ovary syndrome, Kaposi sarcoma, squamous cell carcinoma, leiomyosarcoma, malignant peripheral nerve sheath tumor, Ewing's sarcoma, esophageal neoplasms, colon cancer, lung cancer, breast cancer, pancreatic cancer, stomach cancer, epithelial ovarian cancer, cholectoral cancer, liver cancer, skin cancer, prostate cancer, cervical cancer, ovarian cancer, bladder cancer, oral cavity cancer, and combinations thereof. In other embodiments, the method treats one or more inflammatory diseases, conditions, and illnesses, including, but not limited to, autoinflammatory disease (AID), cryopyrin-associated periodic syndrome (CAPS), systemic lupus erythematosus (SLE), inflammatory bowel disease (IBD) and combinations thereof. In some embodiments, the method treats one or more cardiac diseases, conditions, and illnesses, including, but not limited to, myocardial infarction, heart failure (e.g., refractory or acute decompensated heart failure), arrythmias, pericarditis (e.g., refractory idiopathic pericarditis), myocarditis, sepsis-induced cardiomyopathy, atherosclerosis, coronary artery disease and combinations thereof. In some embodiments, the method treats one or more neurological diseases, conditions, and illnesses, including, but not limited to, acute thrombotic stroke, epilepsy, multiple sclerosis, Alzheimer's Disease and combinations thereof. In some embodiments, the method treats one or more ophthalmic diseases, conditions, and illnesses, including, but not limited to, uveitis, scleritis, Sjogren asthenia, dry eye and combinations thereof. In some embodiments, the method treats one or more diseases, conditions, and illnesses, including, but not limited to,

chronic kidney disease, Type 2 diabetes, gastroesophageal reflux disease (GERD), non-HP-associated peptic ulcer disease, and pulmonary fibrosis.

[00621] In some embodiments, the pharmaceutical composition comprising a CRISPR gene-editing system targets IL1R1 for the treatment of a joint disease or illness. In some embodiments, the pharmaceutical composition comprising a CRISPR gene-editing system targets IL1R1 for the treatment of osteoarthritis. In some embodiments, the pharmaceutical composition comprising a CRISPR gene-editing system targets IL1R1 for the treatment of gout.

[00622] In some embodiments, the pharmaceutical composition comprising a CRISPR gene-editing system targets IL1R1 for the treatment of a musculoskeletal disorder.

[00623] In some embodiments, the pharmaceutical composition comprising a CRISPR gene-editing system targets IL1R1 for the treatment of a back or spine condition or disorder. In some embodiments, the pharmaceutical composition comprising a CRISPR gene-editing system targets IL1R1 for the treatment of low back pain. In some embodiments, the pharmaceutical composition comprising a CRISPR gene-editing system targets IL1R1 for the treatment of degenerative disc disorder. In some embodiments, the pharmaceutical composition comprising a CRISPR gene-editing system targets IL1R1 for the treatment of internal disc disruption.

1. *Treatment of musculoskeletal disorders by targeting an interleukin-1 receptor gene*

[00624] In one aspect, methods and pharmaceutical compositions are provided for treating a musculoskeletal disorder using a CRISPR pharmaceutical composition that targets an interleukin-1 receptor gene. In some embodiments, the CRISPR pharmaceutical composition comprises (i) an RNA-guided nuclease or a nucleic acid encoding an RNA-guided nuclease, and (ii) at least one guide RNA (gRNA), or a nucleic acid encoding at least one gRNA, targeting the interleukin-1 receptor gene, where the gRNA specifically binds a target sequence that is adjacent to a protospacer adjacent motif (PAM) sequence for the RNA-guided nuclease. In some embodiments, the CRISPR pharmaceutical composition comprises (i) an mRNA encoding an RNA-guided nuclease, and (ii) at least one gRNA targeting the interleukin-1 receptor gene. In some embodiments, the mRNA encoding the RNA-guided nuclease and the at least one gRNA are packaged in a lipid nanoparticle (LNP). In some embodiments, the musculoskeletal disorder is Rheumatoid Arthritis, Gout, Osteoarthritis,

Osteoporosis, Intervertebral disc disease (IVDD), Psoriatic arthritis (PsA), Arthritis, Polymyositis, Proliferative synovitis, Malignant bone neoplasm, Sarcoid Myopathy, Cortex Bone Disorders, Idiopathic Scoliosis, Tendinopathy, Myofibrillar Myopathy, Enthesis-Related Arthritis, Ankylosing spondylitis, Degenerative , polyarthritis, Arthropathy, Osteitis Deformans, Prolapsed Lumbar Disc, Polymyositis Ossificans, Idiopathic Polymyositis, Luft Disease, Adult-onset Still's Disease, Osteoarthrosis Deformans, or Bachet's Disease. In some embodiments, a musculoskeletal disorder listed in Figure 3 is treated with a CRISPR pharmaceutical composition targeting a gene listed as associated with the disorder in Figure 3. For example, in some embodiments, Rheumatoid Arthritis is treated with a CRISPR pharmaceutical composition targeting an IL1R1, IL1RAP, IL1R5, IL1R6, IL1R7, or IL1R9 gene.

[00625] In some embodiments, the interleukin-1 receptor gene is an IL1R1 gene. In some embodiments, the IL1R1 gene is a human IL1R1 gene and the guide RNA comprises a crRNA sequence selected from SEQ ID NOs: 680-824. In some embodiments, the IL1R1 gene is a canine IL1R1 gene and the guide RNA comprises a crRNA sequence selected from SEQ ID NOs: 825-892 and SEQ ID NOs: 3336-3420. In some embodiments, the IL1R1 gene is an equine IL1R1 gene and the guide RNA comprises a crRNA sequence selected from SEQ ID NOs: 893-967. In some embodiments, the IL1R1 gene is a feline IL1R1 gene and the guide RNA comprises a crRNA sequence selected from SEQ ID NOs: 968-1039. In some embodiments, editing of the IL1R1 gene results in a knockout of the IL1R1 gene. In some such embodiments, the IL1R1 gene human IL1R1 gene and is a the guide RNA comprises a crRNA sequence selected from SEQ ID NOs: 680-758. In some such embodiments, the IL1R1 gene is a canine IL1R1 gene and the guide RNA comprises a crRNA sequence selected from SEQ ID NOs: 825-892. In some such embodiments, the IL1R1 gene is an equine IL1R1 gene and the guide RNA comprises a crRNA sequence selected from SEQ ID NOs: 893-922. In some such embodiments, the IL1R1 gene is a feline IL1R1 gene and the guide RNA comprises a crRNA sequence selected from SEQ ID NOs: 968-997. In some embodiments, editing of the IL1R1 gene results in a gene that expresses a membrane-bound receptor decoy protein. In some such embodiments, the IL1R1 gene is a human IL1R1 gene and the guide RNA comprises a crRNA sequence selected from SEQ ID NOs: 759-808. In some such embodiments, the IL1R1 gene is a canine IL1R1 gene and the guide RNA comprises a crRNA sequence selected from SEQ ID NOs: 3336-3401. In some such embodiments, the IL1R1 gene is an equine IL1R1 gene and the guide RNA comprises a

crRNA sequence selected from SEQ ID NOs: 942-967. In some such embodiments, the IL1R1 gene is a feline IL1R1 gene and the guide RNA comprises a crRNA sequence selected from SEQ ID NOs: 1010-1039. In some embodiments, editing of the IL1R1 gene results in a gene that expresses a soluble receptor decoy protein. In some such embodiments, the IL1R1 gene is a human IL1R1 gene and the guide RNA comprises a crRNA sequence selected from SEQ ID NOs 758 and 809-811. In some such embodiments, the IL1R1 gene is a canine IL1R1 gene and the guide RNA comprises a crRNA sequence selected from SEQ ID NOs: 865-892. and SEQ ID NOS: 3402-3405. In some such embodiments, the IL1R1 gene is an equine IL1R1 gene and the guide RNA comprises a crRNA sequence selected from SEQ ID NOs: 923-941. In some such embodiments, the IL1R1 gene is a feline IL1R1 gene and the guide RNA comprises a crRNA sequence selected from SEQ ID NOs: 998-1009.

2. *Treatment of neoplasia by targeting an interleukin-1 receptor gene*

[00626] In In one aspect, methods and pharmaceutical compositions are provided for treating a neoplasia using a CRISPR pharmaceutical composition that targets an interleukin-1 receptor gene. In some embodiments, the CRISPR pharmaceutical composition comprises (i) an RNA-guided nuclease or a nucleic acid encoding an RNA-guided nuclease, and (ii) at least one guide RNA (gRNA), or a nucleic acid encoding at least one gRNA, targeting the interleukin-1 receptor gene, where the gRNA specifically binds a target sequence that is adjacent to a protospacer adjacent motif (PAM) sequence for the RNA-guided nuclease. In some embodiments, the CRISPR pharmaceutical composition comprises (i) an mRNA encoding an RNA-guided nuclease, and (ii) at least one gRNA targeting the interleukin-1 receptor gene. In some embodiments, the mRNA encoding the RNA-guided nuclease and the at least one gRNA are packaged in a lipid nanoparticle (LNP). In some embodiments, the neoplasia is Osteosarcoma, Colon Cancer, Metastasis (General), Lung Cancer, Multiple Myeloma. Breast Cancer, Solid Tumors, Lymphoma, Pancreatic Cancer, Stomach Cancer, Epithelial Ovarian Cancer, Mammary Neoplasms, Oropharyngeal Carcinoma, Renal Cell Carcinoma, Chondrosarcoma, Esophageal Neoplasms, B-Cell Lymphoma, Cutaneous Lymphoma T-Cell, Leukemia, Thyroid Carcinoma, Skin carcinogenesis, Cholectoral Cancer, Glioma, Liver Cancer, Melanoma, Neuroblastoma, Polycystic Ovary Syndrome, Glioblastoma, Prostate Cancer, Cervical Cancer, Ovarian Cancer, Bladder Cancer, Squamous cell carcinoma, Kaposi Sarcoma, Oral Cavity Cancer, Leiomyosarcoma, Malignant Peripheral Nerve Sheath Tumor, or Ewing's Sarcoma. In some embodiments, a neoplasia listed in Figure 3 is treated with a CRISPR pharmaceutical composition targeting a gene

listed as associated with the disorder in Figure 3. For example, in some embodiments, Osteosarcoma is treated with a CRISPR pharmaceutical composition targeting an IL1R1 gene.

[00627] In some embodiments, the interleukin-1 receptor gene is an IL1R1 gene. In some embodiments, the IL1R1 gene is a human IL1R1 gene and the guide RNA comprises a crRNA sequence selected from SEQ ID NOs: 680-824. In some embodiments, the IL1R1 gene is a canine IL1R1 gene and the guide RNA comprises a crRNA sequence selected from SEQ ID NOs: 825-892 and SEQ ID NOs: 3336-3420. In some embodiments, the IL1R1 gene is an equine IL1R1 gene and the guide RNA comprises a crRNA sequence selected from SEQ ID NOs: 893-967. In some embodiments, the IL1R1 gene is a feline IL1R1 gene and the guide RNA comprises a crRNA sequence selected from SEQ ID NOs: 968-1039. In some embodiments, editing of the IL1R1 gene results in a knockout of the IL1R1 gene. In some such embodiments, the IL1R1 gene human IL1R1 gene and is a the guide RNA comprises a crRNA sequence selected from SEQ ID NOs: 680-758. In some such embodiments, the IL1R1 gene is a canine IL1R1 gene and the guide RNA comprises a crRNA sequence selected from SEQ ID NOs: 825-892. In some such embodiments, the IL1R1 gene is an equine IL1R1 gene and the guide RNA comprises a crRNA sequence selected from SEQ ID NOs: 893-922. In some such embodiments, the IL1R1 gene is a feline IL1R1 gene and the guide RNA comprises a crRNA sequence selected from SEQ ID NOs: 968-997. In some embodiments, editing of the IL1R1 gene results in a gene that expresses a membrane-bound receptor decoy protein. In some such embodiments, the IL1R1 gene is a human IL1R1 gene and the guide RNA comprises a crRNA sequence selected from SEQ ID NOs: 759-808. In some such embodiments, the IL1R1 gene is a canine IL1R1 gene and the guide RNA comprises a crRNA sequence selected from SEQ ID NOs: 3336-3401. In some such embodiments, the IL1R1 gene is an equine IL1R1 gene and the guide RNA comprises a crRNA sequence selected from SEQ ID NOs: 942-967. In some such embodiments, the IL1R1 gene is a feline IL1R1 gene and the guide RNA comprises a crRNA sequence selected from SEQ ID NOs: 1010-1039. In some embodiments, editing of the IL1R1 gene results in a gene that expresses a soluble receptor decoy protein. In some such embodiments, the IL1R1 gene is a human IL1R1 gene and the guide RNA comprises a crRNA sequence selected from SEQ ID NOs 758 and 809-811. In some such embodiments, the IL1R1 gene is a canine IL1R1 gene and the guide RNA comprises a crRNA sequence selected from SEQ ID NOs: 865-892. and SEQ ID NOS: 3402-3405. In some such embodiments, the IL1R1 gene is an

equine IL1R1 gene and the guide RNA comprises a crRNA sequence selected from SEQ ID NOs: 923-941. In some such embodiments, the IL1R1 gene is a feline IL1R1 gene and the guide RNA comprises a crRNA sequence selected from SEQ ID NOs: 998-1009.

3. *Treatment of neurological disorder by targeting an interleukin-1 receptor gene*

[00628] In one aspect, methods and pharmaceutical compositions are provided for treating a neurological disorder using a CRISPR pharmaceutical composition that targets an interleukin-1 receptor gene. In some embodiments, the CRISPR pharmaceutical composition comprises (i) an RNA-guided nuclease or a nucleic acid encoding an RNA-guided nuclease, and (ii) at least one guide RNA (gRNA), or a nucleic acid encoding at least one gRNA, targeting the interleukin-1 receptor gene, where the gRNA specifically binds a target sequence that is adjacent to a protospacer adjacent motif (PAM) sequence for the RNA-guided nuclease. In some embodiments, the CRISPR pharmaceutical composition comprises (i) an mRNA encoding an RNA-guided nuclease, and (ii) at least one gRNA targeting the interleukin-1 receptor gene. In some embodiments, the mRNA encoding the RNA-guided nuclease and the at least one gRNA are packaged in a lipid nanoparticle (LNP). In some embodiments, the neurological disorder is Acute Thrombotic Stroke, Epilepsy, Multiple Sclerosis, or Alzheimer's Disease. In some embodiments, a neurological disorder listed in Figure 3 is treated with a CRISPR pharmaceutical composition targeting a gene listed as associated with the disorder in Figure 3. For example, in some embodiments, Acute Thrombocytic Stroke is treated with a CRISPR pharmaceutical composition targeting an IL1R1, or an IL1RAP gene.

[00629] In some embodiments, the interleukin-1 receptor gene is an IL1R1 gene. In some embodiments, the IL1R1 gene is a human IL1R1 gene and the guide RNA comprises a crRNA sequence selected from SEQ ID NOs: 680-824. In some embodiments, the IL1R1 gene is a canine IL1R1 gene and the guide RNA comprises a crRNA sequence selected from SEQ ID NOs: 825-892 and SEQ ID NOs: 3336-3420. In some embodiments, the IL1R1 gene is an equine IL1R1 gene and the guide RNA comprises a crRNA sequence selected from SEQ ID NOs: 893-967. In some embodiments, the IL1R1 gene is a feline IL1R1 gene and the guide RNA comprises a crRNA sequence selected from SEQ ID NOs: 968-1039. In some embodiments, editing of the IL1R1 gene results in a knockout of the IL1R1 gene. In some such embodiments, the IL1R1 gene human IL1R1 gene and is a the guide RNA comprises a crRNA sequence selected from SEQ ID NOs: 680-758. In some such embodiments, the

IL1R1 gene is a canine IL1R1 gene and the guide RNA comprises a crRNA sequence selected from SEQ ID NOs: 825-892. In some such embodiments, the IL1R1 gene is an equine IL1R1 gene and the guide RNA comprises a crRNA sequence selected from SEQ ID NOs: 893-922. In some such embodiments, the IL1R1 gene is a feline IL1R1 gene and the guide RNA comprises a crRNA sequence selected from SEQ ID NOs: 968-997. In some embodiments, editing of the IL1R1 gene results in a gene that expresses a membrane-bound receptor decoy protein. In some such embodiments, the IL1R1 gene is a human IL1R1 gene and the guide RNA comprises a crRNA sequence selected from SEQ ID NOs: 759-808. In some such embodiments, the IL1R1 gene is a canine IL1R1 gene and the guide RNA comprises a crRNA sequence selected from SEQ ID NOs: 3336-3401. In some such embodiments, the IL1R1 gene is an equine IL1R1 gene and the guide RNA comprises a crRNA sequence selected from SEQ ID NOs: 942-967. In some such embodiments, the IL1R1 gene is a feline IL1R1 gene and the guide RNA comprises a crRNA sequence selected from SEQ ID NOs: 1010-1039. In some embodiments, editing of the IL1R1 gene results in a gene that expresses a soluble receptor decoy protein. In some such embodiments, the IL1R1 gene is a human IL1R1 gene and the guide RNA comprises a crRNA sequence selected from SEQ ID NOs 758 and 809-811. In some such embodiments, the IL1R1 gene is a canine IL1R1 gene and the guide RNA comprises a crRNA sequence selected from SEQ ID NOs: 865-892. and SEQ ID NOS: 3402-3405. In some such embodiments, the IL1R1 gene is an equine IL1R1 gene and the guide RNA comprises a crRNA sequence selected from SEQ ID NOs: 923-941. In some such embodiments, the IL1R1 gene is a feline IL1R1 gene and the guide RNA comprises a crRNA sequence selected from SEQ ID NOs: 998-1009.

4. *Treatment of cardiac disorder by targeting an interleukin-1 receptor gene*

[00630] In one aspect, methods and pharmaceutical compositions are provided for treating a cardiac disorder using a CRISPR pharmaceutical composition that targets an interleukin-1 receptor gene. In some embodiments, the CRISPR pharmaceutical composition comprises (i) an RNA-guided nuclease or a nucleic acid encoding an RNA-guided nuclease, and (ii) at least one guide RNA (gRNA), or a nucleic acid encoding at least one gRNA, targeting the interleukin-1 receptor gene, where the gRNA specifically binds a target sequence that is adjacent to a protospacer adjacent motif (PAM) sequence for the RNA-guided nuclease. In some embodiments, the CRISPR pharmaceutical composition comprises (i) an mRNA encoding an RNA-guided nuclease, and (ii) at least one gRNA targeting the interleukin-1 receptor gene. In some embodiments, the mRNA encoding the RNA-guided nuclease and the

at least one gRNA are packaged in a lipid nanoparticle (LNP). In some embodiments, the cardiac disorder is Heart disease including but not limited to Acute Myocardial Infarction, refractory heart failure, arrhythmias, pericarditis, myocarditis, and sepsis-induced cardiomyopathy; Acute Decompensated Heart Failure, Refractory Idiopathic Pericarditis, or Atherosclerosis including but not limited to coronary artery disease, myocardial infarction, and cardiac remodeling. In some embodiments, a cardiac disorder listed in Figure 3 is treated with a CRISPR pharmaceutical composition targeting a gene listed as associated with the disorder in Figure 3. For example, in some embodiments, Acute Decompensated Heart Failure is treated with a CRISPR pharmaceutical composition targeting an IL1R1, or an IL1RAP gene.

[00631] In some embodiments, the interleukin-1 receptor gene is an IL1R1 gene. In some embodiments, the IL1R1 gene is a human IL1R1 gene and the guide RNA comprises a crRNA sequence selected from SEQ ID NOs: 680-824. In some embodiments, the IL1R1 gene is a canine IL1R1 gene and the guide RNA comprises a crRNA sequence selected from SEQ ID NOs: 825-892 and SEQ ID NOs: 3336-3420. In some embodiments, the IL1R1 gene is an equine IL1R1 gene and the guide RNA comprises a crRNA sequence selected from SEQ ID NOs: 893-967. In some embodiments, the IL1R1 gene is a feline IL1R1 gene and the guide RNA comprises a crRNA sequence selected from SEQ ID NOs: 968-1039. In some embodiments, editing of the IL1R1 gene results in a knockout of the IL1R1 gene. In some such embodiments, the IL1R1 gene human IL1R1 gene and is a the guide RNA comprises a crRNA sequence selected from SEQ ID NOs: 680-758. In some such embodiments, the IL1R1 gene is a canine IL1R1 gene and the guide RNA comprises a crRNA sequence selected from SEQ ID NOs: 825-892. In some such embodiments, the IL1R1 gene is an equine IL1R1 gene and the guide RNA comprises a crRNA sequence selected from SEQ ID NOs: 893-922. In some such embodiments, the IL1R1 gene is a feline IL1R1 gene and the guide RNA comprises a crRNA sequence selected from SEQ ID NOs: 968-997. In some embodiments, editing of the IL1R1 gene results in a gene that expresses a membrane-bound receptor decoy protein. In some such embodiments, the IL1R1 gene is a human IL1R1 gene and the guide RNA comprises a crRNA sequence selected from SEQ ID NOs: 759-808. In some such embodiments, the IL1R1 gene is a canine IL1R1 gene and the guide RNA comprises a crRNA sequence selected from SEQ ID NOs: 3336-3401. In some such embodiments, the IL1R1 gene is an equine IL1R1 gene and the guide RNA comprises a crRNA sequence selected from SEQ ID NOs: 942-967. In some such embodiments, the

IL1R1 gene is a feline IL1R1 gene and the guide RNA comprises a crRNA sequence selected from SEQ ID NOs: 1010-1039. In some embodiments, editing of the IL1R1 gene results in a gene that expresses a soluble receptor decoy protein. In some such embodiments, the IL1R1 gene is a human IL1R1 gene and the guide RNA comprises a crRNA sequence selected from SEQ ID NOs 758 and 809-811. In some such embodiments, the IL1R1 gene is a canine IL1R1 gene and the guide RNA comprises a crRNA sequence selected from SEQ ID NOs: 865-892. and SEQ ID NOS: 3402-3405. In some such embodiments, the IL1R1 gene is an equine IL1R1 gene and the guide RNA comprises a crRNA sequence selected from SEQ ID NOs: 923-941. In some such embodiments, the IL1R1 gene is a feline IL1R1 gene and the guide RNA comprises a crRNA sequence selected from SEQ ID NOs: 998-1009.

5. *Treatment of inflammatory disorders by targeting an interleukin-1 receptor gene*

[00632] In one aspect, methods and pharmaceutical compositions are provided for treating an inflammatory disorder using a CRISPR pharmaceutical composition that targets an interleukin-1 receptor gene. In some embodiments, the CRISPR pharmaceutical composition comprises (i) an RNA-guided nuclease or a nucleic acid encoding an RNA-guided nuclease, and (ii) at least one guide RNA (gRNA), or a nucleic acid encoding at least one gRNA, targeting the interleukin-1 receptor gene, where the gRNA specifically binds a target sequence that is adjacent to a protospacer adjacent motif (PAM) sequence for the RNA-guided nuclease. In some embodiments, the CRISPR pharmaceutical composition comprises (i) an mRNA encoding an RNA-guided nuclease, and (ii) at least one gRNA targeting the interleukin-1 receptor gene. In some embodiments, the mRNA encoding the RNA-guided nuclease and the at least one gRNA are packaged in a lipid nanoparticle (LNP). In some embodiments, the inflammatory disorder is Autoinflammatory Disease (AID), Cryopyrin Associated Periodic syndrome (CAPS), Familial Mediterranean Fever (FMF), TNF-Receptor Associated Periodic Syndrome (TRAPS), Hyper-IgD Syndrome (HIDS), Systemic Lupus Erythematosus (SLE), or Fibrosis (general). In some embodiments, an inflammatory disorder listed in Figure 3 is treated with a CRISPR pharmaceutical composition targeting a gene listed as associated with the disorder in Figure 3. For example, in some embodiments, an autoinflammatory disease (AID) is treated with a CRISPR pharmaceutical composition targeting an IL1R1, IL1RAP, IL1R5, or an IL1R7 gene.

[00633] In some embodiments, the interleukin-1 receptor gene is an IL1R1 gene. In some embodiments, the IL1R1 gene is a human IL1R1 gene and the guide RNA comprises a

crRNA sequence selected from SEQ ID NOs: 680-824. In some embodiments, the IL1R1 gene is a canine IL1R1 gene and the guide RNA comprises a crRNA sequence selected from SEQ ID NOs: 825-892 and SEQ ID NOs: 3336-3420. In some embodiments, the IL1R1 gene is an equine IL1R1 gene and the guide RNA comprises a crRNA sequence selected from SEQ ID NOs: 893-967. In some embodiments, the IL1R1 gene is a feline IL1R1 gene and the guide RNA comprises a crRNA sequence selected from SEQ ID NOs: 968-1039. In some embodiments, editing of the IL1R1 gene results in a knockout of the IL1R1 gene. In some such embodiments, the IL1R1 gene human IL1R1 gene and is a the guide RNA comprises a crRNA sequence selected from SEQ ID NOs: 680-758. In some such embodiments, the IL1R1 gene is a canine IL1R1 gene and the guide RNA comprises a crRNA sequence selected from SEQ ID NOs: 825-892. In some such embodiments, the IL1R1 gene is an equine IL1R1 gene and the guide RNA comprises a crRNA sequence selected from SEQ ID NOs: 893-922. In some such embodiments, the IL1R1 gene is a feline IL1R1 gene and the guide RNA comprises a crRNA sequence selected from SEQ ID NOs: 968-997. In some embodiments, editing of the IL1R1 gene results in a gene that expresses a membrane-bound receptor decoy protein. In some such embodiments, the IL1R1 gene is a human IL1R1 gene and the guide RNA comprises a crRNA sequence selected from SEQ ID NOs: 759-808. In some such embodiments, the IL1R1 gene is a canine IL1R1 gene and the guide RNA comprises a crRNA sequence selected from SEQ ID NOs: 3336-3401. In some such embodiments, the IL1R1 gene is an equine IL1R1 gene and the guide RNA comprises a crRNA sequence selected from SEQ ID NOs: 942-967. In some such embodiments, the IL1R1 gene is a feline IL1R1 gene and the guide RNA comprises a crRNA sequence selected from SEQ ID NOs: 1010-1039. In some embodiments, editing of the IL1R1 gene results in a gene that expresses a soluble receptor decoy protein. In some such embodiments, the IL1R1 gene is a human IL1R1 gene and the guide RNA comprises a crRNA sequence selected from SEQ ID NOs 758 and 809-811. In some such embodiments, the IL1R1 gene is a canine IL1R1 gene and the guide RNA comprises a crRNA sequence selected from SEQ ID NOs: 865-892. and SEQ ID NOS: 3402-3405. In some such embodiments, the IL1R1 gene is an equine IL1R1 gene and the guide RNA comprises a crRNA sequence selected from SEQ ID NOs: 923-941. In some such embodiments, the IL1R1 gene is a feline IL1R1 gene and the guide RNA comprises a crRNA sequence selected from SEQ ID NOs: 998-1009.

6. *Treatment of digestive disorders by targeting an interleukin-1 receptor gene*

[00634] In one aspect, methods and pharmaceutical compositions are provided for treating a digestive disorder using a CRISPR pharmaceutical composition that targets an interleukin-1 receptor gene. In some embodiments, the CRISPR pharmaceutical composition comprises (i) an RNA-guided nuclease or a nucleic acid encoding an RNA-guided nuclease, and (ii) at least one guide RNA (gRNA), or a nucleic acid encoding at least one gRNA, targeting the interleukin-1 receptor gene, where the gRNA specifically binds a target sequence that is adjacent to a protospacer adjacent motif (PAM) sequence for the RNA-guided nuclease. In some embodiments, the CRISPR pharmaceutical composition comprises (i) an mRNA encoding an RNA-guided nuclease, and (ii) at least one gRNA targeting the interleukin-1 receptor gene. In some embodiments, the mRNA encoding the RNA-guided nuclease and the at least one gRNA are packaged in a lipid nanoparticle (LNP). In some embodiments, the digestive disorder is Inflammatory Bowel Disease (IBD), Gastroesophageal reflux disease (GERD), or Non-HP-associated Peptic Ulcer Disease. In some embodiments, a digestive disorder listed in Figure 3 is treated with a CRISPR pharmaceutical composition targeting a gene listed as associated with the disorder in Figure 3. For example, in some embodiments, an Inflammatory Bowel Disease (IBD) is treated with a CRISPR pharmaceutical composition targeting an IL1R1, IL1RAP, IL1R5, IL1R6, IL1R7, IL1R8, or an IL1R9 gene.

[00635] In some embodiments, the interleukin-1 receptor gene is an IL1R1 gene. In some embodiments, the IL1R1 gene is a human IL1R1 gene and the guide RNA comprises a crRNA sequence selected from SEQ ID NOs: 680-824. In some embodiments, the IL1R1 gene is a canine IL1R1 gene and the guide RNA comprises a crRNA sequence selected from SEQ ID NOs: 825-892 and SEQ ID NOs: 3336-3420. In some embodiments, the IL1R1 gene is an equine IL1R1 gene and the guide RNA comprises a crRNA sequence selected from SEQ ID NOs: 893-967. In some embodiments, the IL1R1 gene is a feline IL1R1 gene and the guide RNA comprises a crRNA sequence selected from SEQ ID NOs: 968-1039. In some embodiments, editing of the IL1R1 gene results in a knockout of the IL1R1 gene. In some such embodiments, the IL1R1 gene human IL1R1 gene and is a the guide RNA comprises a crRNA sequence selected from SEQ ID NOs: 680-758. In some such embodiments, the IL1R1 gene is a canine IL1R1 gene and the guide RNA comprises a crRNA sequence selected from SEQ ID NOs: 825-892. In some such embodiments, the IL1R1 gene is an equine IL1R1 gene and the guide RNA comprises a crRNA sequence selected from SEQ ID NOs: 893-922. In some such embodiments, the IL1R1 gene is a feline IL1R1 gene and the

guide RNA comprises a crRNA sequence selected from SEQ ID NOs: 968-997. In some embodiments, editing of the IL1R1 gene results in a gene that expresses a membrane-bound receptor decoy protein. In some such embodiments, the IL1R1 gene is a human IL1R1 gene and the guide RNA comprises a crRNA sequence selected from SEQ ID NOs: 759-808. In some such embodiments, the IL1R1 gene is a canine IL1R1 gene and the guide RNA comprises a crRNA sequence selected from SEQ ID NOs: 3336-3401. In some such embodiments, the IL1R1 gene is an equine IL1R1 gene and the guide RNA comprises a crRNA sequence selected from SEQ ID NOs: 942-967. In some such embodiments, the IL1R1 gene is a feline IL1R1 gene and the guide RNA comprises a crRNA sequence selected from SEQ ID NOs: 1010-1039. In some embodiments, editing of the IL1R1 gene results in a gene that expresses a soluble receptor decoy protein. In some such embodiments, the IL1R1 gene is a human IL1R1 gene and the guide RNA comprises a crRNA sequence selected from SEQ ID NOs 758 and 809-811. In some such embodiments, the IL1R1 gene is a canine IL1R1 gene and the guide RNA comprises a crRNA sequence selected from SEQ ID NOs: 865-892. and SEQ ID NOS: 3402-3405. In some such embodiments, the IL1R1 gene is an equine IL1R1 gene and the guide RNA comprises a crRNA sequence selected from SEQ ID NOs: 923-941. In some such embodiments, the IL1R1 gene is a feline IL1R1 gene and the guide RNA comprises a crRNA sequence selected from SEQ ID NOs: 998-1009.

7. *Treatment of respiratory disorders by targeting an interleukin-1 receptor gene*

[00636] In one aspect, methods and pharmaceutical compositions are provided for treating a respiratory disorder using a CRISPR pharmaceutical composition that targets an interleukin-1 receptor gene. In some embodiments, the CRISPR pharmaceutical composition comprises (i) an RNA-guided nuclease or a nucleic acid encoding an RNA-guided nuclease, and (ii) at least one guide RNA (gRNA), or a nucleic acid encoding at least one gRNA, targeting the interleukin-1 receptor gene, where the gRNA specifically binds a target sequence that is adjacent to a protospacer adjacent motif (PAM) sequence for the RNA-guided nuclease. In some embodiments, the CRISPR pharmaceutical composition comprises (i) an mRNA encoding an RNA-guided nuclease, and (ii) at least one gRNA targeting the interleukin-1 receptor gene. In some embodiments, the mRNA encoding the RNA-guided nuclease and the at least one gRNA are packaged in a lipid nanoparticle (LNP). In some embodiments, the respiratory disorder is Asthma, or Pulmonary Fibrosis. In some embodiments, a respiratory disorder listed in Figure 3 is treated with a CRISPR pharmaceutical composition targeting a gene listed as associated with the disorder in Figure 3. For example, in some embodiments,

Asthma is treated with a CRISPR pharmaceutical composition targeting an IL1R1, or IL1RAP gene.

[00637] In some embodiments, the interleukin-1 receptor gene is an IL1R1 gene. In some embodiments, the IL1R1 gene is a human IL1R1 gene and the guide RNA comprises a crRNA sequence selected from SEQ ID NOs: 680-824. In some embodiments, the IL1R1 gene is a canine IL1R1 gene and the guide RNA comprises a crRNA sequence selected from SEQ ID NOs: 825-892 and SEQ ID NOs: 3336-3420. In some embodiments, the IL1R1 gene is an equine IL1R1 gene and the guide RNA comprises a crRNA sequence selected from SEQ ID NOs: 893-967. In some embodiments, the IL1R1 gene is a feline IL1R1 gene and the guide RNA comprises a crRNA sequence selected from SEQ ID NOs: 968-1039. In some embodiments, editing of the IL1R1 gene results in a knockout of the IL1R1 gene. In some such embodiments, the IL1R1 gene human IL1R1 gene and is a the guide RNA comprises a crRNA sequence selected from SEQ ID NOs: 680-758. In some such embodiments, the IL1R1 gene is a canine IL1R1 gene and the guide RNA comprises a crRNA sequence selected from SEQ ID NOs: 825-892. In some such embodiments, the IL1R1 gene is an equine IL1R1 gene and the guide RNA comprises a crRNA sequence selected from SEQ ID NOs: 893-922. In some such embodiments, the IL1R1 gene is a feline IL1R1 gene and the guide RNA comprises a crRNA sequence selected from SEQ ID NOs: 968-997. In some embodiments, editing of the IL1R1 gene results in a gene that expresses a membrane-bound receptor decoy protein. In some such embodiments, the IL1R1 gene is a human IL1R1 gene and the guide RNA comprises a crRNA sequence selected from SEQ ID NOs: 759-808. In some such embodiments, the IL1R1 gene is a canine IL1R1 gene and the guide RNA comprises a crRNA sequence selected from SEQ ID NOs: 3336-3401. In some such embodiments, the IL1R1 gene is an equine IL1R1 gene and the guide RNA comprises a crRNA sequence selected from SEQ ID NOs: 942-967. In some such embodiments, the IL1R1 gene is a feline IL1R1 gene and the guide RNA comprises a crRNA sequence selected from SEQ ID NOs: 1010-1039. In some embodiments, editing of the IL1R1 gene results in a gene that expresses a soluble receptor decoy protein. In some such embodiments, the IL1R1 gene is a human IL1R1 gene and the guide RNA comprises a crRNA sequence selected from SEQ ID NOs 758 and 809-811. In some such embodiments, the IL1R1 gene is a canine IL1R1 gene and the guide RNA comprises a crRNA sequence selected from SEQ ID NOs: 865-892. and SEQ ID NOS: 3402-3405. In some such embodiments, the IL1R1 gene is an equine IL1R1 gene and the guide RNA comprises a crRNA sequence selected from SEQ ID

NOs: 923-941. In some such embodiments, the IL1R1 gene is a feline IL1R1 gene and the guide RNA comprises a crRNA sequence selected from SEQ ID NOs: 998-1009.

8. *Treatment of renal, metabolic, or ophthalmic disorders by targeting an interleukin-1 receptor gene*

[00638] In one aspect, methods and pharmaceutical compositions are provided for treating a renal, metabolic, or ophthalmic disorder using a CRISPR pharmaceutical composition that targets an interleukin-1 receptor gene. In some embodiments, the CRISPR pharmaceutical composition comprises (i) an RNA-guided nuclease or a nucleic acid encoding an RNA-guided nuclease, and (ii) at least one guide RNA (gRNA), or a nucleic acid encoding at least one gRNA, targeting the interleukin-1 receptor gene, where the gRNA specifically binds a target sequence that is adjacent to a protospacer adjacent motif (PAM) sequence for the RNA-guided nuclease. In some embodiments, the CRISPR pharmaceutical composition comprises (i) an mRNA encoding an RNA-guided nuclease, and (ii) at least one gRNA targeting the interleukin-1 receptor gene. In some embodiments, the mRNA encoding the RNA-guided nuclease and the at least one gRNA are packaged in a lipid nanoparticle (LNP). In some embodiments, the renal, metabolic, or ophthalmic disorder is Chronic Kidney Disease, Type 2 Diabetes, or Eye Diseases including but not limited to Uveitis, Scleritis, Sjogren asthenia, and dry eye. In some embodiments, a renal, metabolic, or ophthalmic disorder listed in Figure 3 is treated with a CRISPR pharmaceutical composition targeting a gene listed as associated with the disorder in Figure 3. For example, in some embodiments, Chronic Kidney disease is treated with a CRISPR pharmaceutical composition targeting an IL1R1, or IL1RAP gene.

[00639] In some embodiments, the interleukin-1 receptor gene is an IL1R1 gene. In some embodiments, the IL1R1 gene is a human IL1R1 gene and the guide RNA comprises a crRNA sequence selected from SEQ ID NOs: 680-824. In some embodiments, the IL1R1 gene is a canine IL1R1 gene and the guide RNA comprises a crRNA sequence selected from SEQ ID NOs: 825-892 and SEQ ID NOs: 3336-3420. In some embodiments, the IL1R1 gene is an equine IL1R1 gene and the guide RNA comprises a crRNA sequence selected from SEQ ID NOs: 893-967. In some embodiments, the IL1R1 gene is a feline IL1R1 gene and the guide RNA comprises a crRNA sequence selected from SEQ ID NOs: 968-1039. In some embodiments, editing of the IL1R1 gene results in a knockout of the IL1R1 gene. In some such embodiments, the IL1R1 gene human IL1R1 gene and is a the guide RNA comprises a crRNA sequence selected from SEQ ID NOs: 680-758. In some such embodiments, the

IL1R1 gene is a canine IL1R1 gene and the guide RNA comprises a crRNA sequence selected from SEQ ID NOs: 825-892. In some such embodiments, the IL1R1 gene is an equine IL1R1 gene and the guide RNA comprises a crRNA sequence selected from SEQ ID NOs: 893-922. In some such embodiments, the IL1R1 gene is a feline IL1R1 gene and the guide RNA comprises a crRNA sequence selected from SEQ ID NOs: 968-997. In some embodiments, editing of the IL1R1 gene results in a gene that expresses a membrane-bound receptor decoy protein. In some such embodiments, the IL1R1 gene is a human IL1R1 gene and the guide RNA comprises a crRNA sequence selected from SEQ ID NOs: 759-808. In some such embodiments, the IL1R1 gene is a canine IL1R1 gene and the guide RNA comprises a crRNA sequence selected from SEQ ID NOs: 3336-3401. In some such embodiments, the IL1R1 gene is an equine IL1R1 gene and the guide RNA comprises a crRNA sequence selected from SEQ ID NOs: 942-967. In some such embodiments, the IL1R1 gene is a feline IL1R1 gene and the guide RNA comprises a crRNA sequence selected from SEQ ID NOs: 1010-1039. In some embodiments, editing of the IL1R1 gene results in a gene that expresses a soluble receptor decoy protein. In some such embodiments, the IL1R1 gene is a human IL1R1 gene and the guide RNA comprises a crRNA sequence selected from SEQ ID NOs 758 and 809-811. In some such embodiments, the IL1R1 gene is a canine IL1R1 gene and the guide RNA comprises a crRNA sequence selected from SEQ ID NOs: 865-892. and SEQ ID NOS: 3402-3405. In some such embodiments, the IL1R1 gene is an equine IL1R1 gene and the guide RNA comprises a crRNA sequence selected from SEQ ID NOs: 923-941. In some such embodiments, the IL1R1 gene is a feline IL1R1 gene and the guide RNA comprises a crRNA sequence selected from SEQ ID NOs: 998-1009.

B. IL1RAP

[00640] In some embodiments, the pharmaceutical composition comprising a CRISPR gene-editing system targets IL1RAP. In some embodiments, the CRISPR gene-editing system targeting IL1RAP is delivered to a mammalian cell via viral vector. In some embodiments, the CRISPR gene-editing system targeting IL1RAP is delivered to a mammalian cell via an AAV vector. In some embodiments, the CRISPR gene-editing system targeting IL1RAP is delivered to a mammalian cell via a lentiviral vector. In some embodiments, the CRISPR gene-editing system targeting IL1RAP is delivered to a mammalian cell via a lipid nanoparticle. In some embodiments, the CRISPR gene-editing system targeting IL1RAP is delivered to a mammalian cell via a virus-like particle. In some embodiments, the CRISPR

gene-editing system targeting IL1RAP is delivered to a mammalian cell via a liposome. In some embodiments, the CRISPR gene-editing system targeting IL1RAP is delivered to a mammalian cell via a lipid nanocrystal.

[00641] In various embodiments, the pharmaceutical composition comprising a CRISPR gene-editing system that targets the IL1RAP gene is used in a method of treating a mammal in need thereof. In some embodiments, the method treats one or more joint disease or illness or one or more back or spine conditions or disorders. In some embodiments, the method treats one or more musculoskeletal diseases, conditions, and illnesses, including, but not limited to, rheumatoid arthritis, gout, osteoarthritis, osteoporosis, intervertebral disc disease (IVDD), psoriatic arthritis, arthritis, polymyositis, proliferative synovitis, bone neoplasms, sarcoid myopathy, cortex bone disorders, idiopathic scoliosis, tendinopathy, myofibrillar myopathy, enthesis-related arthritis, ankylosing spondylitis, degenerative polyarthritis, arthropathy, osteitis deformans, prolapsed lumbar disc, polymyositis ossificans, idiopathic polymyositis, Luft Disease, adult-onset Still's Disease, osteoarthritis deformans, Bachet's Disease, and combinations thereof. In other embodiments, use of the system treats one or more neoplastic diseases, conditions, and illnesses, including, but not limited to, osteosarcoma, multiple myeloma, lymphoma(e.g., B-cell or cutaneous T-cell lymphoma), leukemia, thyroid carcinoma, glioma, renal cell carcinoma, chondrosarcoma, glioblastoma, melanoma, neuroblastoma, polycystic ovary syndrome, Kaposi sarcoma, squamous cell carcinoma, leiomyosarcoma, malignant peripheral nerve sheath tumor, Ewing's sarcoma, esophageal neoplasms, colon cancer, lung cancer, breast cancer, pancreatic cancer, stomach cancer, epithelial ovarian cancer, cholectoral cancer, liver cancer, skin cancer, prostate cancer, cervical cancer, ovarian cancer, bladder cancer, oral cavity cancer, and combinations thereof. In other embodiments, the method treats one or more inflammatory diseases, conditions, and illnesses, including, but not limited to, autoinflammatory disease (AID), cryopyrin-associated periodic syndrome (CAPS), systemic lupus erythematosus (SLE), inflammatory bowel disease (IBD) and combinations thereof. In some embodiments, the method treats one or more cardiac diseases, conditions, and illnesses, including, but not limited to, myocardial infarction, heart failure (e.g., refractory or acute decompensated heart failure), arrythmias, pericarditis (e.g., refractory idiopathic pericarditis), myocarditis, sepsis-induced cardiomyopathy, atherosclerosis, coronary artery disease and combinations thereof. In some embodiments, the method treats one or more neurological diseases, conditions, and illnesses, including, but not limited to, acute thrombotic stroke, epilepsy, multiple sclerosis,

Alzheimer's Disease and combinations thereof. In some embodiments, the method treats one or more ophthalmic diseases, conditions, and illnesses, including, but not limited to, uveitis, scleritis, Sjogren asthenia, dry eye and combinations thereof. In some embodiments, the method treats one or more diseases, conditions, and illnesses, including, but not limited to, chronic kidney disease, Type 2 diabetes, gastroesophageal reflux disease (GERD), non-HP-associated peptic ulcer disease, and pulmonary fibrosis.

[00642] In some embodiments, the pharmaceutical composition comprising a CRISPR gene-editing system targets IL1RAP for the treatment of a joint disease or illness. In some embodiments, the pharmaceutical composition comprising a CRISPR gene-editing system targets IL1RAP for the treatment of osteoarthritis. In some embodiments, the pharmaceutical composition comprising a CRISPR gene-editing system targets IL1RAP for the treatment of gout.

[00643] In some embodiments, the pharmaceutical composition comprising a CRISPR gene-editing system targets IL1RAP for the treatment of a musculoskeletal disorder.

[00644] In some embodiments, the pharmaceutical composition comprising a CRISPR gene-editing system targets IL1RAP for the treatment of a back or spine condition or disorder. In some embodiments, the pharmaceutical composition comprising a CRISPR gene-editing system targets IL1RAP for the treatment of low back pain. In some embodiments, the pharmaceutical composition comprising a CRISPR gene-editing system targets IL1RAP for the treatment of degenerative disc disorder. In some embodiments, the pharmaceutical composition comprising a CRISPR gene-editing system targets IL1RAP for the treatment of internal disc disruption.

[00645]

1. *Treatment of musculoskeletal disorders by targeting an interleukin-1 receptor gene*

[00646] In one aspect, methods and pharmaceutical compositions are provided for treating a musculoskeletal disorder using a CRISPR pharmaceutical composition that targets an interleukin-1 receptor gene. In some embodiments, the CRISPR pharmaceutical composition comprises (i) an RNA-guided nuclease or a nucleic acid encoding an RNA-guided nuclease, and (ii) at least one guide RNA (gRNA), or a nucleic acid encoding at least one gRNA, targeting the interleukin-1 receptor gene, where the gRNA specifically binds a target sequence that is adjacent to a protospacer adjacent motif (PAM) sequence for the RNA-

guided nuclease. In some embodiments, the CRISPR pharmaceutical composition comprises (i) an mRNA encoding an RNA-guided nuclease, and (ii) at least one gRNA targeting the interleukin-1 receptor gene. In some embodiments, the mRNA encoding the RNA-guided nuclease and the at least one gRNA are packaged in a lipid nanoparticle (LNP). In some embodiments, the musculoskeletal disorder is Rheumatoid Arthritis, Gout, Osteoarthritis, Osteoporosis, Intervertebral disc disease (IVDD), Psoriatic arthritis (PsA), Arthritis, Polymyositis, Proliferative synovitis, Malignant bone neoplasm, Sarcoid Myopathy, Cortex Bone Disorders, Idiopathic Scoliosis, Tendinopathy, Myofibrillar Myopathy, Enthesis-Related Arthritis, Ankylosing spondylitis, Degenerative , polyarthritis, Arthropathy, Osteitis Deformans, Prolapsed Lumbar Disc, Polymyositis Ossificans, Idiopathic Polymyositis, Luft Disease, Adult-onset Still's Disease, Osteoarthrosis Deformans, or Bachet's Disease. In some embodiments, a musculoskeletal disorder listed in Figure 3 is treated with a CRISPR pharmaceutical composition targeting a gene listed as associated with the disorder in Figure 3. For example, in some embodiments, Rheumatoid Arthritis is treated with a CRISPR pharmaceutical composition targeting an IL1R1, IL1RAP, IL1R5, IL1R6, IL1R7, or IL1R9 gene.

[00647] In some embodiments, the interleukin-1 receptor gene is an IL1RAP gene. In some embodiments, the IL1R1 gene is a human IL1RAP gene and the guide RNA comprises a crRNA sequence selected from SEQ ID NOs: 1040-1203. In some embodiments, the IL1RAP gene is a canine IL1RAP gene and the guide RNA comprises a crRNA sequence selected from SEQ ID NOs: 1204-1271 and SEQ ID NOs: 3421-3490. In some embodiments, the IL1RAP gene is an equine IL1RAP gene and the guide RNA comprises a crRNA sequence selected from SEQ ID NOs: 1272-1348. In some embodiments, the IL1R1 gene is a feline IL1RAP gene and the guide RNA comprises a crRNA sequence selected from SEQ ID NOs: 1349-1424. In some embodiments, editing of the IL1RAP gene results in a knockout of the IL1RAP gene. In some such embodiments, the IL1RAP gene is a human IL1RAP gene and the guide RNA comprises a crRNA sequence selected from SEQ ID NOs: 1040-1122. In some such embodiments, the IL1RAP gene is a canine IL1RAP gene and the guide RNA comprises a crRNA sequence selected from SEQ ID NOs: 1204-1271 and SEQ ID NOs: 3421-3458. In some such embodiments, the IL1RAP gene is an equine IL1RAP gene and the guide RNA comprises a crRNA sequence selected from SEQ ID NOs: 1272-1301. In some such embodiments, the IL1RAP gene is a feline IL1RAP gene and the guide RNA comprises a crRNA sequence selected from SEQ ID NOs: 1349-1378. In some embodiments, editing of

the IL1RAP gene results in a gene that expresses a membrane-bound receptor decoy protein. In some such embodiments, the IL1RAP gene is a human IL1RAP gene and the guide RNA comprises a crRNA sequence selected from SEQ ID NOs: 1123-1180 and SEQ ID NOs: 1192-1194. In some such embodiments, the IL1RAP gene is a canine IL1RAP gene and the guide RNA comprises a crRNA sequence selected from SEQ ID NOs: 3459-3485. In some such embodiments, the IL1RAP gene is an equine IL1RAP gene and the guide RNA comprises a crRNA sequence selected from SEQ ID NOs: 1323-1348. In some such embodiments, the IL1RAP gene is a feline IL1RAP gene and the guide RNA comprises a crRNA sequence selected from SEQ ID NOs: 1397-1424. In some embodiments, editing of the IL1RAP gene results in a gene that expresses a soluble receptor decoy protein. In some such embodiments, the IL1RAP gene is a human IL1RAP gene and the guide RNA comprises a crRNA sequence selected from SEQ ID NOs: 1181-1194. In some such embodiments, the IL1RAP gene is a canine IL1RAP gene and the guide RNA comprises a crRNA sequence selected from SEQ ID NOs: 3481-3490 and SEQ ID NOs: 3453-3458. In some such embodiments, the IL1RAP gene is an equine IL1RAP gene and the guide RNA comprises a crRNA sequence selected from SEQ ID NOs: 1302-1322. In some such embodiments, the IL1R1 gene is a feline IL1RAP gene and the guide RNA comprises a crRNA sequence selected from SEQ ID NOs: 1379-1396.

2. *Treatment of neoplasia by targeting an interleukin-1 receptor gene*

[00648] In In one aspect, methods and pharmaceutical compositions are provided for treating a neoplasia using a CRISPR pharmaceutical composition that targets an interleukin-1 receptor gene. In some embodiments, the CRISPR pharmaceutical composition comprises (i) an RNA-guided nuclease or a nucleic acid encoding an RNA-guided nuclease, and (ii) at least one guide RNA (gRNA), or a nucleic acid encoding at least one gRNA, targeting the interleukin-1 receptor gene, where the gRNA specifically binds a target sequence that is adjacent to a protospacer adjacent motif (PAM) sequence for the RNA-guided nuclease. In some embodiments, the CRISPR pharmaceutical composition comprises (i) an mRNA encoding an RNA-guided nuclease, and (ii) at least one gRNA targeting the interleukin-1 receptor gene. In some embodiments, the mRNA encoding the RNA-guided nuclease and the at least one gRNA are packaged in a lipid nanoparticle (LNP). In some embodiments, the neoplasia is Osteosarcoma, Colon Cancer, Metastasis (General), Lung Cancer, Multiple Myeloma. Breast Cancer, Solid Tumors, Lymphoma, Pancreatic Cancer, Stomach Cancer, Epithelial Ovarian Cancer, Mammary Neoplasms, Oropharyngeal Carcinoma, Renal Cell

Carcinoma, Chondrosarcoma, Esophageal Neoplasms, B-Cell Lymphoma, Cutaneous Lymphoma T-Cell, Leukemia, Thyroid Carcinoma, Skin carcinogenesis, Cholectoral Cancer, Glioma, Liver Cancer, Melanoma, Neuroblastoma, Polycystic Ovary Syndrome, Glioblastoma, Prostate Cancer, Cervical Cancer, Ovarian Cancer, Bladder Cancer, Squamous cell carcinoma, Kaposi Sarcoma, Oral Cavity Cancer, Leiomyosarcoma, Malignant Peripheral Nerve Sheath Tumor, or Ewing's Sarcoma. In some embodiments, a neoplasia listed in Figure 3 is treated with a CRISPR pharmaceutical composition targeting a gene listed as associated with the disorder in Figure 3. For example, in some embodiments, Osteosarcoma is treated with a CRISPR pharmaceutical composition targeting an IL1R1 gene.

[00649] In some embodiments, the interleukin-1 receptor gene is an IL1RAP gene. In some embodiments, the IL1R1 gene is a human IL1RAP gene and the guide RNA comprises a crRNA sequence selected from SEQ ID NOs: 1040-1203. In some embodiments, the IL1RAP gene is a canine IL1RAP gene and the guide RNA comprises a crRNA sequence selected from SEQ ID NOs: 1204-1271 and SEQ ID NOs: 3421-3490. In some embodiments, the IL1RAP gene is an equine IL1RAP gene and the guide RNA comprises a crRNA sequence selected from SEQ ID NOs: 1272-1348. In some embodiments, the IL1R1 gene is a feline IL1RAP gene and the guide RNA comprises a crRNA sequence selected from SEQ ID NOs: 1349-1424. In some embodiments, editing of the IL1RAP gene results in a knockout of the IL1RAP gene. In some such embodiments, the IL1RAP gene is a human IL1RAP gene and the guide RNA comprises a crRNA sequence selected from SEQ ID NOs: 1040-1122. In some such embodiments, the IL1RAP gene is a canine IL1RAP gene and the guide RNA comprises a crRNA sequence selected from SEQ ID NOs: 1204-1271 and SEQ ID NOs: 3421-3458. In some such embodiments, the IL1RAP gene is an equine IL1RAP gene and the guide RNA comprises a crRNA sequence selected from SEQ ID NOs: 1272-1301. In some such embodiments, the IL1RAP gene is a feline IL1RAP gene and the guide RNA comprises a crRNA sequence selected from SEQ ID NOs: 1349-1378. In some embodiments, editing of the IL1RAP gene results in a gene that expresses a membrane-bound receptor decoy protein. In some such embodiments, the IL1RAP gene is a human IL1RAP gene and the guide RNA comprises a crRNA sequence selected from SEQ ID NOs: 1123-1180 and SEQ ID NOs: 1192-1194. In some such embodiments, the IL1RAP gene is a canine IL1RAP gene and the guide RNA comprises a crRNA sequence selected from SEQ ID NOs: 3459-3485. In some such embodiments, the IL1RAP gene is an equine IL1RAP gene and the guide RNA

comprises a crRNA sequence selected from SEQ ID NOs: 1323-1348. In some such embodiments, the IL1RAP gene is a feline IL1RAP gene and the guide RNA comprises a crRNA sequence selected from SEQ ID NOs: 1397-1424. In some embodiments, editing of the IL1RAP gene results in a gene that expresses a soluble receptor decoy protein. In some such embodiments, the IL1RAP gene is a human IL1RAP gene and the guide RNA comprises a crRNA sequence selected from SEQ ID NOs: 1181-1194. In some such embodiments, the IL1RAP gene is a canine IL1RAP gene and the guide RNA comprises a crRNA sequence selected from SEQ ID NOs: 3481-3490 and SEQ ID NOs: 3453-3458. In some such embodiments, the IL1RAP gene is an equine IL1RAP gene and the guide RNA comprises a crRNA sequence selected from SEQ ID NOs: 1302-1322. In some such embodiments, the IL1R1 gene is a feline IL1RAP gene and the guide RNA comprises a crRNA sequence selected from SEQ ID NOs: 1379-1396.

3. *Treatment of neurological disorder by targeting an interleukin-1 receptor gene*

[00650] In one aspect, methods and pharmaceutical compositions are provided for treating a neurological disorder using a CRISPR pharmaceutical composition that targets an interleukin-1 receptor gene. In some embodiments, the CRISPR pharmaceutical composition comprises (i) an RNA-guided nuclease or a nucleic acid encoding an RNA-guided nuclease, and (ii) at least one guide RNA (gRNA), or a nucleic acid encoding at least one gRNA, targeting the interleukin-1 receptor gene, where the gRNA specifically binds a target sequence that is adjacent to a protospacer adjacent motif (PAM) sequence for the RNA-guided nuclease. In some embodiments, the CRISPR pharmaceutical composition comprises (i) an mRNA encoding an RNA-guided nuclease, and (ii) at least one gRNA targeting the interleukin-1 receptor gene. In some embodiments, the mRNA encoding the RNA-guided nuclease and the at least one gRNA are packaged in a lipid nanoparticle (LNP). In some embodiments, the neurological disorder is Acute Thrombotic Stroke, Epilepsy, Multiple Sclerosis, or Alzheimer's Disease. In some embodiments, a neurological disorder listed in Figure 3 is treated with a CRISPR pharmaceutical composition targeting a gene listed as associated with the disorder in Figure 3. For example, in some embodiments, Acute Thrombocytic Stroke is treated with a CRISPR pharmaceutical composition targeting an IL1R1, or an IL1RAP gene.

[00651] In some embodiments, the interleukin-1 receptor gene is an IL1RAP gene. In some embodiments, the IL1R1 gene is a human IL1RAP gene and the guide RNA comprises a

crRNA sequence selected from SEQ ID NOs: 1040-1203. In some embodiments, the IL1RAP gene is a canine IL1RAP gene and the guide RNA comprises a crRNA sequence selected from SEQ ID NOs: 1204-1271 and SEQ ID NOs: 3421-3490. In some embodiments, the IL1RAP gene is an equine IL1RAP gene and the guide RNA comprises a crRNA sequence selected from SEQ ID NOs: 1272-1348. In some embodiments, the IL1R1 gene is a feline IL1RAP gene and the guide RNA comprises a crRNA sequence selected from SEQ ID NOs: 1349-1424. In some embodiments, editing of the IL1RAP gene results in a knockout of the IL1RAP gene. In some such embodiments, the IL1RAP gene is a human IL1RAP gene and the guide RNA comprises a crRNA sequence selected from SEQ ID NOs: 1040-1122. In some such embodiments, the IL1RAP gene is a canine IL1RAP gene and the guide RNA comprises a crRNA sequence selected from SEQ ID NOs: 1204-1271 and SEQ ID NOs: 3421-3458. In some such embodiments, the IL1RAP gene is an equine IL1RAP gene and the guide RNA comprises a crRNA sequence selected from SEQ ID NOs: 1272-1301. In some such embodiments, the IL1RAP gene is a feline IL1RAP gene and the guide RNA comprises a crRNA sequence selected from SEQ ID NOs: 1349-1378. In some embodiments, editing of the IL1RAP gene results in a gene that expresses a membrane-bound receptor decoy protein. In some such embodiments, the IL1RAP gene is a human IL1RAP gene and the guide RNA comprises a crRNA sequence selected from SEQ ID NOs: 1123-1180 and SEQ ID NOs: 1192-1194. In some such embodiments, the IL1RAP gene is a canine IL1RAP gene and the guide RNA comprises a crRNA sequence selected from SEQ ID NOs: 3459-3485. In some such embodiments, the IL1RAP gene is an equine IL1RAP gene and the guide RNA comprises a crRNA sequence selected from SEQ ID NOs: 1323-1348. In some such embodiments, the IL1RAP gene is a feline IL1RAP gene and the guide RNA comprises a crRNA sequence selected from SEQ ID NOs: 1397-1424. In some embodiments, editing of the IL1RAP gene results in a gene that expresses a soluble receptor decoy protein. In some such embodiments, the IL1RAP gene is a human IL1RAP gene and the guide RNA comprises a crRNA sequence selected from SEQ ID NOs: 1181-1194. In some such embodiments, the IL1RAP gene is a canine IL1RAP gene and the guide RNA comprises a crRNA sequence selected from SEQ ID NOs: 3481-3490 and SEQ ID NOs: 3453-3458. In some such embodiments, the IL1RAP gene is an equine IL1RAP gene and the guide RNA comprises a crRNA sequence selected from SEQ ID NOs: 1302-1322. In some such embodiments, the IL1R1 gene is a feline IL1RAP gene and the guide RNA comprises a crRNA sequence selected from SEQ ID NOs: 1379-1396.

4. *Treatment of cardiac disorder by targeting an interleukin-1 receptor gene*

[00652] In one aspect, methods and pharmaceutical compositions are provided for treating a cardiac disorder using a CRISPR pharmaceutical composition that targets an interleukin-1 receptor gene. In some embodiments, the CRISPR pharmaceutical composition comprises (i) an RNA-guided nuclease or a nucleic acid encoding an RNA-guided nuclease, and (ii) at least one guide RNA (gRNA), or a nucleic acid encoding at least one gRNA, targeting the interleukin-1 receptor gene, where the gRNA specifically binds a target sequence that is adjacent to a protospacer adjacent motif (PAM) sequence for the RNA-guided nuclease. In some embodiments, the CRISPR pharmaceutical composition comprises (i) an mRNA encoding an RNA-guided nuclease, and (ii) at least one gRNA targeting the interleukin-1 receptor gene. In some embodiments, the mRNA encoding the RNA-guided nuclease and the at least one gRNA are packaged in a lipid nanoparticle (LNP). In some embodiments, the cardiac disorder is Heart disease including but not limited to Acute Myocardial Infarction, refractory heart failure, arrhythmias, pericarditis, myocarditis, and sepsis-induced cardiomyopathy; Acute Decompensated Heart Failure, Refractory Idiopathic Pericarditis, or Atherosclerosis including but not limited to coronary artery disease, myocardial infarction, and cardiac remodeling. In some embodiments, a cardiac disorder listed in Figure 3 is treated with a CRISPR pharmaceutical composition targeting a gene listed as associated with the disorder in Figure 3. For example, in some embodiments, Acute Decompensated Heart Failure is treated with a CRISPR pharmaceutical composition targeting an IL1R1, or an IL1RAP gene.

[00653] In some embodiments, the interleukin-1 receptor gene is an IL1RAP gene. In some embodiments, the IL1R1 gene is a human IL1RAP gene and the guide RNA comprises a crRNA sequence selected from SEQ ID NOs: 1040-1203. In some embodiments, the IL1RAP gene is a canine IL1RAP gene and the guide RNA comprises a crRNA sequence selected from SEQ ID NOs: 1204-1271 and SEQ ID NOs: 3421-3490. In some embodiments, the IL1RAP gene is an equine IL1RAP gene and the guide RNA comprises a crRNA sequence selected from SEQ ID NOs: 1272-1348. In some embodiments, the IL1R1 gene is a feline IL1RAP gene and the guide RNA comprises a crRNA sequence selected from SEQ ID NOs: 1349-1424. In some embodiments, editing of the IL1RAP gene results in a knockout of the IL1RAP gene. In some such embodiments, the IL1RAP gene is a human IL1RAP gene and the guide RNA comprises a crRNA sequence selected from SEQ ID NOs: 1040-1122. In some such embodiments, the IL1RAP gene is a canine IL1RAP gene and the guide RNA

comprises a crRNA sequence selected from SEQ ID NOs: 1204-1271 and SEQ ID NOs: 3421-3458. In some such embodiments, the IL1RAP gene is an equine IL1RAP gene and the guide RNA comprises a crRNA sequence selected from SEQ ID NOs: 1272-1301. In some such embodiments, the IL1RAP gene is a feline IL1RAP gene and the guide RNA comprises a crRNA sequence selected from SEQ ID NOs: 1349-1378. In some embodiments, editing of the IL1RAP gene results in a gene that expresses a membrane-bound receptor decoy protein. In some such embodiments, the IL1RAP gene is a human IL1RAP gene and the guide RNA comprises a crRNA sequence selected from SEQ ID NOs: 1123-1180 and SEQ ID NOs: 1192-1194. In some such embodiments, the IL1RAP gene is a canine IL1RAP gene and the guide RNA comprises a crRNA sequence selected from SEQ ID NOs: 3459-3485. In some such embodiments, the IL1RAP gene is an equine IL1RAP gene and the guide RNA comprises a crRNA sequence selected from SEQ ID NOs: 1323-1348. In some such embodiments, the IL1RAP gene is a feline IL1RAP gene and the guide RNA comprises a crRNA sequence selected from SEQ ID NOs: 1397-1424. In some embodiments, editing of the IL1RAP gene results in a gene that expresses a soluble receptor decoy protein. In some such embodiments, the IL1RAP gene is a human IL1RAP gene and the guide RNA comprises a crRNA sequence selected from SEQ ID NOs: 1181-1194. In some such embodiments, the IL1RAP gene is a canine IL1RAP gene and the guide RNA comprises a crRNA sequence selected from SEQ ID NOs: 3481-3490 and SEQ ID NOs: 3453-3458. In some such embodiments, the IL1RAP gene is an equine IL1RAP gene and the guide RNA comprises a crRNA sequence selected from SEQ ID NOs: 1302-1322. In some such embodiments, the IL1R1 gene is a feline IL1RAP gene and the guide RNA comprises a crRNA sequence selected from SEQ ID NOs: 1379-1396.

5. *Treatment of inflammatory disorders by targeting an interleukin-1 receptor gene*

[00654] In one aspect, methods and pharmaceutical compositions are provided for treating an inflammatory disorder using a CRISPR pharmaceutical composition that targets an interleukin-1 receptor gene. In some embodiments, the CRISPR pharmaceutical composition comprises (i) an RNA-guided nuclease or a nucleic acid encoding an RNA-guided nuclease, and (ii) at least one guide RNA (gRNA), or a nucleic acid encoding at least one gRNA, targeting the interleukin-1 receptor gene, where the gRNA specifically binds a target sequence that is adjacent to a protospacer adjacent motif (PAM) sequence for the RNA-guided nuclease. In some embodiments, the CRISPR pharmaceutical composition comprises

(i) an mRNA encoding an RNA-guided nuclease, and (ii) at least one gRNA targeting the interleukin-1 receptor gene. In some embodiments, the mRNA encoding the RNA-guided nuclease and the at least one gRNA are packaged in a lipid nanoparticle (LNP). In some embodiments, the inflammatory disorder is Autoinflammatory Disease (AID), Cryopyrin Associated Periodic syndrome (CAPS), Familial Mediterranean Fever (FMF), TNF-Receptor Associated Periodic Syndrome (TRAPS), Hyper-IgD Syndrome (HIDS), Systemic Lupus Erythematosus (SLE), or Fibrosis (general). In some embodiments, an inflammatory disorder listed in Figure 3 is treated with a CRISPR pharmaceutical composition targeting a gene listed as associated with the disorder in Figure 3. For example, in some embodiments, an autoinflammatory disease (AID) is treated with a CRISPR pharmaceutical composition targeting an IL1R1, IL1RAP, IL1R5, or an IL1R7 gene.

[00655] In some embodiments, the interleukin-1 receptor gene is an IL1RAP gene. In some embodiments, the IL1R1 gene is a human IL1RAP gene and the guide RNA comprises a crRNA sequence selected from SEQ ID NOs: 1040-1203. In some embodiments, the IL1RAP gene is a canine IL1RAP gene and the guide RNA comprises a crRNA sequence selected from SEQ ID NOs: 1204-1271 and SEQ ID NOs: 3421-3490. In some embodiments, the IL1RAP gene is an equine IL1RAP gene and the guide RNA comprises a crRNA sequence selected from SEQ ID NOs: 1272-1348. In some embodiments, the IL1R1 gene is a feline IL1RAP gene and the guide RNA comprises a crRNA sequence selected from SEQ ID NOs: 1349-1424. In some embodiments, editing of the IL1RAP gene results in a knockout of the IL1RAP gene. In some such embodiments, the IL1RAP gene is a human IL1RAP gene and the guide RNA comprises a crRNA sequence selected from SEQ ID NOs: 1040-1122. In some such embodiments, the IL1RAP gene is a canine IL1RAP gene and the guide RNA comprises a crRNA sequence selected from SEQ ID NOs: 1204-1271 and SEQ ID NOs: 3421-3458. In some such embodiments, the IL1RAP gene is an equine IL1RAP gene and the guide RNA comprises a crRNA sequence selected from SEQ ID NOs: 1272-1301. In some such embodiments, the IL1RAP gene is a feline IL1RAP gene and the guide RNA comprises a crRNA sequence selected from SEQ ID NOs: 1349-1378. In some embodiments, editing of the IL1RAP gene results in a gene that expresses a membrane-bound receptor decoy protein. In some such embodiments, the IL1RAP gene is a human IL1RAP gene and the guide RNA comprises a crRNA sequence selected from SEQ ID NOs: 1123-1180 and SEQ ID NOs: 1192-1194. In some such embodiments, the IL1RAP gene is a canine IL1RAP gene and the guide RNA comprises a crRNA sequence selected from SEQ ID NOs: 3459-3485. In some

such embodiments, the IL1RAP gene is an equine IL1RAP gene and the guide RNA comprises a crRNA sequence selected from SEQ ID NOs: 1323-1348. In some such embodiments, the IL1RAP gene is a feline IL1RAP gene and the guide RNA comprises a crRNA sequence selected from SEQ ID NOs: 1397-1424. In some embodiments, editing of the IL1RAP gene results in a gene that expresses a soluble receptor decoy protein. In some such embodiments, the IL1RAP gene is a human IL1RAP gene and the guide RNA comprises a crRNA sequence selected from SEQ ID NOs: 1181-1194. In some such embodiments, the IL1RAP gene is a canine IL1RAP gene and the guide RNA comprises a crRNA sequence selected from SEQ ID NOs: 3481-3490 and SEQ ID NOs: 3453-3458. In some such embodiments, the IL1RAP gene is an equine IL1RAP gene and the guide RNA comprises a crRNA sequence selected from SEQ ID NOs: 1302-1322. In some such embodiments, the IL1R1 gene is a feline IL1RAP gene and the guide RNA comprises a crRNA sequence selected from SEQ ID NOs: 1379-1396.

6. *Treatment of digestive disorders by targeting an interleukin-1 receptor gene*

[00656] In one aspect, methods and pharmaceutical compositions are provided for treating a digestive disorder using a CRISPR pharmaceutical composition that targets an interleukin-1 receptor gene. In some embodiments, the CRISPR pharmaceutical composition comprises (i) an RNA-guided nuclease or a nucleic acid encoding an RNA-guided nuclease, and (ii) at least one guide RNA (gRNA), or a nucleic acid encoding at least one gRNA, targeting the interleukin-1 receptor gene, where the gRNA specifically binds a target sequence that is adjacent to a protospacer adjacent motif (PAM) sequence for the RNA-guided nuclease. In some embodiments, the CRISPR pharmaceutical composition comprises (i) an mRNA encoding an RNA-guided nuclease, and (ii) at least one gRNA targeting the interleukin-1 receptor gene. In some embodiments, the mRNA encoding the RNA-guided nuclease and the at least one gRNA are packaged in a lipid nanoparticle (LNP). In some embodiments, the digestive disorder is Inflammatory Bowel Disease (IBD), Gastroesophageal reflux disease (GERD), or Non-HP-associated Peptic Ulcer Disease. In some embodiments, a digestive disorder listed in Figure 3 is treated with a CRISPR pharmaceutical composition targeting a gene listed as associated with the disorder in Figure 3. For example, in some embodiments, an Inflammatory Bowel Disease (IBD) is treated with a CRISPR pharmaceutical composition targeting an IL1R1, IL1RAP, IL1R5, IL1R6, IL1R7, IL1R8, or an IL1R9 gene.

[00657] In some embodiments, the interleukin-1 receptor gene is an IL1RAP gene. In some embodiments, the IL1R1 gene is a human IL1RAP gene and the guide RNA comprises a crRNA sequence selected from SEQ ID NOs: 1040-1203. In some embodiments, the IL1RAP gene is a canine IL1RAP gene and the guide RNA comprises a crRNA sequence selected from SEQ ID NOs: 1204-1271 and SEQ ID NOs: 3421-3490. In some embodiments, the IL1RAP gene is an equine IL1RAP gene and the guide RNA comprises a crRNA sequence selected from SEQ ID NOs: 1272-1348. In some embodiments, the IL1R1 gene is a feline IL1RAP gene and the guide RNA comprises a crRNA sequence selected from SEQ ID NOs: 1349-1424. In some embodiments, editing of the IL1RAP gene results in a knockout of the IL1RAP gene. In some such embodiments, the IL1RAP gene is a human IL1RAP gene and the guide RNA comprises a crRNA sequence selected from SEQ ID NOs: 1040-1122. In some such embodiments, the IL1RAP gene is a canine IL1RAP gene and the guide RNA comprises a crRNA sequence selected from SEQ ID NOs: 1204-1271 and SEQ ID NOs: 3421-3458. In some such embodiments, the IL1RAP gene is an equine IL1RAP gene and the guide RNA comprises a crRNA sequence selected from SEQ ID NOs: 1272-1301. In some such embodiments, the IL1RAP gene is a feline IL1RAP gene and the guide RNA comprises a crRNA sequence selected from SEQ ID NOs: 1349-1378. In some embodiments, editing of the IL1RAP gene results in a gene that expresses a membrane-bound receptor decoy protein. In some such embodiments, the IL1RAP gene is a human IL1RAP gene and the guide RNA comprises a crRNA sequence selected from SEQ ID NOs: 1123-1180 and SEQ ID NOs: 1192-1194. In some such embodiments, the IL1RAP gene is a canine IL1RAP gene and the guide RNA comprises a crRNA sequence selected from SEQ ID NOs: 3459-3485. In some such embodiments, the IL1RAP gene is an equine IL1RAP gene and the guide RNA comprises a crRNA sequence selected from SEQ ID NOs: 1323-1348. In some such embodiments, the IL1RAP gene is a feline IL1RAP gene and the guide RNA comprises a crRNA sequence selected from SEQ ID NOs: 1397-1424. In some embodiments, editing of the IL1RAP gene results in a gene that expresses a soluble receptor decoy protein. In some such embodiments, the IL1RAP gene is a human IL1RAP gene and the guide RNA comprises a crRNA sequence selected from SEQ ID NOs: 1181-1194. In some such embodiments, the IL1RAP gene is a canine IL1RAP gene and the guide RNA comprises a crRNA sequence selected from SEQ ID NOs: 3481-3490 and SEQ ID NOs: 3453-3458. In some such embodiments, the IL1RAP gene is an equine IL1RAP gene and the guide RNA comprises a crRNA sequence selected from SEQ ID NOs: 1302-1322. In some such

embodiments, the IL1R1 gene is a feline IL1RAP gene and the guide RNA comprises a crRNA sequence selected from SEQ ID NOs: 1379-1396.

7. *Treatment of respiratory disorders by targeting an interleukin-1 receptor gene*

[00658] In one aspect, methods and pharmaceutical compositions are provided for treating a respiratory disorder using a CRISPR pharmaceutical composition that targets an interleukin-1 receptor gene. In some embodiments, the CRISPR pharmaceutical composition comprises (i) an RNA-guided nuclease or a nucleic acid encoding an RNA-guided nuclease, and (ii) at least one guide RNA (gRNA), or a nucleic acid encoding at least one gRNA, targeting the interleukin-1 receptor gene, where the gRNA specifically binds a target sequence that is adjacent to a protospacer adjacent motif (PAM) sequence for the RNA-guided nuclease. In some embodiments, the CRISPR pharmaceutical composition comprises (i) an mRNA encoding an RNA-guided nuclease, and (ii) at least one gRNA targeting the interleukin-1 receptor gene. In some embodiments, the mRNA encoding the RNA-guided nuclease and the at least one gRNA are packaged in a lipid nanoparticle (LNP). In some embodiments, the respiratory disorder is Asthma, or Pulmonary Fibrosis. In some embodiments, a respiratory disorder listed in Figure 3 is treated with a CRISPR pharmaceutical composition targeting a gene listed as associated with the disorder in Figure 3. For example, in some embodiments, Asthma is treated with a CRISPR pharmaceutical composition targeting an IL1R1, or IL1RAP gene.

[00659] In some embodiments, the interleukin-1 receptor gene is an IL1RAP gene. In some embodiments, the IL1R1 gene is a human IL1RAP gene and the guide RNA comprises a crRNA sequence selected from SEQ ID NOs: 1040-1203. In some embodiments, the IL1RAP gene is a canine IL1RAP gene and the guide RNA comprises a crRNA sequence selected from SEQ ID NOs: 1204-1271 and SEQ ID NOs: 3421-3490. In some embodiments, the IL1RAP gene is an equine IL1RAP gene and the guide RNA comprises a crRNA sequence selected from SEQ ID NOs: 1272-1348. In some embodiments, the IL1R1 gene is a feline IL1RAP gene and the guide RNA comprises a crRNA sequence selected from SEQ ID NOs: 1349-1424. In some embodiments, editing of the IL1RAP gene results in a knockout of the IL1RAP gene. In some such embodiments, the IL1RAP gene is a human IL1RAP gene and the guide RNA comprises a crRNA sequence selected from SEQ ID NOs: 1040-1122. In some such embodiments, the IL1RAP gene is a canine IL1RAP gene and the guide RNA comprises a crRNA sequence selected from SEQ ID NOs: 1204-1271 and SEQ ID NOs:

3421-3458. In some such embodiments, the IL1RAP gene is an equine IL1RAP gene and the guide RNA comprises a crRNA sequence selected from SEQ ID NOs: 1272-1301. In some such embodiments, the IL1RAP gene is a feline IL1RAP gene and the guide RNA comprises a crRNA sequence selected from SEQ ID NOs: 1349-1378. In some embodiments, editing of the IL1RAP gene results in a gene that expresses a membrane-bound receptor decoy protein. In some such embodiments, the IL1RAP gene is a human IL1RAP gene and the guide RNA comprises a crRNA sequence selected from SEQ ID NOs: 1123-1180 and SEQ ID NOs: 1192-1194. In some such embodiments, the IL1RAP gene is a canine IL1RAP gene and the guide RNA comprises a crRNA sequence selected from SEQ ID NOs: 3459-3485. In some such embodiments, the IL1RAP gene is an equine IL1RAP gene and the guide RNA comprises a crRNA sequence selected from SEQ ID NOs: 1323-1348. In some such embodiments, the IL1RAP gene is a feline IL1RAP gene and the guide RNA comprises a crRNA sequence selected from SEQ ID NOs: 1397-1424. In some embodiments, editing of the IL1RAP gene results in a gene that expresses a soluble receptor decoy protein. In some such embodiments, the IL1RAP gene is a human IL1RAP gene and the guide RNA comprises a crRNA sequence selected from SEQ ID NOs: 1181-1194. In some such embodiments, the IL1RAP gene is a canine IL1RAP gene and the guide RNA comprises a crRNA sequence selected from SEQ ID NOs: 3481-3490 and SEQ ID NOs: 3453-3458. In some such embodiments, the IL1RAP gene is an equine IL1RAP gene and the guide RNA comprises a crRNA sequence selected from SEQ ID NOs: 1302-1322. In some such embodiments, the IL1R1 gene is a feline IL1RAP gene and the guide RNA comprises a crRNA sequence selected from SEQ ID NOs: 1379-1396.

8. *Treatment of renal, metabolic, or ophthalmic disorders by targeting an interleukin-1 receptor gene*

[00660] In one aspect, methods and pharmaceutical compositions are provided for treating a renal, metabolic, or ophthalmic disorder using a CRISPR pharmaceutical composition that targets an interleukin-1 receptor gene. In some embodiments, the CRISPR pharmaceutical composition comprises (i) an RNA-guided nuclease or a nucleic acid encoding an RNA-guided nuclease, and (ii) at least one guide RNA (gRNA), or a nucleic acid encoding at least one gRNA, targeting the interleukin-1 receptor gene, where the gRNA specifically binds a target sequence that is adjacent to a protospacer adjacent motif (PAM) sequence for the RNA-guided nuclease. In some embodiments, the CRISPR pharmaceutical composition comprises (i) an mRNA encoding an RNA-guided nuclease, and (ii) at least one gRNA

targeting the interleukin-1 receptor gene. In some embodiments, the mRNA encoding the RNA-guided nuclease and the at least one gRNA are packaged in a lipid nanoparticle (LNP). In some embodiments, the renal, metabolic, or ophthalmic disorder is Chronic Kidney Disease, Type 2 Diabetes, or Eye Diseases including but not limited to Uveitis, Scleritis, Sjogren asthenia, and dry eye. In some embodiments, a renal, metabolic, or ophthalmic disorder listed in Figure 3 is treated with a CRISPR pharmaceutical composition targeting a gene listed as associated with the disorder in Figure 3. For example, in some embodiments, Chronic Kidney disease is treated with a CRISPR pharmaceutical composition targeting an IL1R1, or IL1RAP gene.

[00661] In some embodiments, the interleukin-1 receptor gene is an IL1RAP gene. In some embodiments, the IL1R1 gene is a human IL1RAP gene and the guide RNA comprises a crRNA sequence selected from SEQ ID NOs: 1040-1203. In some embodiments, the IL1RAP gene is a canine IL1RAP gene and the guide RNA comprises a crRNA sequence selected from SEQ ID NOs: 1204-1271 and SEQ ID NOs: 3421-3490. In some embodiments, the IL1RAP gene is an equine IL1RAP gene and the guide RNA comprises a crRNA sequence selected from SEQ ID NOs: 1272-1348. In some embodiments, the IL1R1 gene is a feline IL1RAP gene and the guide RNA comprises a crRNA sequence selected from SEQ ID NOs: 1349-1424. In some embodiments, editing of the IL1RAP gene results in a knockout of the IL1RAP gene. In some such embodiments, the IL1RAP gene is a human IL1RAP gene and the guide RNA comprises a crRNA sequence selected from SEQ ID NOs: 1040-1122. In some such embodiments, the IL1RAP gene is a canine IL1RAP gene and the guide RNA comprises a crRNA sequence selected from SEQ ID NOs: 1204-1271 and SEQ ID NOs: 3421-3458. In some such embodiments, the IL1RAP gene is an equine IL1RAP gene and the guide RNA comprises a crRNA sequence selected from SEQ ID NOs: 1272-1301. In some such embodiments, the IL1RAP gene is a feline IL1RAP gene and the guide RNA comprises a crRNA sequence selected from SEQ ID NOs: 1349-1378. In some embodiments, editing of the IL1RAP gene results in a gene that expresses a membrane-bound receptor decoy protein. In some such embodiments, the IL1RAP gene is a human IL1RAP gene and the guide RNA comprises a crRNA sequence selected from SEQ ID NOs: 1123-1180 and SEQ ID NOs: 1192-1194. In some such embodiments, the IL1RAP gene is a canine IL1RAP gene and the guide RNA comprises a crRNA sequence selected from SEQ ID NOs: 3459-3485. In some such embodiments, the IL1RAP gene is an equine IL1RAP gene and the guide RNA comprises a crRNA sequence selected from SEQ ID NOs: 1323-1348. In some such

embodiments, the IL1RAP gene is a feline IL1RAP gene and the guide RNA comprises a crRNA sequence selected from SEQ ID NOs: 1397-1424. In some embodiments, editing of the IL1RAP gene results in a gene that expresses a soluble receptor decoy protein. In some such embodiments, the IL1RAP gene is a human IL1RAP gene and the guide RNA comprises a crRNA sequence selected from SEQ ID NOs: 1181-1194. In some such embodiments, the IL1RAP gene is a canine IL1RAP gene and the guide RNA comprises a crRNA sequence selected from SEQ ID NOs: 3481-3490 and SEQ ID NOs: 3453-3458. In some such embodiments, the IL1RAP gene is an equine IL1RAP gene and the guide RNA comprises a crRNA sequence selected from SEQ ID NOs: 1302-1322. In some such embodiments, the IL1R1 gene is a feline IL1RAP gene and the guide RNA comprises a crRNA sequence selected from SEQ ID NOs: 1379-1396.

C. TGFBR1

[00662] In some embodiments, the pharmaceutical composition comprising a CRISPR gene-editing system targets TGFBR1. In some embodiments, the CRISPR gene-editing system targeting TGFBR1 is delivered to a mammalian cell via viral vector. In some embodiments, the CRISPR gene-editing system targeting TGFBR1 is delivered to a mammalian cell via an AAV vector. In some embodiments, the CRISPR gene-editing system targeting TGFBR1 is delivered to a mammalian cell via a lentiviral vector. In some embodiments, the CRISPR gene-editing system targeting TGFBR1 is delivered to a mammalian cell via a lipid nanoparticle. In some embodiments, the CRISPR gene-editing system targeting TGFBR1 is delivered to a mammalian cell via a virus-like particle. In some embodiments, the CRISPR gene-editing system targeting TGFBR1 is delivered to a mammalian cell via a liposome. In some embodiments, the CRISPR gene-editing system targeting TGFBR1 is delivered to a mammalian cell via a lipid nanocrystal.

[00663] In various embodiments, the pharmaceutical composition comprising a CRISPR gene-editing system that targets the TGFBR1 gene is used in a method of treating a mammal in need thereof. In some embodiments, the method treats one or more joint disease or illness or one or more back or spine conditions or disorders. In some embodiments, the method treats one or more musculoskeletal diseases, conditions, and illnesses, including, but not limited to, Loeys-Dietz Syndrome, osteoarthritis, Marfan syndrome, aortic aneurysm (e.g., familial thoracic 3 aortic aneurysm), craniofacial abnormalities, and combinations thereof. In other embodiments, the method treats neoplastic diseases, conditions, and illnesses, including, but not limited to, pancreatic cancer, multiple self-healing squamous epithelioma

(Ferguson-Smith disease), gastrointestinal stromal tumors (GIST), hereditary nonpolyposis colorectal cancer (Lynch Syndrome), metastatic colorectal carcinoma, bone neoplasms, anaplastic carcinoma, spindle-cell carcinoma, lung neoplasms, brain neoplasms, and combinations thereof.

[00664] In some embodiments, the pharmaceutical composition comprising a CRISPR gene-editing system targets TGFBR1 for the treatment of a joint disease or illness. In some embodiments, the pharmaceutical composition comprising a CRISPR gene-editing system targets TGFBR1 for the treatment of osteoarthritis. In some embodiments, the pharmaceutical composition comprising a CRISPR gene-editing system targets TGFBR1 for the treatment of gout.

[00665] In some embodiments, the pharmaceutical composition comprising a CRISPR gene-editing system targets TGFBR1 for the treatment of a musculoskeletal disorder.

[00666] In some embodiments, the pharmaceutical composition comprising a CRISPR gene-editing system targets TGFBR1 for the treatment of a back or spine condition or disorder. In some embodiments, the pharmaceutical composition comprising a CRISPR gene-editing system targets TGFBR1 for the treatment of low back pain. In some embodiments, the pharmaceutical composition comprising a CRISPR gene-editing system targets TGFBR1 for the treatment of degenerative disc disorder. In some embodiments, the pharmaceutical composition comprising a CRISPR gene-editing system targets TGFBR1 for the treatment of internal disc disruption.

1. *Treatment of musculoskeletal disorders by targeting an TGF-beta receptor gene*

[00667] In one aspect, methods and pharmaceutical compositions are provided for treating a musculoskeletal disorder using a CRISPR pharmaceutical composition that targets a Transforming Growth Factor Beta Receptor gene. In some embodiments, the CRISPR pharmaceutical composition comprises (i) an RNA-guided nuclease or a nucleic acid encoding an RNA-guided nuclease, and (ii) at least one guide RNA (gRNA), or a nucleic acid encoding at least one gRNA, targeting the Transforming Growth Factor Beta Receptor gene, where the gRNA specifically binds a target sequence that is adjacent to a protospacer adjacent motif (PAM) sequence for the RNA-guided nuclease. In some embodiments, the CRISPR pharmaceutical composition comprises (i) an mRNA encoding an RNA-guided nuclease, and (ii) at least one gRNA targeting the Transforming Growth Factor Beta Receptor

gene. In some embodiments, the mRNA encoding the RNA-guided nuclease and the at least one gRNA are packaged in a lipid nanoparticle (LNP). In some embodiments, the musculoskeletal disorder is Loeys-Dietz Syndrome, Osteoarthrosis, Marfan Syndrome, Aortic aneurysm (familial thoracic 3), or Craniofacial abnormalities. In some embodiments, a musculoskeletal disorder listed in Figure 10 is treated with a CRISPR pharmaceutical composition targeting a gene listed as associated with the disorder in Figure 10. For example, in some embodiments, Osteoarthritis is treated with a CRISPR pharmaceutical composition targeting a TGFBR1 or TGFBR2 gene.

[00668] In some embodiments, the transforming growth factor beta receptor gene is an TGFBR1 gene. In some embodiments, the TGFBR1 gene is a human TGFBR1 gene and the guide RNA comprises a crRNA sequence selected from SEQ ID NOs: 1425-1546. In some embodiments, editing of the TGFBR1 gene results in a knockout of the TGFBR1 gene. In some such embodiments, the TGFBR1 gene is a human TGFBR1 gene and the guide RNA comprises a crRNA sequence selected from SEQ ID NOS: 1425-1454. In some embodiments, editing of the TGFBR1 gene results in a gene that expresses a membrane-bound receptor decoy protein. In some such embodiments, the TGFBR1 gene is a human TGFBR1 gene and the guide RNA comprises a crRNA sequence selected from SEQ ID NOs: 1455-1534. In some embodiments, editing of the TGFBR1 gene results in a gene that expresses a soluble receptor decoy protein. In some such embodiments, the TGFBR1 gene is a human TGFBR1 gene and the guide RNA comprises a crRNA sequence selected from SEQ ID NOs: 1535-1544.

2. *Treatment of neoplasia by targeting a TGF-beta receptor gene*

[00669] In one aspect, methods and pharmaceutical compositions are provided for treating a neoplasia using a CRISPR pharmaceutical composition that targets a Transforming Growth Factor Beta Receptor gene. In some embodiments, the CRISPR pharmaceutical composition comprises (i) an RNA-guided nuclease or a nucleic acid encoding an RNA-guided nuclease, and (ii) at least one guide RNA (gRNA), or a nucleic acid encoding at least one gRNA, targeting the Transforming Growth Factor Beta Receptor gene, where the gRNA specifically binds a target sequence that is adjacent to a protospacer adjacent motif (PAM) sequence for the RNA-guided nuclease. In some embodiments, the CRISPR pharmaceutical composition comprises (i) an mRNA encoding an RNA-guided nuclease, and (ii) at least one gRNA targeting the Transforming Growth Factor Beta Receptor gene. In some embodiments, the

mRNA encoding the RNA-guided nuclease and the at least one gRNA are packaged in a lipid nanoparticle (LNP). In some embodiments, the neoplasia is Pancreatic cancer, Multiple self-healing squamous epithelioma (Ferguson-Smith disease), Pancreatic cancer, Gastrointestinal Stromal Tumors (GIST), Hereditary Nonpolyposis Colorectal Cancer (Lynch Syndrome), Metastasis, Colorectal Carcinoma, Bone neoplasms, Anaplastic carcinoma, Spindle-Cell carcinoma, Malignant Bone Neoplasm, Lung neoplasms, or Malignant brain neoplasm. In some embodiments, a neoplasia listed in Figure 10 is treated with a CRISPR pharmaceutical composition targeting a gene listed as associated with the disorder in Figure 10. For example, in some embodiments, Pancreatic cancer is treated with a CRISPR pharmaceutical composition targeting a TGFBR2 gene.

[00670] In some embodiments, the transforming growth factor beta receptor gene is an TGFBR1 gene. In some embodiments, the TGFBR1 gene is a human TGFBR1 gene and the guide RNA comprises a crRNA sequence selected from SEQ ID NOS: 1425-1544. In some embodiments, editing of the TGFBR1 gene results in a knockout of the TGFBR1 gene. In some such embodiments, the TGFBR1 gene is a human TGFBR1 gene and the guide RNA comprises a crRNA sequence selected from SEQ ID NOS: 1425-1454. In some embodiments, editing of the TGFBR1 gene results in a gene that expresses a membrane-bound receptor decoy protein. In some such embodiments, the TGFBR1 gene is a human TGFBR1 gene and the guide RNA comprises a crRNA sequence selected from SEQ ID NOS: 1455-1534. In some embodiments, editing of the TGFBR1 gene results in a gene that expresses a soluble receptor decoy protein. In some such embodiments, the TGFBR1 gene is a human TGFBR1 gene and the guide RNA comprises a crRNA sequence selected from SEQ ID NOS: 1535-1544.

D. TGFBR2

[00671] In some embodiments, the pharmaceutical composition comprising a CRISPR gene-editing system targets TGFBR2. In some embodiments, the CRISPR gene-editing system targeting TGFBR2 is delivered to a mammalian cell via viral vector. In some embodiments, the CRISPR gene-editing system targeting TGFBR2 is delivered to a mammalian cell via an AAV vector. In some embodiments, the CRISPR gene-editing system targeting TGFBR2 is delivered to a mammalian cell via a lentiviral vector. In some embodiments, the CRISPR gene-editing system targeting TGFBR2 is delivered to a mammalian cell via a lipid nanoparticle. In some embodiments, the CRISPR gene-editing system targeting TGFBR2 is delivered to a mammalian cell via a virus-like particle. In some embodiments, the CRISPR

gene-editing system targeting TGFBR2 is delivered to a mammalian cell via a liposome. In some embodiments, the CRISPR gene-editing system targeting TGFBR2 is delivered to a mammalian cell via a lipid nanocrystal.

[00672] In various embodiments, the pharmaceutical composition comprising a CRISPR gene-editing system that targets the TGFBR2 gene is used in a method of treating a mammal in need thereof. In some embodiments, the method treats one or more joint disease or illness or one or more back or spine conditions or disorders. In some embodiments, the method treats one or more musculoskeletal diseases, conditions, and illnesses, including, but not limited to, Loeys-Dietz Syndrome, osteoarthritis, Marfan syndrome, aortic aneurysm (e.g., familial thoracic 3 aortic aneurysm), craniofacial abnormalities, and combinations thereof. In other embodiments, the method treats neoplastic diseases, conditions, and illnesses, including, but not limited to, pancreatic cancer, multiple self-healing squamous epithelioma (Ferguson-Smith disease), gastrointestinal stromal tumors (GIST), hereditary nonpolyposis colorectal cancer (Lynch Syndrome), metastatic colorectal carcinoma, bone neoplasms, anaplastic carcinoma, spindle-cell carcinoma, lung neoplasms, brain neoplasms, and combinations thereof.

[00673] In some embodiments, the pharmaceutical composition comprising a CRISPR gene-editing system targets TGFBR2 for the treatment of a joint disease or illness. In some embodiments, the pharmaceutical composition comprising a CRISPR gene-editing system targets TGFBR2 for the treatment of osteoarthritis. In some embodiments, the pharmaceutical composition comprising a CRISPR gene-editing system targets TGFBR2 for the treatment of gout.

[00674] In some embodiments, the pharmaceutical composition comprising a CRISPR gene-editing system targets TGFBR2 for the treatment of a musculoskeletal disorder.

[00675] In some embodiments, the pharmaceutical composition comprising a CRISPR gene-editing system targets TGFBR2 for the treatment of a back or spine condition or disorder. In some embodiments, the pharmaceutical composition comprising a CRISPR gene-editing system targets TGFBR2 for the treatment of low back pain. In some embodiments, the pharmaceutical composition comprising a CRISPR gene-editing system targets TGFBR2 for the treatment of degenerative disc disorder. In some embodiments, the pharmaceutical composition comprising a CRISPR gene-editing system targets TGFBR2 for the treatment of internal disc disruption.

1. *Treatment of musculoskeletal disorders by targeting an TGF-beta receptor gene*

[00676] In one aspect, methods and pharmaceutical compositions are provided for treating a musculoskeletal disorder using a CRISPR pharmaceutical composition that targets a Transforming Growth Factor Beta Receptor gene. In some embodiments, the CRISPR pharmaceutical composition comprises (i) an RNA-guided nuclease or a nucleic acid encoding an RNA-guided nuclease, and (ii) at least one guide RNA (gRNA), or a nucleic acid encoding at least one gRNA, targeting the Transforming Growth Factor Beta Receptor gene, where the gRNA specifically binds a target sequence that is adjacent to a protospacer adjacent motif (PAM) sequence for the RNA-guided nuclease. In some embodiments, the CRISPR pharmaceutical composition comprises (i) an mRNA encoding an RNA-guided nuclease, and (ii) at least one gRNA targeting the Transforming Growth Factor Beta Receptor gene. In some embodiments, the mRNA encoding the RNA-guided nuclease and the at least one gRNA are packaged in a lipid nanoparticle (LNP). In some embodiments, the musculoskeletal disorder is Loeys-Dietz Syndrome, Osteoarthrosis, Marfan Syndrome, Aortic aneurysm (familial thoracic 3), or Craniofacial abnormalities. In some embodiments, a musculoskeletal disorder listed in Figure 10 is treated with a CRISPR pharmaceutical composition targeting a gene listed as associated with the disorder in Figure 10. For example, in some embodiments, Osteoarthritis is treated with a CRISPR pharmaceutical composition targeting a TGFBR1 or TGFBR2 gene.

[00677] In some embodiments, the transforming growth factor beta receptor gene is an TGFBR2 gene. In some embodiments, the TGFBR2 gene is a human TGFBR2 gene and the guide RNA comprises a crRNA sequence selected from SEQ ID NOs: 1547-1734. In some embodiments, editing of the TGFBR2 gene results in a knockout of the TGFBR2 gene. In some such embodiments, the TGFBR2 gene is a human TGFBR2 gene and the guide RNA comprises a crRNA sequence selected from SEQ ID NOs: 1547-1580. In some embodiments, editing of the TGFBR2 gene results in a gene that expresses a membrane-bound receptor decoy protein. In some such embodiments, the TGFBR2 gene is a human TGFBR2 gene and the guide RNA comprises a crRNA sequence selected from SEQ ID NOs: 1581-1724. In some embodiments, editing of the TGFBR2 gene results in a gene that expresses a soluble receptor decoy protein. In some such embodiments, the TGFBR2 gene is a human TGFBR2 gene and the guide RNA comprises a crRNA sequence selected from SEQ ID NOs: 1725-1734.

2. *Treatment of neoplasia by targeting a TGF-beta receptor gene*

[00678] In one aspect, methods and pharmaceutical compositions are provided for treating a neoplasia using a CRISPR pharmaceutical composition that targets a Transforming Growth Factor Beta Receptor gene. In some embodiments, the CRISPR pharmaceutical composition comprises (i) an RNA-guided nuclease or a nucleic acid encoding an RNA-guided nuclease, and (ii) at least one guide RNA (gRNA), or a nucleic acid encoding at least one gRNA, targeting the Transforming Growth Factor Beta Receptor gene, where the gRNA specifically binds a target sequence that is adjacent to a protospacer adjacent motif (PAM) sequence for the RNA-guided nuclease. In some embodiments, the CRISPR pharmaceutical composition comprises (i) an mRNA encoding an RNA-guided nuclease, and (ii) at least one gRNA targeting the Transforming Growth Factor Beta Receptor gene. In some embodiments, the mRNA encoding the RNA-guided nuclease and the at least one gRNA are packaged in a lipid nanoparticle (LNP). In some embodiments, the neoplasia is Pancreatic cancer, Multiple self-healing squamous epithelioma (Ferguson-Smith disease), Pancreatic cancer, Gastrointestinal Stromal Tumors (GIST), Hereditary Nonpolyposis Colorectal Cancer (Lynch Syndrome), Metastasis, Colorectal Carcinoma, Bone neoplasms, Anaplastic carcinoma, Spindle-Cell carcinoma, Malignant Bone Neoplasm, Lung neoplasms, or Malignant brain neoplasm. In some embodiments, a neoplasia listed in Figure 10 is treated with a CRISPR pharmaceutical composition targeting a gene listed as associated with the disorder in Figure 10. For example, in some embodiments, Pancreatic cancer is treated with a CRISPR pharmaceutical composition targeting a TGFBR2 gene.

[00679] In some embodiments, the transforming growth factor beta receptor gene is an TGFBR2 gene. In some embodiments, the TGFBR2 gene is a human TGFBR2 gene and the guide RNA comprises a crRNA sequence selected from SEQ ID NOs: 1547-1734. In some embodiments, editing of the TGFBR2 gene results in a knockout of the TGFBR2 gene. In some such embodiments, the TGFBR2 gene is a human TGFBR2 gene and the guide RNA comprises a crRNA sequence selected from SEQ ID NOs: 1547-1580. In some embodiments, editing of the TGFBR2 gene results in a gene that expresses a membrane-bound receptor decoy protein. In some such embodiments, the TGFBR2 gene is a human TGFBR2 gene and the guide RNA comprises a crRNA sequence selected from SEQ ID NOs: 1581-1724. In some embodiments, editing of the TGFBR2 gene results in a gene that

expresses a soluble receptor decoy protein. In some such embodiments, the TGFBR2 gene is a human TGFBR2 gene and the guide RNA comprises a crRNA sequence selected from SEQ ID NOs: 1725-1734.

[00680]

E. IL6R

[00681] In some embodiments, the pharmaceutical composition comprising a CRISPR gene-editing system targets IL6R. In some embodiments, the CRISPR gene-editing system targeting IL6R is delivered to a mammalian cell via viral vector. In some embodiments, the CRISPR gene-editing system targeting IL6R is delivered to a mammalian cell via an AAV vector. In some embodiments, the CRISPR gene-editing system targeting IL6R is delivered to a mammalian cell via a lentiviral vector. In some embodiments, the CRISPR gene-editing system targeting IL6R is delivered to a mammalian cell via a lipid nanoparticle. In some embodiments, the CRISPR gene-editing system targeting IL6R is delivered to a mammalian cell via a virus-like particle. In some embodiments, the CRISPR gene-editing system targeting IL6R is delivered to a mammalian cell via a liposome. In some embodiments, the CRISPR gene-editing system targeting IL6R is delivered to a mammalian cell via a lipid nanocrystal.

[00682] In various embodiments, the pharmaceutical composition comprising a CRISPR gene-editing system that targets the IL6R gene is used in a method of treating a mammal in need thereof. In some embodiments, the method treats one or more joint disease or illness or one or more back or spine conditions or disorders. In some embodiments, the method treats one or more musculoskeletal diseases, conditions, and illnesses, including, but not limited to, rheumatoid arthritis, gout, osteoarthritis, osteoporosis, intervertebral disc disease (IVDD), psoriatic arthritis, arthritis, polymyositis, proliferative synovitis, bone neoplasms, sarcoid myopathy, cortex bone disorders, idiopathic scoliosis, tendinopathy, myofibrillar myopathy, enthesis-related arthritis, ankylosing spondylitis, degenerative polyarthritis, arthropathy, osteitis deformans, prolapsed lumbar disc, polymyositis ossificans, idiopathic polymyositis, Luft Disease, adult-onset Still's Disease, osteoarthritis deformans, Bachet's Disease, and combinations thereof. In other embodiments, use of the system treats one or more neoplastic diseases, conditions, and illnesses, including, but not limited to, osteosarcoma, multiple myeloma, lymphoma(e.g., B-cell or cutaneous T-cell lymphoma), leukemia, thyroid carcinoma, glioma, renal cell carcinoma, chondrosarcoma, glioblastoma, melanoma, neuroblastoma, polycystic ovary syndrome, Kaposi sarcoma, squamous cell carcinoma,

leiomyosarcoma, malignant peripheral nerve sheath tumor, Ewing's sarcoma, esophageal neoplasms, colon cancer, lung cancer, breast cancer, pancreatic cancer, stomach cancer, epithelial ovarian cancer, cholectoral cancer, liver cancer, skin cancer, prostate cancer, cervical cancer, ovarian cancer, bladder cancer, oral cavity cancer, and combinations thereof. In other embodiments, the method treats one or more inflammatory diseases, conditions, and illnesses, including, but not limited to, autoinflammatory disease (AID), cryopyrin-associated periodic syndrome (CAPS), systemic lupus erythematosus (SLE), inflammatory bowel disease (IBD) and combinations thereof. In some embodiments, the method treats one or more cardiac diseases, conditions, and illnesses, including, but not limited to, myocardial infarction, heart failure (e.g., refractory or acute decompensated heart failure), arrythmias, pericarditis (e.g., refractory idiopathic pericarditis), myocarditis, sepsis-induced cardiomyopathy, atherosclerosis, coronary artery disease and combinations thereof. In some embodiments, the method treats one or more neurological diseases, conditions, and illnesses, including, but not limited to, acute thrombotic stroke, epilepsy, multiple sclerosis, Alzheimer's Disease and combinations thereof. In some embodiments, the method treats one or more ophthalmic diseases, conditions, and illnesses, including, but not limited to, uveitis, scleritis, Sjogren asthenia, dry eye and combinations thereof. In some embodiments, the method treats one or more diseases, conditions, and illnesses, including, but not limited to, chronic kidney disease, Type 2 diabetes, gastroesophageal reflux disease (GERD), non-HP-associated peptic ulcer disease, and pulmonary fibrosis.

[00683] In some embodiments, the pharmaceutical composition comprising a CRISPR gene-editing system targets IL6R for the treatment of a joint disease or illness. In some embodiments, the pharmaceutical composition comprising a CRISPR gene-editing system targets IL6R for the treatment of osteoarthritis. In some embodiments, the pharmaceutical composition comprising a CRISPR gene-editing system targets IL6R for the treatment of gout.

[00684] In some embodiments, the pharmaceutical composition comprising a CRISPR gene-editing system targets IL6R for the treatment of a musculoskeletal disorder.

[00685] In some embodiments, the pharmaceutical composition comprising a CRISPR gene-editing system targets IL6R for the treatment of a back or spine condition or disorder. In some embodiments, the pharmaceutical composition comprising a CRISPR gene-editing system targets IL6R for the treatment of low back pain. In some embodiments, the pharmaceutical composition comprising a CRISPR gene-editing system targets IL6R for the

treatment of degenerative disc disorder. In some embodiments, the pharmaceutical composition comprising a CRISPR gene-editing system targets IL6R for the treatment of internal disc disruption.

1. *Treatment of musculoskeletal disorders by targeting an interleukin-6 receptor gene*

[00686] In one aspect, methods and pharmaceutical compositions are provided for treating a musculoskeletal disorder using a CRISPR pharmaceutical composition that targets an interleukin-6 receptor gene. In some embodiments, the CRISPR pharmaceutical composition comprises (i) an RNA-guided nuclease or a nucleic acid encoding an RNA-guided nuclease, and (ii) at least one guide RNA (gRNA), or a nucleic acid encoding at least one gRNA, targeting the interleukin-6 receptor gene, where the gRNA specifically binds a target sequence that is adjacent to a protospacer adjacent motif (PAM) sequence for the RNA-guided nuclease. In some embodiments, the CRISPR pharmaceutical composition comprises (i) an mRNA encoding an RNA-guided nuclease, and (ii) at least one gRNA targeting the interleukin-6 receptor gene. In some embodiments, the mRNA encoding the RNA-guided nuclease and the at least one gRNA are packaged in a lipid nanoparticle (LNP). In some embodiments, the musculoskeletal disorder is Rheumatoid arthritis, Idiopathic osteoporosis, Post-menopausal osteoporosis, Paget's disease, Osteoarthritis, Juvenile idiopathic arthritis (JIA), Still's disease, Ankylosing spondylitis, Polymyalgia rheumatica, Arthritis, Secondary malignant neoplasm of bone, Type II, Mucolipidosis, Sjogren's Syndrome, Psoriatic arthritis, Rheumatism, Castleman's disease, Degenerative Polyarthritis, Arthropathy, Bone neoplasm, Osteoporosis, Massive osteolysis, Bone fracture healing, Systemic sclerosis, Systemic Juvenile Idiopathic, Arthritis, or Synovitis. In some embodiments, a musculoskeletal disorder listed in Figure 4 is treated with a CRISPR pharmaceutical composition targeting a gene listed as associated with the disorder in Figure 4. For example, in some embodiments, Rheumatoid Arthritis is treated with a CRISPR pharmaceutical composition targeting an IL6R or IL6ST gene.

[00687] In some embodiments, the interleukin-6 receptor gene is an IL6R gene. In some embodiments, the IL6R gene is a human IL6R gene and the guide RNA comprises a crRNA sequence selected from SEQ ID NOs: 1746-1968. In some embodiments, editing of the IL6R gene results in a knockout of the IL6R gene. In some such embodiments, the IL6R gene is a human IL6R gene and the guide RNA comprises a crRNA sequence selected from SEQ ID SEQ ID NOs: 1746-1907. In some embodiments, editing of the IL6R gene results in a gene

that expresses a soluble receptor decoy protein. In some such embodiments, the IL6R gene is a human IL6R gene and the guide RNA comprises a crRNA sequence selected from SEQ ID SEQ ID NOs: 1835-1920.

2. *Treatment of neoplasia by targeting an interleukin-6 receptor gene*

[00688] In one aspect, methods and pharmaceutical compositions are provided for treating a neoplasia using a CRISPR pharmaceutical composition that targets an interleukin-6 receptor gene. In some embodiments, the CRISPR pharmaceutical composition comprises (i) an RNA-guided nuclease or a nucleic acid encoding an RNA-guided nuclease, and (ii) at least one guide RNA (gRNA), or a nucleic acid encoding at least one gRNA, targeting the interleukin-6 receptor gene, where the gRNA specifically binds a target sequence that is adjacent to a protospacer adjacent motif (PAM) sequence for the RNA-guided nuclease. In some embodiments, the CRISPR pharmaceutical composition comprises (i) an mRNA encoding an RNA-guided nuclease, and (ii) at least one gRNA targeting the interleukin-6 receptor gene. In some embodiments, the mRNA encoding the RNA-guided nuclease and the at least one gRNA are packaged in a lipid nanoparticle (LNP). In some embodiments, the neoplasia is Multiple myeloma, Lung Cancer, Stomach Cancer, Breast Cancer, Kidney Cancer, Neoplasm Metastasis, Colorectal Neoplasms, Ovarian cancer, Osteosarcoma, Cholangiocarcinoma, Leukemia, Prostate cancer, Plasmacytoma, Pancreatic cancer, Cervical cancer, Lymphoma, Liver neoplasms, Neuroblastoma, Melanoma, Mastocytosis, Endometrial cancer, Bladder Cancer, Squamous cell carcinoma, Gallbladder carcinoma, Adenocarcinoma, Thyroid Cancer, prostate neoplasms, stomach cancer, liver carcinoma, pituitary neoplasms, hepatoblastoma, multiple myeloma, hepatocellular adenoma, breast carcinoma, carcinogenesis, leukemia, colon carcinoma, melanoma, metastasis (general), lung cancer, pancreatic cancer, Kaposi sarcoma, medulloblastoma, carcinoma of bladder, squamous cell carcinoma, mast cell neoplasm, glioma, mastocytoma, brain neoplasms, ovarian neoplasms, bone neoplasm, rhabdomyosarcoma, solid tumors, metastatic kidney cancer, or metastatic renal cell carcinoma. In some embodiments, a neoplasia listed in Figure 4 is treated with a CRISPR pharmaceutical composition targeting a gene listed as associated with the disorder in Figure 4. For example, in some embodiments, Prostate Cancer is treated with a CRISPR pharmaceutical composition targeting an IL6R or IL6ST gene.

[00689] In some embodiments, the interleukin-6 receptor gene is an IL6R gene. In some embodiments, the IL6R gene is a human IL6R gene and the guide RNA comprises a crRNA

sequence selected from SEQ ID NOs: 1746-1968. In some embodiments, editing of the IL6R gene results in a knockout of the IL6R gene. In some such embodiments, the IL6R gene is a human IL6R gene and the guide RNA comprises a crRNA sequence selected from SEQ ID SEQ ID NOs: 1746-1907. In some embodiments, editing of the IL6R gene results in a gene that expresses a soluble receptor decoy protein. In some such embodiments, the IL6R gene is a human IL6R gene and the guide RNA comprises a crRNA sequence selected from SEQ ID SEQ ID NOs: 1835-1920.

3. *Treatment of inflammatory disorders by targeting an interleukin-6 receptor gene*

[00690] In one aspect, methods and pharmaceutical compositions are provided for treating an inflammatory disorder using a CRISPR pharmaceutical composition that targets an interleukin-6 receptor gene. In some embodiments, the CRISPR pharmaceutical composition comprises (i) an RNA-guided nuclease or a nucleic acid encoding an RNA-guided nuclease, and (ii) at least one guide RNA (gRNA), or a nucleic acid encoding at least one gRNA, targeting the interleukin-6 receptor gene, where the gRNA specifically binds a target sequence that is adjacent to a protospacer adjacent motif (PAM) sequence for the RNA-guided nuclease. In some embodiments, the CRISPR pharmaceutical composition comprises (i) an mRNA encoding an RNA-guided nuclease, and (ii) at least one gRNA targeting the interleukin-6 receptor gene. In some embodiments, the mRNA encoding the RNA-guided nuclease and the at least one gRNA are packaged in a lipid nanoparticle (LNP). In some embodiments, the inflammatory disorder is an Inflammatory disease (e.g. cytokine storm in COVID 19 or post- CAR-T therapy), acute local inflammation, inflammatory bowel disease, Crohn's disease, Experimental sepsis, or Castleman's disease.

[00691] In some embodiments, the interleukin-6 receptor gene is an IL6R gene. In some embodiments, the IL6R gene is a human IL6R gene and the guide RNA comprises a crRNA sequence selected from SEQ ID NOs: 1746-1968. In some embodiments, editing of the IL6R gene results in a knockout of the IL6R gene. In some such embodiments, the IL6R gene is a human IL6R gene and the guide RNA comprises a crRNA sequence selected from SEQ ID SEQ ID NOs: 1746-1907. In some embodiments, editing of the IL6R gene results in a gene that expresses a soluble receptor decoy protein. In some such embodiments, the IL6R gene is a human IL6R gene and the guide RNA comprises a crRNA sequence selected from SEQ ID SEQ ID NOs: 1835-1920.

4. *Treatment of cardiac disorder by targeting an interleukin-6 receptor gene*

[00692] In one aspect, methods and pharmaceutical compositions are provided for treating a cardiac disorder using a CRISPR pharmaceutical composition that targets an interleukin-6 receptor gene. In some embodiments, the CRISPR pharmaceutical composition comprises (i) an RNA-guided nuclease or a nucleic acid encoding an RNA-guided nuclease, and (ii) at least one guide RNA (gRNA), or a nucleic acid encoding at least one gRNA, targeting the interleukin-6 receptor gene, where the gRNA specifically binds a target sequence that is adjacent to a protospacer adjacent motif (PAM) sequence for the RNA-guided nuclease. In some embodiments, the CRISPR pharmaceutical composition comprises (i) an mRNA encoding an RNA-guided nuclease, and (ii) at least one gRNA targeting the interleukin-6 receptor gene. In some embodiments, the mRNA encoding the RNA-guided nuclease and the at least one gRNA are packaged in a lipid nanoparticle (LNP). In some embodiments, the cardiac disorder is atherosclerosis, or abdominal aortic aneurism. In some embodiments, a cardiac disorder listed in Figure 4 is treated with a CRISPR pharmaceutical composition targeting a gene listed as associated with the disorder in Figure 4. For example, in some embodiments, atherosclerosis is treated with a CRISPR pharmaceutical composition targeting an IL6R or IL6ST gene.

[00693] In some embodiments, the interleukin-6 receptor gene is an IL6R gene. In some embodiments, the IL6R gene is a human IL6R gene and the guide RNA comprises a crRNA sequence selected from SEQ ID NOs: 1746-1968. In some embodiments, editing of the IL6R gene results in a knockout of the IL6R gene. In some such embodiments, the IL6R gene is a human IL6R gene and the guide RNA comprises a crRNA sequence selected from SEQ ID SEQ ID NOs: 1746-1907. In some embodiments, editing of the IL6R gene results in a gene that expresses a soluble receptor decoy protein. In some such embodiments, the IL6R gene is a human IL6R gene and the guide RNA comprises a crRNA sequence selected from SEQ ID SEQ ID NOs: 1835-1920.

5. *Treatment of autoimmune disorder by targeting an interleukin-6 receptor gene*

[00694] In one aspect, methods and pharmaceutical compositions are provided for treating an autoimmune disorder using a CRISPR pharmaceutical composition that targets an interleukin-6 receptor gene. In some embodiments, the CRISPR pharmaceutical composition comprises (i) an RNA-guided nuclease or a nucleic acid encoding an RNA-guided nuclease, and (ii) at least one guide RNA (gRNA), or a nucleic acid encoding at least one gRNA,

targeting the interleukin-6 receptor gene, where the gRNA specifically binds a target sequence that is adjacent to a protospacer adjacent motif (PAM) sequence for the RNA-guided nuclease. In some embodiments, the CRISPR pharmaceutical composition comprises (i) an mRNA encoding an RNA-guided nuclease, and (ii) at least one gRNA targeting the interleukin-6 receptor gene. In some embodiments, the mRNA encoding the RNA-guided nuclease and the at least one gRNA are packaged in a lipid nanoparticle (LNP). In some embodiments, the autoimmune disorder is Systemic Lupus Erythematosus. In some embodiments, an autoimmune disorder listed in Figure 4 is treated with a CRISPR pharmaceutical composition targeting a gene listed as associated with the disorder in Figure 4. For example, in some embodiments, Systemic Lupus Erythematosus is treated with a CRISPR pharmaceutical composition targeting an IL6R or IL6ST gene.

[00695] In some embodiments, the interleukin-6 receptor gene is an IL6R gene. In some embodiments, the IL6R gene is a human IL6R gene and the guide RNA comprises a crRNA sequence selected from SEQ ID NOs: 1746-1968. In some embodiments, editing of the IL6R gene results in a knockout of the IL6R gene. In some such embodiments, the IL6R gene is a human IL6R gene and the guide RNA comprises a crRNA sequence selected from SEQ ID SEQ ID NOs: 1746-1907. In some embodiments, editing of the IL6R gene results in a gene that expresses a soluble receptor decoy protein. In some such embodiments, the IL6R gene is a human IL6R gene and the guide RNA comprises a crRNA sequence selected from SEQ ID SEQ ID NOs: 1835-1920.

F. IL6ST

[00696] In some embodiments, the pharmaceutical composition comprising a CRISPR gene-editing system targets IL6ST. In some embodiments, the CRISPR gene-editing system targeting IL6ST is delivered to a mammalian cell via viral vector. In some embodiments, the CRISPR gene-editing system targeting IL6ST is delivered to a mammalian cell via an AAV vector. In some embodiments, the CRISPR gene-editing system targeting IL6ST is delivered to a mammalian cell via a lentiviral vector. In some embodiments, the CRISPR gene-editing system targeting IL6ST is delivered to a mammalian cell via a lipid nanoparticle. In some embodiments, the CRISPR gene-editing system targeting IL6ST is delivered to a mammalian cell via a virus-like particle. In some embodiments, the CRISPR gene-editing system targeting IL6ST is delivered to a mammalian cell via a liposome. In some embodiments, the CRISPR gene-editing system targeting IL6ST is delivered to a mammalian cell via a lipid nanocrystal.

[00697] In various embodiments, the pharmaceutical composition comprising a CRISPR gene-editing system that targets the IL6ST gene is used in a method of treating a mammal in need thereof. In some embodiments, the method treats one or more joint disease or illness or one or more back or spine conditions or disorders. In some embodiments, the method treats one or more musculoskeletal diseases, conditions, and illnesses, including, but not limited to, rheumatoid arthritis, gout, osteoarthritis, osteoporosis, intervertebral disc disease (IVDD), psoriatic arthritis, arthritis, polymyositis, proliferative synovitis, bone neoplasms, sarcoid myopathy, cortex bone disorders, idiopathic scoliosis, tendinopathy, myofibrillar myopathy, enthesis-related arthritis, ankylosing spondylitis, degenerative polyarthritis, arthropathy, osteitis deformans, prolapsed lumbar disc, polymyositis ossificans, idiopathic polymyositis, Luft Disease, adult-onset Still's Disease, osteoarthritis deformans, Bachet's Disease, and combinations thereof. In other embodiments, use of the system treats one or more neoplastic diseases, conditions, and illnesses, including, but not limited to, osteosarcoma, multiple myeloma, lymphoma(e.g., B-cell or cutaneous T-cell lymphoma), leukemia, thyroid carcinoma, glioma, renal cell carcinoma, chondrosarcoma, glioblastoma, melanoma, neuroblastoma, polycystic ovary syndrome, Kaposi sarcoma, squamous cell carcinoma, leiomyosarcoma, malignant peripheral nerve sheath tumor, Ewing's sarcoma, esophageal neoplasms, colon cancer, lung cancer, breast cancer, pancreatic cancer, stomach cancer, epithelial ovarian cancer, cholectoral cancer, liver cancer, skin cancer, prostate cancer, cervical cancer, ovarian cancer, bladder cancer, oral cavity cancer, and combinations thereof. In other embodiments, the method treats one or more inflammatory diseases, conditions, and illnesses, including, but not limited to, autoinflammatory disease (AID), cryopyrin-associated periodic syndrome (CAPS), systemic lupus erythematosus (SLE), inflammatory bowel disease (IBD) and combinations thereof. In some embodiments, the method treats one or more cardiac diseases, conditions, and illnesses, including, but not limited to, myocardial infarction, heart failure (e.g., refractory or acute decompensated heart failure), arrythmias, pericarditis (e.g., refractory idiopathic pericarditis), myocarditis, sepsis-induced cardiomyopathy, atherosclerosis, coronary artery disease and combinations thereof. In some embodiments, the method treats one or more neurological diseases, conditions, and illnesses, including, but not limited to, acute thrombotic stroke, epilepsy, multiple sclerosis, Alzheimer's Disease and combinations thereof. In some embodiments, the method treats one or more ophthalmic diseases, conditions, and illnesses, including, but not limited to, uveitis, scleritis, Sjogren asthenia, dry eye and combinations thereof. In some embodiments, the method treats one or more diseases, conditions, and illnesses, including, but not limited to,

chronic kidney disease, Type 2 diabetes, gastroesophageal reflux disease (GERD), non-HP-associated peptic ulcer disease, and pulmonary fibrosis.

[00698] In some embodiments, the pharmaceutical composition comprising a CRISPR gene-editing system targets IL6ST for the treatment of a joint disease or illness. In some embodiments, the pharmaceutical composition comprising a CRISPR gene-editing system targets IL6ST for the treatment of osteoarthritis. In some embodiments, the pharmaceutical composition comprising a CRISPR gene-editing system targets IL6ST for the treatment of gout.

[00699] In some embodiments, the pharmaceutical composition comprising a CRISPR gene-editing system targets IL6ST for the treatment of a musculoskeletal disorder.

[00700] In some embodiments, the pharmaceutical composition comprising a CRISPR gene-editing system targets IL6ST for the treatment of a back or spine condition or disorder. In some embodiments, the pharmaceutical composition comprising a CRISPR gene-editing system targets IL6ST for the treatment of low back pain. In some embodiments, the pharmaceutical composition comprising a CRISPR gene-editing system targets IL6ST for the treatment of degenerative disc disorder. In some embodiments, the pharmaceutical composition comprising a CRISPR gene-editing system targets IL6ST for the treatment of internal disc disruption.

1. *Treatment of musculoskeletal disorders by targeting an interleukin-6 receptor gene*

[00701] In one aspect, methods and pharmaceutical compositions are provided for treating a musculoskeletal disorder using a CRISPR pharmaceutical composition that targets an interleukin-6 receptor gene. In some embodiments, the CRISPR pharmaceutical composition comprises (i) an RNA-guided nuclease or a nucleic acid encoding an RNA-guided nuclease, and (ii) at least one guide RNA (gRNA), or a nucleic acid encoding at least one gRNA, targeting the interleukin-6 receptor gene, where the gRNA specifically binds a target sequence that is adjacent to a protospacer adjacent motif (PAM) sequence for the RNA-guided nuclease. In some embodiments, the CRISPR pharmaceutical composition comprises (i) an mRNA encoding an RNA-guided nuclease, and (ii) at least one gRNA targeting the interleukin-6 receptor gene. In some embodiments, the mRNA encoding the RNA-guided nuclease and the at least one gRNA are packaged in a lipid nanoparticle (LNP). In some embodiments, the musculoskeletal disorder is Rheumatoid arthritis, Idiopathic osteoporosis,

Post-menopausal osteoporosis, Paget's disease, Osteoarthritis, Juvenile idiopathic arthritis (JIA), Still's disease, Ankylosing spondylitis, Polymyalgia rheumatica, Arthritis, Secondary malignant neoplasm of bone, Type II, Mucolipidosis, Sjogren's Syndrome, Psoriatic arthritis, Rheumatism, Castleman's disease, Degenerative Polyarthritis, Arthropathy, Bone neoplasm, Osteoporosis, Massive osteolysis, Bone fracture healing, Systemic sclerosis, Systemic Juvenile Idiopathic, Arthritis, or Synovitis. In some embodiments, a musculoskeletal disorder listed in Figure 4 is treated with a CRISPR pharmaceutical composition targeting a gene listed as associated with the disorder in Figure 4. For example, in some embodiments, Rheumatoid Arthritis is treated with a CRISPR pharmaceutical composition targeting an IL6R or IL6ST gene.

[00702] In some embodiments, the interleukin-6 receptor gene is an IL6ST gene. In some embodiments, the IL6ST gene is a human IL6ST gene and the guide RNA comprises a crRNA sequence selected from SEQ ID NOs: 1969-2178. In some embodiments, editing of the IL6ST gene results in a knockout of the IL6ST gene. In some such embodiments, the IL6ST gene is a human IL6ST gene and the guide RNA comprises a crRNA sequence selected from SEQ ID NOs: 1969-2037. In some embodiments, editing of the IL6ST gene results in a gene that expresses a membrane-bound receptor decoy protein. In some such embodiments, the IL6ST gene is a human IL6ST gene and the guide RNA comprises a crRNA sequence selected from SEQ ID NOs: 2038-2102. In some embodiments, editing of the IL6ST gene results in a gene that expresses a soluble receptor decoy protein. In some such embodiments, the IL6ST gene is a human IL6ST gene and the guide RNA comprises a crRNA sequence selected from SEQ ID NOs: 2103-2176.

2. *Treatment of neoplasia by targeting an interleukin-6 receptor gene*

[00703] In one aspect, methods and pharmaceutical compositions are provided for treating a neoplasia using a CRISPR pharmaceutical composition that targets an interleukin-6 receptor gene. In some embodiments, the CRISPR pharmaceutical composition comprises (i) an RNA-guided nuclease or a nucleic acid encoding an RNA-guided nuclease, and (ii) at least one guide RNA (gRNA), or a nucleic acid encoding at least one gRNA, targeting the interleukin-6 receptor gene, where the gRNA specifically binds a target sequence that is adjacent to a protospacer adjacent motif (PAM) sequence for the RNA-guided nuclease. In some embodiments, the CRISPR pharmaceutical composition comprises (i) an mRNA encoding an RNA-guided nuclease, and (ii) at least one gRNA targeting the interleukin-6

receptor gene. In some embodiments, the mRNA encoding the RNA-guided nuclease and the at least one gRNA are packaged in a lipid nanoparticle (LNP). In some embodiments, the neoplasia is Multiple myeloma, Lung Cancer, Stomach Cancer, Breast Cancer, Kidney Cancer, Neoplasm Metastasis, Colorectal Neoplasms, Ovarian cancer, Osteosarcoma, Cholangiocarcinoma, Leukemia, Prostate cancer, Plasmacytoma, Pancreatic cancer, Cervical cancer, Lymphoma, Liver neoplasms, Neuroblastoma, Melanoma, Mastocytosis, Endometrial cancer, Bladder Cancer, Squamous cell carcinoma, Gallbladder carcinoma, Adenocarcinoma, Thyroid Cancer, prostate neoplasms, stomach cancer, liver carcinoma, pituitary neoplasms, hepatoblastoma, multiple myeloma, hepatocellular adenoma, breast carcinoma, carcinogenesis, leukemia, colon carcinoma, melanoma, metastasis (general), lung cancer, pancreatic cancer, Kaposi sarcoma, medulloblastoma, carcinoma of bladder, squamous cell carcinoma, mast cell neoplasm, glioma, mastocytoma, brain neoplasms, ovarian neoplasms, bone neoplasm, rhabdomyosarcoma, solid tumors, metastatic kidney cancer, or metastatic renal cell carcinoma. In some embodiments, a neoplasia listed in Figure 4 is treated with a CRISPR pharmaceutical composition targeting a gene listed as associated with the disorder in Figure 4. For example, in some embodiments, Prostate Cancer is treated with a CRISPR pharmaceutical composition targeting an IL6R or IL6ST gene.

[00704] In some embodiments, the interleukin-6 receptor gene is an IL6ST gene. In some embodiments, the IL6ST gene is a human IL6ST gene and the guide RNA comprises a crRNA sequence selected from SEQ ID NOs: 1969-2178. In some embodiments, editing of the IL6ST gene results in a knockout of the IL6ST gene. In some such embodiments, the IL6ST gene is a human IL6ST gene and the guide RNA comprises a crRNA sequence selected from SEQ ID NOs: 1969-2037. In some embodiments, editing of the IL6ST gene results in a gene that expresses a membrane-bound receptor decoy protein. In some such embodiments, the IL6ST gene is a human IL6ST gene and the guide RNA comprises a crRNA sequence selected from SEQ ID NOs: 2038-2102. In some embodiments, editing of the IL6ST gene results in a gene that expresses a soluble receptor decoy protein. In some such embodiments, the IL6ST gene is a human IL6ST gene and the guide RNA comprises a crRNA sequence selected from SEQ ID NOs: 2103-2176.

3. *Treatment of inflammatory disorders by targeting an interleukin-6 receptor gene*

[00705] In one aspect, methods and pharmaceutical compositions are provided for treating an inflammatory disorder using a CRISPR pharmaceutical composition that targets an

interleukin-6 receptor gene. In some embodiments, the CRISPR pharmaceutical composition comprises (i) an RNA-guided nuclease or a nucleic acid encoding an RNA-guided nuclease, and (ii) at least one guide RNA (gRNA), or a nucleic acid encoding at least one gRNA, targeting the interleukin-6 receptor gene, where the gRNA specifically binds a target sequence that is adjacent to a protospacer adjacent motif (PAM) sequence for the RNA-guided nuclease. In some embodiments, the CRISPR pharmaceutical composition comprises (i) an mRNA encoding an RNA-guided nuclease, and (ii) at least one gRNA targeting the interleukin-6 receptor gene. In some embodiments, the mRNA encoding the RNA-guided nuclease and the at least one gRNA are packaged in a lipid nanoparticle (LNP). In some embodiments, the inflammatory disorder is an Inflammatory disease (e.g. cytokine storm in COVID 19 or post-CAR-T therapy), acute local inflammation, inflammatory bowel disease, Crohn's disease, Experimental sepsis, or Castleman's disease.

[00706] In some embodiments, the interleukin-6 receptor gene is an IL6ST gene. In some embodiments, the IL6ST gene is a human IL6ST gene and the guide RNA comprises a crRNA sequence selected from SEQ ID NOs: 1969-2178. In some embodiments, editing of the IL6ST gene results in a knockout of the IL6ST gene. In some such embodiments, the IL6ST gene is a human IL6ST gene and the guide RNA comprises a crRNA sequence selected from SEQ ID NOs: 1969-2037. In some embodiments, editing of the IL6ST gene results in a gene that expresses a membrane-bound receptor decoy protein. In some such embodiments, the IL6ST gene is a human IL6ST gene and the guide RNA comprises a crRNA sequence selected from SEQ ID NOs: 2038-2102. In some embodiments, editing of the IL6ST gene results in a gene that expresses a soluble receptor decoy protein. In some such embodiments, the IL6ST gene is a human IL6ST gene and the guide RNA comprises a crRNA sequence selected from SEQ ID NOs: 2103-2176.

4. *Treatment of cardiac disorder by targeting an interleukin-6 receptor gene*

[00707] In one aspect, methods and pharmaceutical compositions are provided for treating a cardiac disorder using a CRISPR pharmaceutical composition that targets an interleukin-6 receptor gene. In some embodiments, the CRISPR pharmaceutical composition comprises (i) an RNA-guided nuclease or a nucleic acid encoding an RNA-guided nuclease, and (ii) at least one guide RNA (gRNA), or a nucleic acid encoding at least one gRNA, targeting the interleukin-6 receptor gene, where the gRNA specifically binds a target sequence that is adjacent to a protospacer adjacent motif (PAM) sequence for the RNA-guided nuclease. In

some embodiments, the CRISPR pharmaceutical composition comprises (i) an mRNA encoding an RNA-guided nuclease, and (ii) at least one gRNA targeting the interleukin-6 receptor gene. In some embodiments, the mRNA encoding the RNA-guided nuclease and the at least one gRNA are packaged in a lipid nanoparticle (LNP). In some embodiments, the cardiac disorder is atherosclerosis, or abdominal aortic aneurism. In some embodiments, a cardiac disorder listed in Figure 4 is treated with a CRISPR pharmaceutical composition targeting a gene listed as associated with the disorder in Figure 4. For example, in some embodiments, atherosclerosis is treated with a CRISPR pharmaceutical composition targeting an IL6R or IL6ST gene.

[00708] In some embodiments, the interleukin-6 receptor gene is an IL6ST gene. In some embodiments, the IL6ST gene is a human IL6ST gene and the guide RNA comprises a crRNA sequence selected from SEQ ID NOs: 1969-2178. In some embodiments, editing of the IL6ST gene results in a knockout of the IL6ST gene. In some such embodiments, the IL6ST gene is a human IL6ST gene and the guide RNA comprises a crRNA sequence selected from SEQ ID NOs: 1969-2037. In some embodiments, editing of the IL6ST gene results in a gene that expresses a membrane-bound receptor decoy protein. In some such embodiments, the IL6ST gene is a human IL6ST gene and the guide RNA comprises a crRNA sequence selected from SEQ ID NOs: 2038-2102. In some embodiments, editing of the IL6ST gene results in a gene that expresses a soluble receptor decoy protein. In some such embodiments, the IL6ST gene is a human IL6ST gene and the guide RNA comprises a crRNA sequence selected from SEQ ID NOs: 2103-2176.

5. *Treatment of autoimmune disorder by targeting an interleukin-6 receptor gene*

[00709] In one aspect, methods and pharmaceutical compositions are provided for treating an autoimmune disorder using a CRISPR pharmaceutical composition that targets an interleukin-6 receptor gene. In some embodiments, the CRISPR pharmaceutical composition comprises (i) an RNA-guided nuclease or a nucleic acid encoding an RNA-guided nuclease, and (ii) at least one guide RNA (gRNA), or a nucleic acid encoding at least one gRNA, targeting the interleukin-6 receptor gene, where the gRNA specifically binds a target sequence that is adjacent to a protospacer adjacent motif (PAM) sequence for the RNA-guided nuclease. In some embodiments, the CRISPR pharmaceutical composition comprises (i) an mRNA encoding an RNA-guided nuclease, and (ii) at least one gRNA targeting the interleukin-6 receptor gene. In some embodiments, the mRNA encoding the RNA-guided

nuclease and the at least one gRNA are packaged in a lipid nanoparticle (LNP). In some embodiments, the autoimmune disorder is Systemic Lupus Erythematosus. In some embodiments, an autoimmune disorder listed in Figure 4 is treated with a CRISPR pharmaceutical composition targeting a gene listed as associated with the disorder in Figure 4. For example, in some embodiments, Systemic Lupus Erythematosus is treated with a CRISPR pharmaceutical composition targeting an IL6R or IL6ST gene.

[00710] In some embodiments, the interleukin-6 receptor gene is an IL6ST gene. In some embodiments, the IL6ST gene is a human IL6ST gene and the guide RNA comprises a crRNA sequence selected from SEQ ID NOs: 1969-2178. In some embodiments, editing of the IL6ST gene results in a knockout of the IL6ST gene. In some such embodiments, the IL6ST gene is a human IL6ST gene and the guide RNA comprises a crRNA sequence selected from SEQ ID NOs: 1969-2037. In some embodiments, editing of the IL6ST gene results in a gene that expresses a membrane-bound receptor decoy protein. In some such embodiments, the IL6ST gene is a human IL6ST gene and the guide RNA comprises a crRNA sequence selected from SEQ ID NOs: 2038-2102. In some embodiments, editing of the IL6ST gene results in a gene that expresses a soluble receptor decoy protein. In some such embodiments, the IL6ST gene is a human IL6ST gene and the guide RNA comprises a crRNA sequence selected from SEQ ID NOs: 2103-2176.

[00711]

[00712]

G. TNFRSF1A

[00713] In some embodiments, the pharmaceutical composition comprising a CRISPR gene-editing system targets TNFRSF1A. In some embodiments, the CRISPR gene-editing system targeting TNFRSF1A is delivered to a mammalian cell via viral vector. In some embodiments, the CRISPR gene-editing system targeting TNFRSF1A is delivered to a mammalian cell via an AAV vector. In some embodiments, the CRISPR gene-editing system targeting TNFRSF1A is delivered to a mammalian cell via a lentiviral vector. In some embodiments, the CRISPR gene-editing system targeting TNFRSF1A is delivered to a mammalian cell via a lipid nanoparticle. In some embodiments, the CRISPR gene-editing system targeting TNFRSF1A is delivered to a mammalian cell via a virus-like particle. In some embodiments, the CRISPR gene-editing system targeting TNFRSF1A is delivered to a

mammalian cell via a liposome. In some embodiments, the CRISPR gene-editing system targeting TNFRSF1A is delivered to a mammalian cell via a lipid nanocrystal.

[00714] In various embodiments, the pharmaceutical composition comprising a CRISPR gene-editing system that targets the TNFRSF1A gene is used in a method of treating a mammal in need thereof. In some embodiments, the method treats one or more joint disease or illness or one or more back or spine conditions or disorders. In some embodiments, the method treats one or more musculoskeletal diseases, conditions, and illnesses, including, but not limited to, rheumatoid arthritis, gout, osteoarthritis, osteoporosis, intervertebral disc disease (IVDD), psoriatic arthritis, arthritis, polymyositis, proliferative synovitis, bone neoplasms, sarcoid myopathy, cortex bone disorders, idiopathic scoliosis, tendinopathy, myofibrillar myopathy, enthesis-related arthritis, ankylosing spondylitis, degenerative polyarthritis, arthropathy, osteitis deformans, prolapsed lumbar disc, polymyositis ossificans, idiopathic polymyositis, Luft Disease, adult-onset Still's Disease, osteoarthritis deformans, Bachet's Disease, and combinations thereof. In other embodiments, use of the system treats one or more neoplastic diseases, conditions, and illnesses, including, but not limited to, osteosarcoma, multiple myeloma, lymphoma(e.g., B-cell or cutaneous T-cell lymphoma), leukemia, thyroid carcinoma, glioma, renal cell carcinoma, chondrosarcoma, glioblastoma, melanoma, neuroblastoma, polycystic ovary syndrome, Kaposi sarcoma, squamous cell carcinoma, leiomyosarcoma, malignant peripheral nerve sheath tumor, Ewing's sarcoma, esophageal neoplasms, colon cancer, lung cancer, breast cancer, pancreatic cancer, stomach cancer, epithelial ovarian cancer, cholectoral cancer, liver cancer, skin cancer, prostate cancer, cervical cancer, ovarian cancer, bladder cancer, oral cavity cancer, and combinations thereof. In other embodiments, the method treats one or more inflammatory diseases, conditions, and illnesses, including, but not limited to, autoinflammatory disease (AID), cryopyrin-associated periodic syndrome (CAPS), systemic lupus erythematosus (SLE), inflammatory bowel disease (IBD) and combinations thereof. In some embodiments, the method treats one or more cardiac diseases, conditions, and illnesses, including, but not limited to, myocardial infarction, heart failure (e.g., refractory or acute decompensated heart failure), arrythmias, pericarditis (e.g., refractory idiopathic pericarditis), myocarditis, sepsis-induced cardiomyopathy, atherosclerosis, coronary artery disease and combinations thereof. In some embodiments, the method treats one or more neurological diseases, conditions, and illnesses, including, but not limited to, acute thrombotic stroke, epilepsy, multiple sclerosis, Alzheimer's Disease and combinations thereof. In some embodiments, the method treats one

or more ophthalmic diseases, conditions, and illnesses, including, but not limited to, uveitis, scleritis, Sjogren asthenia, dry eye and combinations thereof. In some embodiments, the method treats one or more diseases, conditions, and illnesses, including, but not limited to, chronic kidney disease, Type 2 diabetes, gastroesophageal reflux disease (GERD), non-HP-associated peptic ulcer disease, and pulmonary fibrosis.

[00715] In some embodiments, the pharmaceutical composition comprising a CRISPR gene-editing system targets TNFRSF1A for the treatment of a joint disease or illness. In some embodiments, the pharmaceutical composition comprising a CRISPR gene-editing system targets TNFRSF1A for the treatment of osteoarthritis. In some embodiments, the pharmaceutical composition comprising a CRISPR gene-editing system targets TNFRSF1A for the treatment of gout.

[00716] In some embodiments, the pharmaceutical composition comprising a CRISPR gene-editing system targets TNFRSF1A for the treatment of a musculoskeletal disorder.

[00717] In some embodiments, the pharmaceutical composition comprising a CRISPR gene-editing system targets TNFRSF1A for the treatment of a back or spine condition or disorder. In some embodiments, the pharmaceutical composition comprising a CRISPR gene-editing system targets TNFRSF1A for the treatment of low back pain. In some embodiments, the pharmaceutical composition comprising a CRISPR gene-editing system targets TNFRSF1A for the treatment of degenerative disc disorder. In some embodiments, the pharmaceutical composition comprising a CRISPR gene-editing system targets TNFRSF1A for the treatment of internal disc disruption.

1. *Treatment of musculoskeletal disorders by targeting a tumor necrosis factor receptor superfamily gene*

[00718] In one aspect, methods and pharmaceutical compositions are provided for treating a musculoskeletal disorder using a CRISPR pharmaceutical composition that targets a Tumor Necrosis Factor Receptor Superfamily gene. In some embodiments, the CRISPR pharmaceutical composition comprises (i) an RNA-guided nuclease or a nucleic acid encoding an RNA-guided nuclease, and (ii) at least one guide RNA (gRNA), or a nucleic acid encoding at least one gRNA, targeting the Tumor Necrosis Factor Receptor Superfamily gene, where the gRNA specifically binds a target sequence that is adjacent to a protospacer adjacent motif (PAM) sequence for the RNA-guided nuclease. In some embodiments, the CRISPR pharmaceutical composition comprises (i) an mRNA encoding an RNA-guided

nuclease, and (ii) at least one gRNA targeting the Tumor Necrosis Factor Receptor Superfamily gene. In some embodiments, the mRNA encoding the RNA-guided nuclease and the at least one gRNA are packaged in a lipid nanoparticle (LNP). In some embodiments, the musculoskeletal disorder is Arthritis, Infectious Intermittent joint effusion, Ankylosing spondylitis, Arthritis, Osteoarthritis, Spondylarthritis, Plantar fasciitis, Degenerative polyarthritis, Hemophilic arthropathy, Inflammatory myopathy with abundant macrophages, Polymyositis, Tendinosis, Malignant Bone Neoplasm, Osteoporosis, Psoriatic arthritis, Rheumatism, Rheumatoid arthritis, Adult Still's disease, Juvenile arthritis, Early rheumatoid arthritis, Palindromic rheumatism, Gout, Infectious Arthritis, Myotonic dystrophy, Dermatomyositis, Hemophilic arthropathy, Osteopenia, Sjogren's syndrome, Juvenile Idiopathic Arthritis, Myasthenia gravis, Osteolysis, Inflammation, Degenerative polyarthritis, Osteitis deformans, Pigmented villonodular synovitis, or Hyperphosphatasemia with bone disease. In some embodiments, a musculoskeletal disorder listed in Figure 5, 6, 7, 8, or 9 is treated with a CRISPR pharmaceutical composition targeting a gene listed as associated with the disorder in Figure 5, 6, 7, 8, or 9. For example, in some embodiments, Rheumatoid Arthritis is treated with a CRISPR pharmaceutical composition targeting a TNFRSF1A, TNFRSF1B, TNFRSF3, TNFRSF4, or TNFRSF11A gene.

[00719] In some embodiments, the tumor necrosis factor receptor superfamily gene is an TNFRSF1A gene. In some embodiments, the TNFRSF1A gene is a human TNFRSF1A gene and the guide RNA comprises a crRNA sequence selected from SEQ ID NOs: 2179-2383. In some embodiments, editing of the TNFRSF1A gene results in a knockout of the TNFRSF1A gene. In some such embodiments, the TNFRSF1A gene is a human TNFRSF1A gene and the guide RNA comprises a crRNA sequence selected from SEQ ID NOs: 2179-2247. In some embodiments, editing of the TNFRSF1A gene results in a gene that expresses a membrane-bound receptor decoy protein. In some such embodiments, the TNFRSF1A gene is a human TNFRSF1A gene and the guide RNA comprises a crRNA sequence selected from SEQ ID NOs: 2248-2369. In some embodiments, editing of the TNFRSF1A gene results in a gene that expresses a soluble receptor decoy protein. In some such embodiments, the TNFRSF1A gene is a human TNFRSF1A gene and the guide RNA comprises a crRNA sequence selected from SEQ ID NOs: 2370-2383.

2. *Treatment of neoplasia by targeting a tumor necrosis factor receptor superfamily gene*

[00720] In one aspect, methods and pharmaceutical compositions are provided for treating a neoplasia using a CRISPR pharmaceutical composition that targets a Tumor Necrosis Factor Receptor Superfamily gene. In some embodiments, the CRISPR pharmaceutical composition comprises (i) an RNA-guided nuclease or a nucleic acid encoding an RNA-guided nuclease, and (ii) at least one guide RNA (gRNA), or a nucleic acid encoding at least one gRNA, targeting the Tumor Necrosis Factor Receptor Superfamily gene, where the gRNA specifically binds a target sequence that is adjacent to a protospacer adjacent motif (PAM) sequence for the RNA-guided nuclease. In some embodiments, the CRISPR pharmaceutical composition comprises (i) an mRNA encoding an RNA-guided nuclease, and (ii) at least one gRNA targeting the Tumor Necrosis Factor Receptor Superfamily gene. In some embodiments, the mRNA encoding the RNA-guided nuclease and the at least one gRNA are packaged in a lipid nanoparticle (LNP). In some embodiments, the neoplasia is Neoplasms, Glioblastoma, Astrocytoma, Adenocarcinoma, Osteosarcoma, Squamous cell carcinoma, Metastasis, Ameloblastoma, Cholangiocarcinoma, Choriocarcinoma, Ovarian cancer, Prostate cancer, Lung Cancer, Larynx Cancer, Breast Cancer, Lip and Oral Cavity Carcinoma, Squamous intraepithelial lesion, Neuroblastoma, Non-Hodgkin lymphomas, Malignant Neoplasms, Skin Neoplasms, Neuroblastoma, Neoplasm Metastasis, Colorectal Cancer, Fibrosarcoma, Myeloid Leukemia, Myelofibrosis, Hodgkin Lymphomas, Non-Small Cell Lung Carcinoma, Cervical Cancer, Liver cancer, Extrapulmonary small cell carcinoma, Basal cell carcinoma, Kidney cancer, Pancreatic carcinoma, Mesothelioma, Gastric cancer, Polycystic Ovary Syndrome, Chordoma, Cholangiocarcinoma, Malignant ascites, Nasopharyngeal carcinoma, Head and Neck Carcinoma, Cancer metastasis, Prostate carcinoma, Fibrosarcoma, Liver carcinoma, Carcinoma of bladder, T-Cell Lymphoblastic Leukemia, Bladder Neoplasm, melanoma, Leukemia (such as acute myeloid leukemia), Hepatocellular carcinoma, Colorectal cancer, or Lymphoma (such as Mycosis fungoides and Sézary syndrome). In some embodiments, a neoplasia listed in Figure 5, 6, 7, 8, or 9 is treated with a CRISPR pharmaceutical composition targeting a gene listed as associated with the disorder in Figure 5, 6, 7, 8, or 9. For example, in some embodiments, Glioblastoma is treated with a CRISPR pharmaceutical composition targeting a TNFRSF1A, TNFRSF1B, TNFRSF3, TNFRSF4, or TNFRSF11A gene.

[00721] In some embodiments, the tumor necrosis factor receptor superfamily gene is an TNFRSF1A gene. In some embodiments, the TNFRSF1A gene is a human TNFRSF1A gene and the guide RNA comprises a crRNA sequence selected from SEQ ID NOs: 2179-2383. In some embodiments, editing of the TNFRSF1A gene results in a knockout of the TNFRSF1A gene. In some such embodiments, the TNFRSF1A gene is a human TNFRSF1A gene and the guide RNA comprises a crRNA sequence selected from SEQ ID NOs: 2179-2247. In some embodiments, editing of the TNFRSF1A gene results in a gene that expresses a membrane-bound receptor decoy protein. In some such embodiments, the TNFRSF1A gene is a human TNFRSF1A gene and the guide RNA comprises a crRNA sequence selected from SEQ ID NOs: 2248-2369. In some embodiments, editing of the TNFRSF1A gene results in a gene that expresses a soluble receptor decoy protein. In some such embodiments, the TNFRSF1A gene is a human TNFRSF1A gene and the guide RNA comprises a crRNA sequence selected from SEQ ID NOs: 2370-2383.

3. *Treatment of autoimmune or inflammatory disorders by targeting a tumor necrosis factor receptor superfamily gene*

[00722] In one aspect, methods and pharmaceutical compositions are provided for treating an autoimmune or inflammatory disorder using a CRISPR pharmaceutical composition that targets a Tumor Necrosis Factor Receptor Superfamily gene. In some embodiments, the CRISPR pharmaceutical composition comprises (i) an RNA-guided nuclease or a nucleic acid encoding an RNA-guided nuclease, and (ii) at least one guide RNA (gRNA), or a nucleic acid encoding at least one gRNA, targeting the Tumor Necrosis Factor Receptor Superfamily gene, where the gRNA specifically binds a target sequence that is adjacent to a protospacer adjacent motif (PAM) sequence for the RNA-guided nuclease. In some embodiments, the CRISPR pharmaceutical composition comprises (i) an mRNA encoding an RNA-guided nuclease, and (ii) at least one gRNA targeting the Tumor Necrosis Factor Receptor Superfamily gene. In some embodiments, the mRNA encoding the RNA-guided nuclease and the at least one gRNA are packaged in a lipid nanoparticle (LNP). In some embodiments, the autoimmune or inflammatory disorder is Allergy, Asthma, Multiple sclerosis, Psoriasis, Inflammatory bowel disease, Autoimmune experimental uveitis, Colitis, Hypersensitivity reaction disease, Diabetes, Crohn's disease, Systemic lupus erythematosus, Pulmonary sarcoidosis, Leishmaniasis, Experimental autoimmune encephalomyelitis, HTLV-1-associated myelopathy, Tropical spastic paraparesis, Scleroderma, or Idiopathic inflammatory myopathy (such as polymyositis and dermatomyositis). In some embodiments,

an autoimmune or inflammatory disorder listed in Figure 5, 6, 7, 8, or 9 is treated with a CRISPR pharmaceutical composition targeting a gene listed as associated with the disorder in Figure 5, 6, 7, 8, or 9. For example, in some embodiments, allergies are treated with a CRISPR pharmaceutical composition targeting a TNFRSF1A, TNFRSF1B, TNFRSF3, TNFRSF4, or TNFRSF11A gene.

[00723] In some embodiments, the tumor necrosis factor receptor superfamily gene is an TNFRSF1A gene. In some embodiments, the TNFRSF1A gene is a human TNFRSF1A gene and the guide RNA comprises a crRNA sequence selected from SEQ ID NOs: 2179-2383. In some embodiments, editing of the TNFRSF1A gene results in a knockout of the TNFRSF1A gene. In some such embodiments, the TNFRSF1A gene is a human TNFRSF1A gene and the guide RNA comprises a crRNA sequence selected from SEQ ID NOs: 2179-2247. In some embodiments, editing of the TNFRSF1A gene results in a gene that expresses a membrane-bound receptor decoy protein. In some such embodiments, the TNFRSF1A gene is a human TNFRSF1A gene and the guide RNA comprises a crRNA sequence selected from SEQ ID NOs: 2248-2369. In some embodiments, editing of the TNFRSF1A gene results in a gene that expresses a soluble receptor decoy protein. In some such embodiments, the TNFRSF1A gene is a human TNFRSF1A gene and the guide RNA comprises a crRNA sequence selected from SEQ ID NOs: 2370-2383.

H. TNFRSF1B

[00724] In some embodiments, the pharmaceutical composition comprising a CRISPR gene-editing system targets TNFRSF1B. In some embodiments, the CRISPR gene-editing system targeting TNFRSF1B is delivered to a mammalian cell via viral vector. In some embodiments, the CRISPR gene-editing system targeting TNFRSF1B is delivered to a mammalian cell via an AAV vector. In some embodiments, the CRISPR gene-editing system targeting TNFRSF1B is delivered to a mammalian cell via a lentiviral vector. In some embodiments, the CRISPR gene-editing system targeting TNFRSF1B is delivered to a mammalian cell via a lipid nanoparticle. In some embodiments, the CRISPR gene-editing system targeting TNFRSF1B is delivered to a mammalian cell via a virus-like particle. In some embodiments, the CRISPR gene-editing system targeting TNFRSF1B is delivered to a mammalian cell via a liposome. In some embodiments, the CRISPR gene-editing system targeting TNFRSF1B is delivered to a mammalian cell via a lipid nanocrystal.

[00725] In various embodiments, the pharmaceutical composition comprising a CRISPR gene-editing system that targets the TNFRSF1B gene is used in a method of treating a

mammal in need thereof. In some embodiments, the method treats one or more joint disease or illness or one or more back or spine conditions or disorders. In some embodiments, the method treats one or more musculoskeletal diseases, conditions, and illnesses, including, but not limited to, rheumatoid arthritis, gout, osteoarthritis, osteoporosis, intervertebral disc disease (IVDD), psoriatic arthritis, arthritis, polymyositis, proliferative synovitis, bone neoplasms, sarcoid myopathy, cortex bone disorders, idiopathic scoliosis, tendinopathy, myofibrillar myopathy, enthesis-related arthritis, ankylosing spondylitis, degenerative polyarthritis, arthropathy, osteitis deformans, prolapsed lumbar disc, polymyositis ossificans, idiopathic polymyositis, Luft Disease, adult-onset Still's Disease, osteoarthritis deformans, Bachet's Disease, and combinations thereof. In other embodiments, use of the system treats one or more neoplastic diseases, conditions, and illnesses, including, but not limited to, osteosarcoma, multiple myeloma, lymphoma(e.g., B-cell or cutaneous T-cell lymphoma), leukemia, thyroid carcinoma, glioma, renal cell carcinoma, chondrosarcoma, glioblastoma, melanoma, neuroblastoma, polycystic ovary syndrome, Kaposi sarcoma, squamous cell carcinoma, leiomyosarcoma, malignant peripheral nerve sheath tumor, Ewing's sarcoma, esophageal neoplasms, colon cancer, lung cancer, breast cancer, pancreatic cancer, stomach cancer, epithelial ovarian cancer, cholectoral cancer, liver cancer, skin cancer, prostate cancer, cervical cancer, ovarian cancer, bladder cancer, oral cavity cancer, and combinations thereof. In other embodiments, the method treats one or more inflammatory diseases, conditions, and illnesses, including, but not limited to, autoinflammatory disease (AID), cryopyrin-associated periodic syndrome (CAPS), systemic lupus erythematosus (SLE), inflammatory bowel disease (IBD) and combinations thereof. In some embodiments, the method treats one or more cardiac diseases, conditions, and illnesses, including, but not limited to, myocardial infarction, heart failure (e.g., refractory or acute decompensated heart failure), arrythmias, pericarditis (e.g., refractory idiopathic pericarditis), myocarditis, sepsis-induced cardiomyopathy, atherosclerosis, coronary artery disease and combinations thereof. In some embodiments, the method treats one or more neurological diseases, conditions, and illnesses, including, but not limited to, acute thrombotic stroke, epilepsy, multiple sclerosis, Alzheimer's Disease and combinations thereof. In some embodiments, the method treats one or more ophthalmic diseases, conditions, and illnesses, including, but not limited to, uveitis, scleritis, Sjogren asthenia, dry eye and combinations thereof. In some embodiments, the method treats one or more diseases, conditions, and illnesses, including, but not limited to, chronic kidney disease, Type 2 diabetes, gastroesophageal reflux disease (GERD), non-HP-associated peptic ulcer disease, and pulmonary fibrosis.

[00726] In some embodiments, the pharmaceutical composition comprising a CRISPR gene-editing system targets TNFRSF1B for the treatment of a joint disease or illness. In some embodiments, the pharmaceutical composition comprising a CRISPR gene-editing system targets TNFRSF1B for the treatment of osteoarthritis. In some embodiments, the pharmaceutical composition comprising a CRISPR gene-editing system targets TNFRSF1B for the treatment of gout.

[00727] In some embodiments, the pharmaceutical composition comprising a CRISPR gene-editing system targets TNFRSF1B for the treatment of a musculoskeletal disorder.

[00728] In some embodiments, the pharmaceutical composition comprising a CRISPR gene-editing system targets TNFRSF1B for the treatment of a back or spine condition or disorder. In some embodiments, the pharmaceutical composition comprising a CRISPR gene-editing system targets TNFRSF1B for the treatment of low back pain. In some embodiments, the pharmaceutical composition comprising a CRISPR gene-editing system targets TNFRSF1B for the treatment of degenerative disc disorder. In some embodiments, the pharmaceutical composition comprising a CRISPR gene-editing system targets TNFRSF1B for the treatment of internal disc disruption.

1. *Treatment of musculoskeletal disorders by targeting a tumor necrosis factor receptor superfamily gene*

[00729] In one aspect, methods and pharmaceutical compositions are provided for treating a musculoskeletal disorder using a CRISPR pharmaceutical composition that targets a Tumor Necrosis Factor Receptor Superfamily gene. In some embodiments, the CRISPR pharmaceutical composition comprises (i) an RNA-guided nuclease or a nucleic acid encoding an RNA-guided nuclease, and (ii) at least one guide RNA (gRNA), or a nucleic acid encoding at least one gRNA, targeting the Tumor Necrosis Factor Receptor Superfamily gene, where the gRNA specifically binds a target sequence that is adjacent to a protospacer adjacent motif (PAM) sequence for the RNA-guided nuclease. In some embodiments, the CRISPR pharmaceutical composition comprises (i) an mRNA encoding an RNA-guided nuclease, and (ii) at least one gRNA targeting the Tumor Necrosis Factor Receptor Superfamily gene. In some embodiments, the mRNA encoding the RNA-guided nuclease and the at least one gRNA are packaged in a lipid nanoparticle (LNP). In some embodiments, the musculoskeletal disorder is Arthritis, Infectious Intermittent joint effusion, Ankylosing spondylitis, Arthritis, Osteoarthritis, Spondylarthritis, Plantar fasciitis,

Degenerative polyarthritis, Hemophilic arthropathy, Inflammatory myopathy with abundant macrophages, Polymyositis, Tendinosis, Malignant Bone Neoplasm, Osteoporosis, Psoriatic arthritis, Rheumatism, Rheumatoid arthritis, Adult Still's disease, Juvenile arthritis, Early rheumatoid arthritis, Palindromic rheumatism, Gout, Infectious Arthritis, Myotonic dystrophy, Dermatomyositis, Hemophilic arthropathy, Osteopenia, Sjogren's syndrome, Juvenile Idiopathic Arthritis, Myasthenia gravis, Osteolysis, Inflammation, Degenerative polyarthritis, Osteitis deformans, Pigmented villonodular synovitis, or Hyperphosphatasemia with bone disease. In some embodiments, a musculoskeletal disorder listed in Figure 5, 6, 7, 8, or 9 is treated with a CRISPR pharmaceutical composition targeting a gene listed as associated with the disorder in Figure 5, 6, 7, 8, or 9. For example, in some embodiments, Rheumatoid Arthritis is treated with a CRISPR pharmaceutical composition targeting a TNFRSF1A, TNFRSF1B, TNFRSF3, TNFRSF4, or TNFRSF11A gene.

[00730] In some embodiments, the tumor necrosis factor receptor superfamily gene is an TNFRSF1B gene. In some embodiments, the TNFRSF1B gene is a human TNFRSF1B gene and the guide RNA comprises a crRNA sequence selected from SEQ ID NOs: 2396-2642. In some embodiments, editing of the TNFRSF1B gene results in a knockout of the TNFRSF1B gene. In some such embodiments, the TNFRSF1B gene is a human TNFRSF1B gene and the guide RNA comprises a crRNA sequence selected from SEQ ID NOs: 2396-2482. In some embodiments, editing of the TNFRSF1B gene results in a gene that expresses a membrane-bound receptor decoy protein. In some such embodiments, the TNFRSF1B gene is a human TNFRSF1B gene and the guide RNA comprises a crRNA sequence selected from SEQ ID NOs: 2483-2574. In some embodiments, editing of the TNFRSF1B gene results in a gene that expresses a soluble receptor decoy protein. In some such embodiments, the TNFRSF1B gene is a human TNFRSF1B gene and the guide RNA comprises a crRNA sequence selected from SEQ ID NOs: 2575-2622.

2. *Treatment of neoplasia by targeting a tumor necrosis factor receptor superfamily gene*

[00731] In one aspect, methods and pharmaceutical compositions are provided for treating a neoplasia using a CRISPR pharmaceutical composition that targets a Tumor Necrosis Factor Receptor Superfamily gene. In some embodiments, the CRISPR pharmaceutical composition comprises (i) an RNA-guided nuclease or a nucleic acid encoding an RNA-guided nuclease, and (ii) at least one guide RNA (gRNA), or a nucleic acid encoding at least one gRNA, targeting the Tumor Necrosis Factor Receptor Superfamily gene, where the gRNA

specifically binds a target sequence that is adjacent to a protospacer adjacent motif (PAM) sequence for the RNA-guided nuclease. In some embodiments, the CRISPR pharmaceutical composition comprises (i) an mRNA encoding an RNA-guided nuclease, and (ii) at least one gRNA targeting the Tumor Necrosis Factor Receptor Superfamily gene. In some embodiments, the mRNA encoding the RNA-guided nuclease and the at least one gRNA are packaged in a lipid nanoparticle (LNP). In some embodiments, the neoplasia is Neoplasms, Glioblastoma, Astrocytoma, Adenocarcinoma, Osteosarcoma, Squamous cell carcinoma, Metastasis, Ameloblastoma, Cholangiocarcinoma, Choriocarcinoma, Ovarian cancer, Prostate cancer, Lung Cancer, Larynx Cancer, Breast Cancer, Lip and Oral Cavity Carcinoma, Squamous intraepithelial lesion, Neuroblastoma, Non-Hodgkin lymphomas, Malignant Neoplasms, Skin Neoplasms, Neuroblastoma, Neoplasm Metastasis, Colorectal Cancer, Fibrosarcoma, Myeloid Leukemia, Myelofibrosis, Hodgkin Lymphomas, Non-Small Cell Lung Carcinoma, Cervical Cancer, Liver cancer, Extrapulmonary small cell carcinoma, Basal cell carcinoma, Kidney cancer, Pancreatic carcinoma, Mesothelioma, Gastric cancer, Polycystic Ovary Syndrome, Chordoma, Cholangiocarcinoma, Malignant ascites, Nasopharyngeal carcinoma, Head and Neck Carcinoma, Cancer metastasis, Prostate carcinoma, Fibrosarcoma, Liver carcinoma, Carcinoma of bladder, T-Cell Lymphoblastic Leukemia, Bladder Neoplasm, melanoma, Leukemia (such as acute myeloid leukemia), Hepatocellular carcinoma, Colorectal cancer, or Lymphoma (such as Mycosis fungoides and Sézary syndrome). In some embodiments, a neoplasia listed in Figure 5, 6, 7, 8, or 9 is treated with a CRISPR pharmaceutical composition targeting a gene listed as associated with the disorder in Figure 5, 6, 7, 8, or 9. For example, in some embodiments, Glioblastoma is treated with a CRISPR pharmaceutical composition targeting a TNFRSF1A, TNFRSF1B, TNFRSF3, TNFRSF4, or TNFRSF11A gene.

[00732] In some embodiments, the tumor necrosis factor receptor superfamily gene is an TNFRSF1B gene. In some embodiments, the TNFRSF1B gene is a human TNFRSF1B gene and the guide RNA comprises a crRNA sequence selected from SEQ ID NOs: 2396-2642. In some embodiments, editing of the TNFRSF1B gene results in a knockout of the TNFRSF1B gene. In some such embodiments, the TNFRSF1B gene is a human TNFRSF1B gene and the guide RNA comprises a crRNA sequence selected from SEQ ID NOs: 2396-2482. In some embodiments, editing of the TNFRSF1B gene results in a gene that expresses a membrane-bound receptor decoy protein. In some such embodiments, the TNFRSF1B gene is a human TNFRSF1B gene and the guide RNA comprises a crRNA sequence selected from SEQ ID

NOs: 2483-2574. In some embodiments, editing of the TNFRSF1B gene results in a gene that expresses a soluble receptor decoy protein. In some such embodiments, the TNFRSF1B gene is a human TNFRSF1B gene and the guide RNA comprises a crRNA sequence selected from SEQ ID NOs: 2575-2622.

3. *Treatment of autoimmune or inflammatory disorders by targeting a tumor necrosis factor receptor superfamily gene*

[00733] In one aspect, methods and pharmaceutical compositions are provided for treating an autoimmune or inflammatory disorder using a CRISPR pharmaceutical composition that targets a Tumor Necrosis Factor Receptor Superfamily gene. In some embodiments, the CRISPR pharmaceutical composition comprises (i) an RNA-guided nuclease or a nucleic acid encoding an RNA-guided nuclease, and (ii) at least one guide RNA (gRNA), or a nucleic acid encoding at least one gRNA, targeting the Tumor Necrosis Factor Receptor Superfamily gene, where the gRNA specifically binds a target sequence that is adjacent to a protospacer adjacent motif (PAM) sequence for the RNA-guided nuclease. In some embodiments, the CRISPR pharmaceutical composition comprises (i) an mRNA encoding an RNA-guided nuclease, and (ii) at least one gRNA targeting the Tumor Necrosis Factor Receptor Superfamily gene. In some embodiments, the mRNA encoding the RNA-guided nuclease and the at least one gRNA are packaged in a lipid nanoparticle (LNP). In some embodiments, the autoimmune or inflammatory disorder is Allergy, Asthma, Multiple sclerosis, Psoriasis, Inflammatory bowel disease, Autoimmune experimental uveitis, Colitis, Hypersensitivity reaction disease, Diabetes, Crohn's disease, Systemic lupus erythematosus, Pulmonary sarcoidosis, Leishmaniasis, Experimental autoimmune encephalomyelitis, HTLV-1-associated myelopathy, Tropical spastic paraparesis, Scleroderma, or Idiopathic inflammatory myopathy (such as polymyositis and dermatomyositis). In some embodiments, an autoimmune or inflammatory disorder listed in Figure 5, 6, 7, 8, or 9 is treated with a CRISPR pharmaceutical composition targeting a gene listed as associated with the disorder in Figure 5, 6, 7, 8, or 9. For example, in some embodiments, allergies are treated with a CRISPR pharmaceutical composition targeting a TNFRSF1A, TNFRSF1B, TNFRSF3, TNFRSF4, or TNFRSF11A gene.

[00734] In some embodiments, the tumor necrosis factor receptor superfamily gene is an TNFRSF1B gene. In some embodiments, the TNFRSF1B gene is a human TNFRSF1B gene and the guide RNA comprises a crRNA sequence selected from SEQ ID NOs: 2396-2642. In some embodiments, editing of the TNFRSF1B gene results in a knockout of the TNFRSF1B

gene. In some such embodiments, the TNFRSF1B gene is a human TNFRSF1B gene and the guide RNA comprises a crRNA sequence selected from SEQ ID NOs: 2396-2482. In some embodiments, editing of the TNFRSF1B gene results in a gene that expresses a membrane-bound receptor decoy protein. In some such embodiments, the TNFRSF1B gene is a human TNFRSF1B gene and the guide RNA comprises a crRNA sequence selected from SEQ ID NOs: 2483-2574. In some embodiments, editing of the TNFRSF1B gene results in a gene that expresses a soluble receptor decoy protein. In some such embodiments, the TNFRSF1B gene is a human TNFRSF1B gene and the guide RNA comprises a crRNA sequence selected from SEQ ID NOs: 2575-2622.

I. TNFRSF3

[00735] In some embodiments, the pharmaceutical composition comprising a CRISPR gene-editing system targets TNFRSF3. In some embodiments, the CRISPR gene-editing system targeting TNFRSF3 is delivered to a mammalian cell via viral vector. In some embodiments, the CRISPR gene-editing system targeting TNFRSF3 is delivered to a mammalian cell via an AAV vector. In some embodiments, the CRISPR gene-editing system targeting TNFRSF3 is delivered to a mammalian cell via a lentiviral vector. In some embodiments, the CRISPR gene-editing system targeting TNFRSF3 is delivered to a mammalian cell via a lipid nanoparticle. In some embodiments, the CRISPR gene-editing system targeting TNFRSF3 is delivered to a mammalian cell via a virus-like particle. In some embodiments, the CRISPR gene-editing system targeting TNFRSF3 is delivered to a mammalian cell via a liposome. In some embodiments, the CRISPR gene-editing system targeting TNFRSF3 is delivered to a mammalian cell via a lipid nanocrystal.

[00736] In various embodiments, the pharmaceutical composition comprising a CRISPR gene-editing system that targets the TNFRSF3 gene is used in a method of treating a mammal in need thereof. In some embodiments, the method treats one or more joint disease or illness or one or more back or spine conditions or disorders. In some embodiments, the method treats one or more musculoskeletal diseases, conditions, and illnesses, including, but not limited to, rheumatoid arthritis, gout, osteoarthritis, osteoporosis, intervertebral disc disease (IVDD), psoriatic arthritis, arthritis, polymyositis, proliferative synovitis, bone neoplasms, sarcoid myopathy, cortex bone disorders, idiopathic scoliosis, tendinopathy, myofibrillar myopathy, enthesis-related arthritis, ankylosing spondylitis, degenerative polyarthritis, arthropathy, osteitis deformans, prolapsed lumbar disc, polymyositis ossificans, idiopathic polymyositis, Luft Disease, adult-onset Still's Disease, osteoarthritis deformans, Bachet's

Disease, and combinations thereof. In other embodiments, use of the system treats one or more neoplastic diseases, conditions, and illnesses, including, but not limited to, osteosarcoma, multiple myeloma, lymphoma(e.g., B-cell or cutaneous T-cell lymphoma), leukemia, thyroid carcinoma, glioma, renal cell carcinoma, chondrosarcoma, glioblastoma, melanoma, neuroblastoma, polycystic ovary syndrome, Kaposi sarcoma, squamous cell carcinoma, leiomyosarcoma, malignant peripheral nerve sheath tumor, Ewing's sarcoma, esophageal neoplasms, colon cancer, lung cancer, breast cancer, pancreatic cancer, stomach cancer, epithelial ovarian cancer, cholectoral cancer, liver cancer, skin cancer, prostate cancer, cervical cancer, ovarian cancer, bladder cancer, oral cavity cancer, and combinations thereof. In other embodiments, the method treats one or more inflammatory diseases, conditions, and illnesses, including, but not limited to, autoinflammatory disease (AID), cryopyrin-associated periodic syndrome (CAPS), systemic lupus erythematosus (SLE), inflammatory bowel disease (IBD) and combinations thereof. In some embodiments, the method treats one or more cardiac diseases, conditions, and illnesses, including, but not limited to, myocardial infarction, heart failure (e.g., refractory or acute decompensated heart failure), arrythmias, pericarditis (e.g., refractory idiopathic pericarditis), myocarditis, sepsis-induced cardiomyopathy, atherosclerosis, coronary artery disease and combinations thereof. In some embodiments, the method treats one or more neurological diseases, conditions, and illnesses, including, but not limited to, acute thrombotic stroke, epilepsy, multiple sclerosis, Alzheimer's Disease and combinations thereof. In some embodiments, the method treats one or more ophthalmic diseases, conditions, and illnesses, including, but not limited to, uveitis, scleritis, Sjogren asthenia, dry eye and combinations thereof. In some embodiments, the method treats one or more diseases, conditions, and illnesses, including, but not limited to, chronic kidney disease, Type 2 diabetes, gastroesophageal reflux disease (GERD), non-HP-associated peptic ulcer disease, and pulmonary fibrosis.

[00737] In some embodiments, the pharmaceutical composition comprising a CRISPR gene-editing system targets TNFRSF3 for the treatment of a joint disease or illness. In some embodiments, the pharmaceutical composition comprising a CRISPR gene-editing system targets TNFRSF3 for the treatment of osteoarthritis. In some embodiments, the pharmaceutical composition comprising a CRISPR gene-editing system targets TNFRSF3 for the treatment of gout.

[00738] In some embodiments, the pharmaceutical composition comprising a CRISPR gene-editing system targets TNFRSF3 for the treatment of a musculoskeletal disorder.

[00739] In some embodiments, the pharmaceutical composition comprising a CRISPR gene-editing system targets TNFRSF3 for the treatment of a back or spine condition or disorder. In some embodiments, the pharmaceutical composition comprising a CRISPR gene-editing system targets TNFRSF3 for the treatment of low back pain. In some embodiments, the pharmaceutical composition comprising a CRISPR gene-editing system targets TNFRSF3 for the treatment of degenerative disc disorder. In some embodiments, the pharmaceutical composition comprising a CRISPR gene-editing system targets TNFRSF3 for the treatment of internal disc disruption.

1. *Treatment of musculoskeletal disorders by targeting a tumor necrosis factor receptor superfamily gene*

[00740] In one aspect, methods and pharmaceutical compositions are provided for treating a musculoskeletal disorder using a CRISPR pharmaceutical composition that targets a Tumor Necrosis Factor Receptor Superfamily gene. In some embodiments, the CRISPR pharmaceutical composition comprises (i) an RNA-guided nuclease or a nucleic acid encoding an RNA-guided nuclease, and (ii) at least one guide RNA (gRNA), or a nucleic acid encoding at least one gRNA, targeting the Tumor Necrosis Factor Receptor Superfamily gene, where the gRNA specifically binds a target sequence that is adjacent to a protospacer adjacent motif (PAM) sequence for the RNA-guided nuclease. In some embodiments, the CRISPR pharmaceutical composition comprises (i) an mRNA encoding an RNA-guided nuclease, and (ii) at least one gRNA targeting the Tumor Necrosis Factor Receptor Superfamily gene. In some embodiments, the mRNA encoding the RNA-guided nuclease and the at least one gRNA are packaged in a lipid nanoparticle (LNP). In some embodiments, the musculoskeletal disorder is Arthritis, Infectious Intermittent joint effusion, Ankylosing spondylitis, Arthritis, Osteoarthritis, Spondylarthritis, Plantar fasciitis, Degenerative polyarthritis, Hemophilic arthropathy, Inflammatory myopathy with abundant macrophages, Polymyositis, Tendinosis, Malignant Bone Neoplasm, Osteoporosis, Psoriatic arthritis, Rheumatism, Rheumatoid arthritis, Adult Still's disease, Juvenile arthritis, Early rheumatoid arthritis, Palindromic rheumatism, Gout, Infectious Arthritis, Myotonic dystrophy, Dermatomyositis, Hemophilic arthropathy, Osteopenia, Sjogren's syndrome, Juvenile Idiopathic Arthritis, Myasthenia gravis, Osteolysis, Inflammation, Degenerative polyarthritis, Osteitis deformans, Pigmented villonodular synovitis, or Hyperphosphatasemia with bone disease. In some embodiments, a musculoskeletal disorder listed in Figure 5, 6, 7, 8, or 9 is treated with a CRISPR pharmaceutical composition targeting a gene listed as

associated with the disorder in Figure 5, 6, 7, 8, or 9. For example, in some embodiments, Rheumatoid Arthritis is treated with a CRISPR pharmaceutical composition targeting a TNFRSF1A, TNFRSF1B, TNFRSF3, TNFRSF4, or TNFRSF11A gene.

[00741] In some embodiments, the tumor necrosis factor receptor superfamily gene is an TNFRSF3 gene. In some embodiments, the TNFRSF3 gene is a human TNFRSF3 gene and the guide RNA comprises a crRNA sequence selected from SEQ ID NOs: 2643-2866. In some embodiments, editing of the TNFRSF3 gene results in a knockout of the TNFRSF3 gene. In some such embodiments, the TNFRSF3 gene is a human TNFRSF3 gene and the guide RNA comprises a crRNA sequence selected from SEQ ID NOs: 2643-2737. In some embodiments, editing of the TNFRSF3 gene results in a gene that expresses a membrane-bound receptor decoy protein. In some such embodiments, the TNFRSF3 gene is a human TNFRSF3 gene and the guide RNA comprises a crRNA sequence selected from SEQ ID NOs: 2738-2846. In some embodiments, editing of the TNFRSF3 gene results in a gene that expresses a soluble receptor decoy protein. In some such embodiments, the TNFRSF3 gene is a human TNFRSF3 gene and the guide RNA comprises a crRNA sequence selected from SEQ ID NOs: 2847-2852.

2. *Treatment of neoplasia by targeting a tumor necrosis factor receptor superfamily gene*

[00742] In one aspect, methods and pharmaceutical compositions are provided for treating a neoplasia using a CRISPR pharmaceutical composition that targets a Tumor Necrosis Factor Receptor Superfamily gene. In some embodiments, the CRISPR pharmaceutical composition comprises (i) an RNA-guided nuclease or a nucleic acid encoding an RNA-guided nuclease, and (ii) at least one guide RNA (gRNA), or a nucleic acid encoding at least one gRNA, targeting the Tumor Necrosis Factor Receptor Superfamily gene, where the gRNA specifically binds a target sequence that is adjacent to a protospacer adjacent motif (PAM) sequence for the RNA-guided nuclease. In some embodiments, the CRISPR pharmaceutical composition comprises (i) an mRNA encoding an RNA-guided nuclease, and (ii) at least one gRNA targeting the Tumor Necrosis Factor Receptor Superfamily gene. In some embodiments, the mRNA encoding the RNA-guided nuclease and the at least one gRNA are packaged in a lipid nanoparticle (LNP). In some embodiments, the neoplasia is Neoplasms, Glioblastoma, Astrocytoma, Adenocarcinoma, Osteosarcoma, Squamous cell carcinoma, Metastasis, Ameloblastoma, Cholangiocarcinoma, Choriocarcinoma, Ovarian cancer, Prostate cancer, Lung Cancer, Larynx Cancer, Breast Cancer, Lip and Oral Cavity

Carcinoma, Squamous intraepithelial lesion, Neuroblastoma, Non-Hodgkin lymphomas, Malignant Neoplasms, Skin Neoplasms, Neuroblastoma, Neoplasm Metastasis, Colorectal Cancer, Fibrosarcoma, Myeloid Leukemia, Myelofibrosis, Hodgkin Lymphomas, Non-Small Cell Lung Carcinoma, Cervical Cancer, Liver cancer, Extrapulmonary small cell carcinoma, Basal cell carcinoma, Kidney cancer, Pancreatic carcinoma, Mesothelioma, Gastric cancer, Polycystic Ovary Syndrome, Chordoma, Cholangiocarcinoma, Malignant ascites, Nasopharyngeal carcinoma, Head and Neck Carcinoma, Cancer metastasis, Prostate carcinoma, Fibrosarcoma, Liver carcinoma, Carcinoma of bladder, T-Cell Lymphoblastic Leukemia, Bladder Neoplasm, melanoma, Leukemia (such as acute myeloid leukemia), Hepatocellular carcinoma, Colorectal cancer, or Lymphoma (such as Mycosis fungoides and Sézary syndrome). In some embodiments, a neoplasia listed in Figure 5, 6, 7, 8, or 9 is treated with a CRISPR pharmaceutical composition targeting a gene listed as associated with the disorder in Figure 5, 6, 7, 8, or 9. For example, in some embodiments, Glioblastoma is treated with a CRISPR pharmaceutical composition targeting a TNFRSF1A, TNFRSF1B, TNFRSF3, TNFRSF4, or TNFRSF11A gene.

[00743] In some embodiments, the tumor necrosis factor receptor superfamily gene is an TNFRSF3 gene. In some embodiments, the TNFRSF3 gene is a human TNFRSF3 gene and the guide RNA comprises a crRNA sequence selected from SEQ ID NOs: 2643-2866. In some embodiments, editing of the TNFRSF3 gene results in a knockout of the TNFRSF3 gene. In some such embodiments, the TNFRSF3 gene is a human TNFRSF3 gene and the guide RNA comprises a crRNA sequence selected from SEQ ID NOs: 2643-2737. In some embodiments, editing of the TNFRSF3 gene results in a gene that expresses a membrane-bound receptor decoy protein. In some such embodiments, the TNFRSF3 gene is a human TNFRSF3 gene and the guide RNA comprises a crRNA sequence selected from SEQ ID NOs: 2738-2846. In some embodiments, editing of the TNFRSF3 gene results in a gene that expresses a soluble receptor decoy protein. In some such embodiments, the TNFRSF3 gene is a human TNFRSF3 gene and the guide RNA comprises a crRNA sequence selected from SEQ ID NOs: 2847-2852.

3. *Treatment of autoimmune or inflammatory disorders by targeting a tumor necrosis factor receptor superfamily gene*

[00744] In one aspect, methods and pharmaceutical compositions are provided for treating an autoimmune or inflammatory disorder using a CRISPR pharmaceutical composition that targets a Tumor Necrosis Factor Receptor Superfamily gene. In some embodiments, the

CRISPR pharmaceutical composition comprises (i) an RNA-guided nuclease or a nucleic acid encoding an RNA-guided nuclease, and (ii) at least one guide RNA (gRNA), or a nucleic acid encoding at least one gRNA, targeting the Tumor Necrosis Factor Receptor Superfamily gene, where the gRNA specifically binds a target sequence that is adjacent to a protospacer adjacent motif (PAM) sequence for the RNA-guided nuclease. In some embodiments, the CRISPR pharmaceutical composition comprises (i) an mRNA encoding an RNA-guided nuclease, and (ii) at least one gRNA targeting the Tumor Necrosis Factor Receptor Superfamily gene. In some embodiments, the mRNA encoding the RNA-guided nuclease and the at least one gRNA are packaged in a lipid nanoparticle (LNP). In some embodiments, the autoimmune or inflammatory disorder is Allergy, Asthma, Multiple sclerosis, Psoriasis, Inflammatory bowel disease, Autoimmune experimental uveitis, Colitis, Hypersensitivity reaction disease, Diabetes, Crohn's disease, Systemic lupus erythematosus, Pulmonary sarcoidosis, Leishmaniasis, Experimental autoimmune encephalomyelitis, HTLV-1-associated myelopathy, Tropical spastic paraparesis, Scleroderma, or Idiopathic inflammatory myopathy (such as polymyositis and dermatomyositis). In some embodiments, an autoimmune or inflammatory disorder listed in Figure 5, 6, 7, 8, or 9 is treated with a CRISPR pharmaceutical composition targeting a gene listed as associated with the disorder in Figure 5, 6, 7, 8, or 9. For example, in some embodiments, allergies are treated with a CRISPR pharmaceutical composition targeting a TNFRSF1A, TNFRSF1B, TNFRSF3, TNFRSF4, or TNFRSF11A gene.

[00745] In some embodiments, the tumor necrosis factor receptor superfamily gene is an TNFRSF3 gene. In some embodiments, the TNFRSF3 gene is a human TNFRSF3 gene and the guide RNA comprises a crRNA sequence selected from SEQ ID NOs: 2643-2866. In some embodiments, editing of the TNFRSF3 gene results in a knockout of the TNFRSF3 gene. In some such embodiments, the TNFRSF3 gene is a human TNFRSF3 gene and the guide RNA comprises a crRNA sequence selected from SEQ ID NOs: 2643-2737. In some embodiments, editing of the TNFRSF3 gene results in a gene that expresses a membrane-bound receptor decoy protein. In some such embodiments, the TNFRSF3 gene is a human TNFRSF3 gene and the guide RNA comprises a crRNA sequence selected from SEQ ID NOs: 2738-2846. In some embodiments, editing of the TNFRSF3 gene results in a gene that expresses a soluble receptor decoy protein. In some such embodiments, the TNFRSF3 gene is a human TNFRSF3 gene and the guide RNA comprises a crRNA sequence selected from SEQ ID NOs: 2847-2852.

J. TNFRSF4

[00746] In some embodiments, the pharmaceutical composition comprising a CRISPR gene-editing system targets TNFRSF4. In some embodiments, the CRISPR gene-editing system targeting TNFRSF4 is delivered to a mammalian cell via viral vector. In some embodiments, the CRISPR gene-editing system targeting TNFRSF4 is delivered to a mammalian cell via an AAV vector. In some embodiments, the CRISPR gene-editing system targeting TNFRSF4 is delivered to a mammalian cell via a lentiviral vector. In some embodiments, the CRISPR gene-editing system targeting TNFRSF4 is delivered to a mammalian cell via a lipid nanoparticle. In some embodiments, the CRISPR gene-editing system targeting TNFRSF4 is delivered to a mammalian cell via a virus-like particle. In some embodiments, the CRISPR gene-editing system targeting TNFRSF4 is delivered to a mammalian cell via a liposome. In some embodiments, the CRISPR gene-editing system targeting TNFRSF4 is delivered to a mammalian cell via a lipid nanocrystal.

[00747] In various embodiments, the pharmaceutical composition comprising a CRISPR gene-editing system that targets the TNFRSF4 gene is used in a method of treating a mammal in need thereof. In some embodiments, the method treats one or more joint disease or illness or one or more back or spine conditions or disorders. In some embodiments, the method treats one or more musculoskeletal diseases, conditions, and illnesses, including, but not limited to, rheumatoid arthritis, gout, osteoarthritis, osteoporosis, intervertebral disc disease (IVDD), psoriatic arthritis, arthritis, polymyositis, proliferative synovitis, bone neoplasms, sarcoid myopathy, cortex bone disorders, idiopathic scoliosis, tendinopathy, myofibrillar myopathy, enthesis-related arthritis, ankylosing spondylitis, degenerative polyarthritis, arthropathy, osteitis deformans, prolapsed lumbar disc, polymyositis ossificans, idiopathic polymyositis, Luft Disease, adult-onset Still's Disease, osteoarthritis deformans, Bachet's Disease, and combinations thereof. In other embodiments, use of the system treats one or more neoplastic diseases, conditions, and illnesses, including, but not limited to, osteosarcoma, multiple myeloma, lymphoma(e.g., B-cell or cutaneous T-cell lymphoma), leukemia, thyroid carcinoma, glioma, renal cell carcinoma, chondrosarcoma, glioblastoma, melanoma, neuroblastoma, polycystic ovary syndrome, Kaposi sarcoma, squamous cell carcinoma, leiomyosarcoma, malignant peripheral nerve sheath tumor, Ewing's sarcoma, esophageal neoplasms, colon cancer, lung cancer, breast cancer, pancreatic cancer, stomach cancer, epithelial ovarian cancer, cholectoral cancer, liver cancer, skin cancer, prostate cancer, cervical cancer, ovarian cancer, bladder cancer, oral cavity cancer, and combinations

thereof. In other embodiments, the method treats one or more inflammatory diseases, conditions, and illnesses, including, but not limited to, autoinflammatory disease (AID), cryopyrin-associated periodic syndrome (CAPS), systemic lupus erythematosus (SLE), inflammatory bowel disease (IBD) and combinations thereof. In some embodiments, the method treats one or more cardiac diseases, conditions, and illnesses, including, but not limited to, myocardial infarction, heart failure (e.g., refractory or acute decompensated heart failure), arrythmias, pericarditis (e.g., refractory idiopathic pericarditis), myocarditis, sepsis-induced cardiomyopathy, atherosclerosis, coronary artery disease and combinations thereof. In some embodiments, the method treats one or more neurological diseases, conditions, and illnesses, including, but not limited to, acute thrombotic stroke, epilepsy, multiple sclerosis, Alzheimer's Disease and combinations thereof. In some embodiments, the method treats one or more ophthalmic diseases, conditions, and illnesses, including, but not limited to, uveitis, scleritis, Sjogren asthenia, dry eye and combinations thereof. In some embodiments, the method treats one or more diseases, conditions, and illnesses, including, but not limited to, chronic kidney disease, Type 2 diabetes, gastroesophageal reflux disease (GERD), non-HP-associated peptic ulcer disease, and pulmonary fibrosis.

[00748] In some embodiments, the pharmaceutical composition comprising a CRISPR gene-editing system targets TNFRSF4 for the treatment of a joint disease or illness. In some embodiments, the pharmaceutical composition comprising a CRISPR gene-editing system targets TNFRSF4 for the treatment of osteoarthritis. In some embodiments, the pharmaceutical composition comprising a CRISPR gene-editing system targets TNFRSF4 for the treatment of gout.

[00749] In some embodiments, the pharmaceutical composition comprising a CRISPR gene-editing system targets TNFRSF4 for the treatment of a musculoskeletal disorder.

[00750] In some embodiments, the pharmaceutical composition comprising a CRISPR gene-editing system targets TNFRSF4 for the treatment of a back or spine condition or disorder. In some embodiments, the pharmaceutical composition comprising a CRISPR gene-editing system targets TNFRSF4 for the treatment of low back pain. In some embodiments, the pharmaceutical composition comprising a CRISPR gene-editing system targets TNFRSF4 for the treatment of degenerative disc disorder. In some embodiments, the pharmaceutical composition comprising a CRISPR gene-editing system targets TNFRSF4 for the treatment of internal disc disruption.

1. *Treatment of musculoskeletal disorders by targeting a tumor necrosis factor receptor superfamily gene*

[00751] In one aspect, methods and pharmaceutical compositions are provided for treating a musculoskeletal disorder using a CRISPR pharmaceutical composition that targets a Tumor Necrosis Factor Receptor Superfamily gene. In some embodiments, the CRISPR pharmaceutical composition comprises (i) an RNA-guided nuclease or a nucleic acid encoding an RNA-guided nuclease, and (ii) at least one guide RNA (gRNA), or a nucleic acid encoding at least one gRNA, targeting the Tumor Necrosis Factor Receptor Superfamily gene, where the gRNA specifically binds a target sequence that is adjacent to a protospacer adjacent motif (PAM) sequence for the RNA-guided nuclease. In some embodiments, the CRISPR pharmaceutical composition comprises (i) an mRNA encoding an RNA-guided nuclease, and (ii) at least one gRNA targeting the Tumor Necrosis Factor Receptor Superfamily gene. In some embodiments, the mRNA encoding the RNA-guided nuclease and the at least one gRNA are packaged in a lipid nanoparticle (LNP). In some embodiments, the musculoskeletal disorder is Arthritis, Infectious Intermittent joint effusion, Ankylosing spondylitis, Arthritis, Osteoarthritis, Spondylarthritis, Plantar fasciitis, Degenerative polyarthritis, Hemophilic arthropathy, Inflammatory myopathy with abundant macrophages, Polymyositis, Tendinosis, Malignant Bone Neoplasm, Osteoporosis, Psoriatic arthritis, Rheumatism, Rheumatoid arthritis, Adult Still's disease, Juvenile arthritis, Early rheumatoid arthritis, Palindromic rheumatism, Gout, Infectious Arthritis, Myotonic dystrophy, Dermatomyositis, Hemophilic arthropathy, Osteopenia, Sjogren's syndrome, Juvenile Idiopathic Arthritis, Myasthenia gravis, Osteolysis, Inflammation, Degenerative polyarthritis, Osteitis deformans, Pigmented villonodular synovitis, or Hyperphosphatasemia with bone disease. In some embodiments, a musculoskeletal disorder listed in Figure 5, 6, 7, 8, or 9 is treated with a CRISPR pharmaceutical composition targeting a gene listed as associated with the disorder in Figure 5, 6, 7, 8, or 9. For example, in some embodiments, Rheumatoid Arthritis is treated with a CRISPR pharmaceutical composition targeting a TNFRSF1A, TNFRSF1B, TNFRSF3, TNFRSF4, or TNFRSF11A gene.

[00752] In some embodiments, the tumor necrosis factor receptor superfamily gene is an TNFRSF4 gene. In some embodiments, the TNFRSF4 gene is a human TNFRSF4 gene and the guide RNA comprises a crRNA sequence selected from SEQ ID NOs: 2867-3041. In some embodiments, editing of the TNFRSF4 gene results in a knockout of the TNFRSF4 gene. In some such embodiments, the TNFRSF4 gene is a human TNFRSF4 gene and the

guide RNA comprises a crRNA sequence selected from SEQ ID NOs: 2867-2950. In some embodiments, editing of the TNFRSF4 gene results in a gene that expresses a membrane-bound receptor decoy protein. In some such embodiments, the TNFRSF4 gene is a human TNFRSF4 gene and the guide RNA comprises a crRNA sequence selected from SEQ ID NOs: 2951-2981. In some embodiments, editing of the TNFRSF4 gene results in a gene that expresses a soluble receptor decoy protein. In some such embodiments, the TNFRSF4 gene is a human TNFRSF4 gene and the guide RNA comprises a crRNA sequence selected from SEQ ID NOs: 2982-3035.

2. *Treatment of neoplasia by targeting a tumor necrosis factor receptor superfamily gene*

[00753] In one aspect, methods and pharmaceutical compositions are provided for treating a neoplasia using a CRISPR pharmaceutical composition that targets a Tumor Necrosis Factor Receptor Superfamily gene. In some embodiments, the CRISPR pharmaceutical composition comprises (i) an RNA-guided nuclease or a nucleic acid encoding an RNA-guided nuclease, and (ii) at least one guide RNA (gRNA), or a nucleic acid encoding at least one gRNA, targeting the Tumor Necrosis Factor Receptor Superfamily gene, where the gRNA specifically binds a target sequence that is adjacent to a protospacer adjacent motif (PAM) sequence for the RNA-guided nuclease. In some embodiments, the CRISPR pharmaceutical composition comprises (i) an mRNA encoding an RNA-guided nuclease, and (ii) at least one gRNA targeting the Tumor Necrosis Factor Receptor Superfamily gene. In some embodiments, the mRNA encoding the RNA-guided nuclease and the at least one gRNA are packaged in a lipid nanoparticle (LNP). In some embodiments, the neoplasia is Neoplasms, Glioblastoma, Astrocytoma, Adenocarcinoma, Osteosarcoma, Squamous cell carcinoma, Metastasis, Ameloblastoma, Cholangiocarcinoma, Choriocarcinoma, Ovarian cancer, Prostate cancer, Lung Cancer, Larynx Cancer, Breast Cancer, Lip and Oral Cavity Carcinoma, Squamous intraepithelial lesion, Neuroblastoma, Non-Hodgkin lymphomas, Malignant Neoplasms, Skin Neoplasms, Neuroblastoma, Neoplasm Metastasis, Colorectal Cancer, Fibrosarcoma, Myeloid Leukemia, Myelofibrosis, Hodgkin Lymphomas, Non-Small Cell Lung Carcinoma, Cervical Cancer, Liver cancer, Extrapulmonary small cell carcinoma, Basal cell carcinoma, Kidney cancer, Pancreatic carcinoma, Mesothelioma, Gastric cancer, Polycystic Ovary Syndrome, Chordoma, Cholangiocarcinoma, Malignant ascites, Nasopharyngeal carcinoma, Head and Neck Carcinoma, Cancer metastasis, Prostate carcinoma, Fibrosarcoma, Liver carcinoma, Carcinoma of bladder, T-Cell Lymphoblastic

Leukemia, Bladder Neoplasm, melanoma, Leukemia (such as acute myeloid leukemia), Hepatocellular carcinoma, Colorectal cancer, or Lymphoma (such as Mycosis fungoides and Sézary syndrome). In some embodiments, a neoplasia listed in Figure 5, 6, 7, 8, or 9 is treated with a CRISPR pharmaceutical composition targeting a gene listed as associated with the disorder in Figure 5, 6, 7, 8, or 9. For example, in some embodiments, Glioblastoma is treated with a CRISPR pharmaceutical composition targeting a TNFRSF1A, TNFRSF1B, TNFRSF3, TNFRSF4, or TNFRSF11A gene.

[00754] In some embodiments, the tumor necrosis factor receptor superfamily gene is an TNFRSF4 gene. In some embodiments, the TNFRSF4 gene is a human TNFRSF4 gene and the guide RNA comprises a crRNA sequence selected from SEQ ID NOs: 2867-3041. In some embodiments, editing of the TNFRSF4 gene results in a knockout of the TNFRSF4 gene. In some such embodiments, the TNFRSF4 gene is a human TNFRSF4 gene and the guide RNA comprises a crRNA sequence selected from SEQ ID NOs: 2867-2950. In some embodiments, editing of the TNFRSF4 gene results in a gene that expresses a membrane-bound receptor decoy protein. In some such embodiments, the TNFRSF4 gene is a human TNFRSF4 gene and the guide RNA comprises a crRNA sequence selected from SEQ ID NOs: 2951-2981. In some embodiments, editing of the TNFRSF4 gene results in a gene that expresses a soluble receptor decoy protein. In some such embodiments, the TNFRSF4 gene is a human TNFRSF4 gene and the guide RNA comprises a crRNA sequence selected from SEQ ID NOs: 2982-3035.

3. *Treatment of autoimmune or inflammatory disorders by targeting a tumor necrosis factor receptor superfamily gene*

[00755] In one aspect, methods and pharmaceutical compositions are provided for treating an autoimmune or inflammatory disorder using a CRISPR pharmaceutical composition that targets a Tumor Necrosis Factor Receptor Superfamily gene. In some embodiments, the CRISPR pharmaceutical composition comprises (i) an RNA-guided nuclease or a nucleic acid encoding an RNA-guided nuclease, and (ii) at least one guide RNA (gRNA), or a nucleic acid encoding at least one gRNA, targeting the Tumor Necrosis Factor Receptor Superfamily gene, where the gRNA specifically binds a target sequence that is adjacent to a protospacer adjacent motif (PAM) sequence for the RNA-guided nuclease. In some embodiments, the CRISPR pharmaceutical composition comprises (i) an mRNA encoding an RNA-guided nuclease, and (ii) at least one gRNA targeting the Tumor Necrosis Factor Receptor Superfamily gene. In some embodiments, the mRNA encoding the RNA-guided nuclease

and the at least one gRNA are packaged in a lipid nanoparticle (LNP). In some embodiments, the autoimmune or inflammatory disorder is Allergy, Asthma, Multiple sclerosis, Psoriasis, Inflammatory bowel disease, Autoimmune experimental uveitis, Colitis, Hypersensitivity reaction disease, Diabetes, Crohn's disease, Systemic lupus erythematosus, Pulmonary sarcoidosis, Leishmaniasis, Experimental autoimmune encephalomyelitis, HTLV-1-associated myelopathy, Tropical spastic paraparesis, Scleroderma, or Idiopathic inflammatory myopathy (such as polymyositis and dermatomyositis). In some embodiments, an autoimmune or inflammatory disorder listed in Figure 5, 6, 7, 8, or 9 is treated with a CRISPR pharmaceutical composition targeting a gene listed as associated with the disorder in Figure 5, 6, 7, 8, or 9. For example, in some embodiments, allergies are treated with a CRISPR pharmaceutical composition targeting a TNFRSF1A, TNFRSF1B, TNFRSF3, TNFRSF4, or TNFRSF11A gene.

[00756] In some embodiments, the tumor necrosis factor receptor superfamily gene is an TNFRSF4 gene. In some embodiments, the TNFRSF4 gene is a human TNFRSF4 gene and the guide RNA comprises a crRNA sequence selected from SEQ ID NOs: 2867-3041. In some embodiments, editing of the TNFRSF4 gene results in a knockout of the TNFRSF4 gene. In some such embodiments, the TNFRSF4 gene is a human TNFRSF4 gene and the guide RNA comprises a crRNA sequence selected from SEQ ID NOs: 2867-2950. In some embodiments, editing of the TNFRSF4 gene results in a gene that expresses a membrane-bound receptor decoy protein. In some such embodiments, the TNFRSF4 gene is a human TNFRSF4 gene and the guide RNA comprises a crRNA sequence selected from SEQ ID NOs: 2951-2981. In some embodiments, editing of the TNFRSF4 gene results in a gene that expresses a soluble receptor decoy protein. In some such embodiments, the TNFRSF4 gene is a human TNFRSF4 gene and the guide RNA comprises a crRNA sequence selected from SEQ ID NOs: 2982-3035.

K. TNFRSF11A

[00757] In some embodiments, the pharmaceutical composition comprising a CRISPR gene-editing system targets TNFRSF11A. In some embodiments, the CRISPR gene-editing system targeting TNFRSF11A is delivered to a mammalian cell via viral vector. In some embodiments, the CRISPR gene-editing system targeting TNFRSF11A is delivered to a mammalian cell via an AAV vector. In some embodiments, the CRISPR gene-editing system targeting TNFRSF11A is delivered to a mammalian cell via a lentiviral vector. In some embodiments, the CRISPR gene-editing system targeting TNFRSF11A is delivered to a

mammalian cell via a lipid nanoparticle. In some embodiments, the CRISPR gene-editing system targeting TNFRSF11A is delivered to a mammalian cell via a virus-like particle. In some embodiments, the CRISPR gene-editing system targeting TNFRSF11A is delivered to a mammalian cell via a liposome. In some embodiments, the CRISPR gene-editing system targeting TNFRSF11A is delivered to a mammalian cell via a lipid nanocrystal.

[00758] In various embodiments, the pharmaceutical composition comprising a CRISPR gene-editing system that targets the TNFRSF11A gene is used in a method of treating a mammal in need thereof. In some embodiments, the method treats one or more joint disease or illness or one or more back or spine conditions or disorders. In some embodiments, the method treats one or more musculoskeletal diseases, conditions, and illnesses, including, but not limited to, rheumatoid arthritis, gout, osteoarthritis, osteoporosis, intervertebral disc disease (IVDD), psoriatic arthritis, arthritis, polymyositis, proliferative synovitis, bone neoplasms, sarcoid myopathy, cortex bone disorders, idiopathic scoliosis, tendinopathy, myofibrillar myopathy, enthesis-related arthritis, ankylosing spondylitis, degenerative polyarthritis, arthropathy, osteitis deformans, prolapsed lumbar disc, polymyositis ossificans, idiopathic polymyositis, Luft Disease, adult-onset Still's Disease, osteoarthritis deformans, Bachet's Disease, and combinations thereof. In other embodiments, use of the system treats one or more neoplastic diseases, conditions, and illnesses, including, but not limited to, osteosarcoma, multiple myeloma, lymphoma(e.g., B-cell or cutaneous T-cell lymphoma), leukemia, thyroid carcinoma, glioma, renal cell carcinoma, chondrosarcoma, glioblastoma, melanoma, neuroblastoma, polycystic ovary syndrome, Kaposi sarcoma, squamous cell carcinoma, leiomyosarcoma, malignant peripheral nerve sheath tumor, Ewing's sarcoma, esophageal neoplasms, colon cancer, lung cancer, breast cancer, pancreatic cancer, stomach cancer, epithelial ovarian cancer, cholectoral cancer, liver cancer, skin cancer, prostate cancer, cervical cancer, ovarian cancer, bladder cancer, oral cavity cancer, and combinations thereof. In other embodiments, the method treats one or more inflammatory diseases, conditions, and illnesses, including, but not limited to, autoinflammatory disease (AID), cryopyrin-associated periodic syndrome (CAPS), systemic lupus erythematosus (SLE), inflammatory bowel disease (IBD) and combinations thereof. In some embodiments, the method treats one or more cardiac diseases, conditions, and illnesses, including, but not limited to, myocardial infarction, heart failure (e.g., refractory or acute decompensated heart failure), arrythmias, pericarditis (e.g., refractory idiopathic pericarditis), myocarditis, sepsis-induced cardiomyopathy, atherosclerosis, coronary artery disease and combinations thereof.

In some embodiments, the method treats one or more neurological diseases, conditions, and illnesses, including, but not limited to, acute thrombotic stroke, epilepsy, multiple sclerosis, Alzheimer's Disease and combinations thereof. In some embodiments, the method treats one or more ophthalmic diseases, conditions, and illnesses, including, but not limited to, uveitis, scleritis, Sjogren asthenia, dry eye and combinations thereof. In some embodiments, the method treats one or more diseases, conditions, and illnesses, including, but not limited to, chronic kidney disease, Type 2 diabetes, gastroesophageal reflux disease (GERD), non-HP-associated peptic ulcer disease, and pulmonary fibrosis.

[00759] In some embodiments, the pharmaceutical composition comprising a CRISPR gene-editing system targets TNFRSF11A for the treatment of a joint disease or illness. In some embodiments, the pharmaceutical composition comprising a CRISPR gene-editing system targets TNFRSF11A for the treatment of osteoarthritis. In some embodiments, the pharmaceutical composition comprising a CRISPR gene-editing system targets TNFRSF11A for the treatment of gout.

[00760] In some embodiments, the pharmaceutical composition comprising a CRISPR gene-editing system targets TNFRSF11A for the treatment of a musculoskeletal disorder.

[00761] In some embodiments, the pharmaceutical composition comprising a CRISPR gene-editing system targets TNFRSF11A for the treatment of a back or spine condition or disorder. In some embodiments, the pharmaceutical composition comprising a CRISPR gene-editing system targets TNFRSF11A for the treatment of low back pain. In some embodiments, the pharmaceutical composition comprising a CRISPR gene-editing system targets TNFRSF11A for the treatment of degenerative disc disorder. In some embodiments, the pharmaceutical composition comprising a CRISPR gene-editing system targets TNFRSF11A for the treatment of internal disc disruption.

1. *Treatment of musculoskeletal disorders by targeting a tumor necrosis factor receptor superfamily gene*

[00762] In one aspect, methods and pharmaceutical compositions are provided for treating a musculoskeletal disorder using a CRISPR pharmaceutical composition that targets a Tumor Necrosis Factor Receptor Superfamily gene. In some embodiments, the CRISPR pharmaceutical composition comprises (i) an RNA-guided nuclease or a nucleic acid encoding an RNA-guided nuclease, and (ii) at least one guide RNA (gRNA), or a nucleic acid encoding at least one gRNA, targeting the Tumor Necrosis Factor Receptor Superfamily

gene, where the gRNA specifically binds a target sequence that is adjacent to a protospacer adjacent motif (PAM) sequence for the RNA-guided nuclease. In some embodiments, the CRISPR pharmaceutical composition comprises (i) an mRNA encoding an RNA-guided nuclease, and (ii) at least one gRNA targeting the Tumor Necrosis Factor Receptor Superfamily gene. In some embodiments, the mRNA encoding the RNA-guided nuclease and the at least one gRNA are packaged in a lipid nanoparticle (LNP). In some embodiments, the musculoskeletal disorder is Arthritis, Infectious Intermittent joint effusion, Ankylosing spondylitis, Arthritis, Osteoarthritis, Spondylarthritis, Plantar fasciitis, Degenerative polyarthritis, Hemophilic arthropathy, Inflammatory myopathy with abundant macrophages, Polymyositis, Tendinosis, Malignant Bone Neoplasm, Osteoporosis, Psoriatic arthritis, Rheumatism, Rheumatoid arthritis, Adult Still's disease, Juvenile arthritis, Early rheumatoid arthritis, Palindromic rheumatism, Gout, Infectious Arthritis, Myotonic dystrophy, Dermatomyositis, Hemophilic arthropathy, Osteopenia, Sjogren's syndrome, Juvenile Idiopathic Arthritis, Myasthenia gravis, Osteolysis, Inflammation, Degenerative polyarthritis, Osteitis deformans, Pigmented villonodular synovitis, or Hyperphosphatasemia with bone disease. In some embodiments, a musculoskeletal disorder listed in Figure 5, 6, 7, 8, or 9 is treated with a CRISPR pharmaceutical composition targeting a gene listed as associated with the disorder in Figure 5, 6, 7, 8, or 9. For example, in some embodiments, Rheumatoid Arthritis is treated with a CRISPR pharmaceutical composition targeting a TNFRSF1A, TNFRSF1B, TNFRSF3, TNFRSF4, or TNFRSF11A gene.

[00763] In some embodiments, the tumor necrosis factor receptor superfamily gene is an TNFRSF11A gene. In some embodiments, the TNFRSF11A gene is a human TNFRSF11A gene and the guide RNA comprises a crRNA sequence selected from SEQ ID NOs: 3042-3335. In some embodiments, editing of the TNFRSF11A gene results in a knockout of the TNFRSF11A gene. In some such embodiments, the TNFRSF11A gene is a human TNFRSF11A gene and the guide RNA comprises a crRNA sequence selected from SEQ ID NOs: 3042-3106. In some embodiments, editing of the TNFRSF11A gene results in a gene that expresses a membrane-bound receptor decoy protein. In some such embodiments, the TNFRSF11A gene is a human TNFRSF11A gene and the guide RNA comprises a crRNA sequence selected from SEQ ID NOs: 3107-3322. In some embodiments, editing of the TNFRSF11A gene results in a gene that expresses a soluble receptor decoy protein. In some such embodiments, the TNFRSF11A gene is a human TNFRSF11A gene and the guide RNA comprises a crRNA sequence selected from SEQ ID NOs: 3323-3331.

2. *Treatment of neoplasia by targeting a tumor necrosis factor receptor superfamily gene*

[00764] In one aspect, methods and pharmaceutical compositions are provided for treating a neoplasia using a CRISPR pharmaceutical composition that targets a Tumor Necrosis Factor Receptor Superfamily gene. In some embodiments, the CRISPR pharmaceutical composition comprises (i) an RNA-guided nuclease or a nucleic acid encoding an RNA-guided nuclease, and (ii) at least one guide RNA (gRNA), or a nucleic acid encoding at least one gRNA, targeting the Tumor Necrosis Factor Receptor Superfamily gene, where the gRNA specifically binds a target sequence that is adjacent to a protospacer adjacent motif (PAM) sequence for the RNA-guided nuclease. In some embodiments, the CRISPR pharmaceutical composition comprises (i) an mRNA encoding an RNA-guided nuclease, and (ii) at least one gRNA targeting the Tumor Necrosis Factor Receptor Superfamily gene. In some embodiments, the mRNA encoding the RNA-guided nuclease and the at least one gRNA are packaged in a lipid nanoparticle (LNP). In some embodiments, the neoplasia is Neoplasms, Glioblastoma, Astrocytoma, Adenocarcinoma, Osteosarcoma, Squamous cell carcinoma, Metastasis, Ameloblastoma, Cholangiocarcinoma, Choriocarcinoma, Ovarian cancer, Prostate cancer, Lung Cancer, Larynx Cancer, Breast Cancer, Lip and Oral Cavity Carcinoma, Squamous intraepithelial lesion, Neuroblastoma, Non-Hodgkin lymphomas, Malignant Neoplasms, Skin Neoplasms, Neuroblastoma, Neoplasm Metastasis, Colorectal Cancer, Fibrosarcoma, Myeloid Leukemia, Myelofibrosis, Hodgkin Lymphomas, Non-Small Cell Lung Carcinoma, Cervical Cancer, Liver cancer, Extrapulmonary small cell carcinoma, Basal cell carcinoma, Kidney cancer, Pancreatic carcinoma, Mesothelioma, Gastric cancer, Polycystic Ovary Syndrome, Chordoma, Cholangiocarcinoma, Malignant ascites, Nasopharyngeal carcinoma, Head and Neck Carcinoma, Cancer metastasis, Prostate carcinoma, Fibrosarcoma, Liver carcinoma, Carcinoma of bladder, T-Cell Lymphoblastic Leukemia, Bladder Neoplasm, melanoma, Leukemia (such as acute myeloid leukemia), Hepatocellular carcinoma, Colorectal cancer, or Lymphoma (such as Mycosis fungoides and Sézary syndrome). In some embodiments, a neoplasia listed in Figure 5, 6, 7, 8, or 9 is treated with a CRISPR pharmaceutical composition targeting a gene listed as associated with the disorder in Figure 5, 6, 7, 8, or 9. For example, in some embodiments, Glioblastoma is treated with a CRISPR pharmaceutical composition targeting a TNFRSF1A, TNFRSF1B, TNFRSF3, TNFRSF4, or TNFRSF11A gene.

[00765] In some embodiments, the tumor necrosis factor receptor superfamily gene is an TNFRSF11A gene. In some embodiments, the TNFRSF11A gene is a human TNFRSF11A gene and the guide RNA comprises a crRNA sequence selected from SEQ ID NOs: 3042-3335. In some embodiments, editing of the TNFRSF11A gene results in a knockout of the TNFRSF11A gene. In some such embodiments, the TNFRSF11A gene is a human TNFRSF11A gene and the guide RNA comprises a crRNA sequence selected from SEQ ID NOs: 3042-3106. In some embodiments, editing of the TNFRSF11A gene results in a gene that expresses a membrane-bound receptor decoy protein. In some such embodiments, the TNFRSF11A gene is a human TNFRSF11A gene and the guide RNA comprises a crRNA sequence selected from SEQ ID NOs: 3107-3322. In some embodiments, editing of the TNFRSF11A gene results in a gene that expresses a soluble receptor decoy protein. In some such embodiments, the TNFRSF11A gene is a human TNFRSF11A gene and the guide RNA comprises a crRNA sequence selected from SEQ ID NOs: 3323-3331.

3. *Treatment of autoimmune or inflammatory disorders by targeting a tumor necrosis factor receptor superfamily gene*

[00766] In one aspect, methods and pharmaceutical compositions are provided for treating an autoimmune or inflammatory disorder using a CRISPR pharmaceutical composition that targets a Tumor Necrosis Factor Receptor Superfamily gene. In some embodiments, the CRISPR pharmaceutical composition comprises (i) an RNA-guided nuclease or a nucleic acid encoding an RNA-guided nuclease, and (ii) at least one guide RNA (gRNA), or a nucleic acid encoding at least one gRNA, targeting the Tumor Necrosis Factor Receptor Superfamily gene, where the gRNA specifically binds a target sequence that is adjacent to a protospacer adjacent motif (PAM) sequence for the RNA-guided nuclease. In some embodiments, the CRISPR pharmaceutical composition comprises (i) an mRNA encoding an RNA-guided nuclease, and (ii) at least one gRNA targeting the Tumor Necrosis Factor Receptor Superfamily gene. In some embodiments, the mRNA encoding the RNA-guided nuclease and the at least one gRNA are packaged in a lipid nanoparticle (LNP). In some embodiments, the autoimmune or inflammatory disorder is Allergy, Asthma, Multiple sclerosis, Psoriasis, Inflammatory bowel disease, Autoimmune experimental uveitis, Colitis, Hypersensitivity reaction disease, Diabetes, Crohn's disease, Systemic lupus erythematosus, Pulmonary sarcoidosis, Leishmaniasis, Experimental autoimmune encephalomyelitis, HTLV-1-associated myelopathy, Tropical spastic paraparesis, Scleroderma, or Idiopathic inflammatory myopathy (such as polymyositis and dermatomyositis). In some embodiments,

an autoimmune or inflammatory disorder listed in Figure 5, 6, 7, 8, or 9 is treated with a CRISPR pharmaceutical composition targeting a gene listed as associated with the disorder in Figure 5, 6, 7, 8, or 9. For example, in some embodiments, allergies are treated with a CRISPR pharmaceutical composition targeting a TNFRSF1A, TNFRSF1B, TNFRSF3, TNFRSF4, or TNFRSF11A gene.

[00767] In some embodiments, the tumor necrosis factor receptor superfamily gene is an TNFRSF11A gene. In some embodiments, the TNFRSF11A gene is a human TNFRSF11A gene and the guide RNA comprises a crRNA sequence selected from SEQ ID NOs: 3042-3335. In some embodiments, editing of the TNFRSF11A gene results in a knockout of the TNFRSF11A gene. In some such embodiments, the TNFRSF11A gene is a human TNFRSF11A gene and the guide RNA comprises a crRNA sequence selected from SEQ ID NOs: 3042-3106. In some embodiments, editing of the TNFRSF11A gene results in a gene that expresses a membrane-bound receptor decoy protein. In some such embodiments, the TNFRSF11A gene is a human TNFRSF11A gene and the guide RNA comprises a crRNA sequence selected from SEQ ID NOs: 3107-3322. In some embodiments, editing of the TNFRSF11A gene results in a gene that expresses a soluble receptor decoy protein. In some such embodiments, the TNFRSF11A gene is a human TNFRSF11A gene and the guide RNA comprises a crRNA sequence selected from SEQ ID NOs: 3323-3331.

VIII. Administration routes

[00768] The methods and compositions herein described encompass the use of pharmaceutical compositions comprising a CRISPR gene-editing system as an active ingredient.

[00769] Depending on the method/route of administration, pharmaceutical dosage forms come in several types. These include many kinds of liquid, solid, and semisolid dosage forms. Common pharmaceutical dosage forms include pill, tablet, or capsule, drink or syrup, and natural or herbal form such as plant or food of sorts, among many others. Notably, the route of administration (ROA) for drug delivery is dependent on the dosage form of the substance in question. A liquid pharmaceutical dosage form is the liquid form of a dose of a chemical compound used as a drug or medication intended for administration or consumption.

[00770] As described below, a composition of the present disclosure can be delivered to a subject subcutaneously (e.g., intra-articular or intradiscal injection), dermally (e.g.,

transdermally via patch), and/or via implant. Exemplary pharmaceutical dosage forms include, e.g., pills, osmotic delivery systems, elixirs, emulsions, hydrogels, suspensions, syrups, capsules, tablets, orally dissolving tablets (ODTs), gel capsules, thin films, adhesive topical patches, lollipops, lozenges, chewing gum, dry powder inhalers (DPIs), vaporizers, nebulizers, metered dose inhalers (MDIs), ointments, transdermal patches, intradermal implant.

[00771] As used herein, "dermal delivery" or "dermal administration" can refer to a route of administration wherein the pharmaceutical dosage form is taken to, or through, the dermis (i.e., layer of skin between the epidermis (with which it makes up the cutis) and subcutaneous tissues). "Subcutaneous delivery" can refer to a route of administration wherein the pharmaceutical dosage form is to or beneath the subcutaneous tissue layer.

[00772] Methods of formulating suitable pharmaceutical compositions are known in the art, see, e.g., Remington: The Science and Practice of Pharmacy, 21st ed., 2005; and the books in the series Drugs and the Pharmaceutical Sciences: a Series of Textbooks and Monographs (Dekker, N.Y.). For example, solutions or suspensions used for parenteral, intradermal, or subcutaneous application can include the following components: a sterile diluent such as water for injection, saline solution, fixed oils, polyethylene glycols, glycerin, propylene glycol or other synthetic solvents; antibacterial agents such as benzyl alcohol or methyl parabens; antioxidants such as ascorbic acid or sodium bisulfate; chelating agents such as ethylenediaminetetraacetic acid; buffers such as acetates, citrates or phosphates and agents for the adjustment of tonicity such as sodium chloride or dextrose. pH can be adjusted with acids or bases, such as hydrochloric acid or sodium hydroxide. The parenteral preparation can be enclosed in ampoules, disposable syringes or multiple dose vials made of glass or plastic.

[00773] Pharmaceutical compositions suitable for injectable use can include sterile aqueous solutions (where water soluble) or dispersions and sterile powders for the extemporaneous preparation of sterile injectable solutions or dispersion. For intravenous administration, suitable carriers include physiological saline, bacteriostatic water, Cremophor EL™ (BASF, Parsippany, N.J.) or phosphate buffered saline (PBS). In all cases, the composition must be sterile and should be fluid to the extent that easy syringability exists. It should be stable under the conditions of manufacture and storage and must be preserved against the contaminating action of microorganisms such as bacteria and fungi. The carrier can be a solvent or dispersion medium containing, for example, water, ethanol, polyol (for example, glycerol, propylene glycol, and liquid polyethylene glycol, and the like), and suitable mixtures thereof.

The proper fluidity can be maintained, for example, by the use of a coating such as lecithin, by the maintenance of the required particle size in the case of dispersion and by the use of surfactants. Prevention of the action of microorganisms can be achieved by various antibacterial and antifungal agents, for example, parabens, chlorobutanol, phenol, ascorbic acid, thimerosal, and the like. In many cases, it will be preferable to include isotonic agents, for example, sugars, polyalcohols such as mannitol, sorbitol, sodium chloride in the composition. Prolonged absorption of the injectable compositions can be brought about by including in the composition an agent that delays absorption, for example, aluminum monostearate and gelatin.

[00774] Sterile injectable solutions can be prepared by incorporating the active compound in the required amount in an appropriate solvent with one or a combination of ingredients enumerated above, as required, followed by filtered sterilization. Generally, dispersions are prepared by incorporating the active compound into a sterile vehicle, which contains a basic dispersion medium and the required other ingredients from those enumerated above. In the case of sterile powders for the preparation of sterile injectable solutions, the preferred methods of preparation are vacuum drying and freeze-drying, which yield a powder of the active ingredient plus any additional desired ingredient from a previously sterile-filtered solution thereof.

[00775] Therapeutic compounds that are or include nucleic acids can be administered by any method suitable for administration of nucleic acid agents, such as a DNA vaccine. These methods include gene guns, bio injectors, and skin patches as well as needle-free methods such as the micro-particle DNA vaccine technology disclosed in U.S. Pat. No. 6,194,389, and the mammalian transdermal needle-free vaccination with powder-form vaccine as disclosed in U.S. Pat. No. 6,168,587. Additionally, intranasal delivery is possible, as described in, inter alia, Hamajima et al., Clin. Immunol. Immunopathol., 88(2), 205-10 (1998). Liposomes (e.g., as described in U.S. Pat. No. 6,472,375) and microencapsulation can also be used. Biodegradable targetable microparticle delivery systems can also be used (e.g., as described in U.S. Pat. No. 6,471,996).

[00776] Therapeutic compounds can be prepared with carriers that will protect the therapeutic compounds against rapid elimination from the body, such as a controlled release formulation, including implants and microencapsulated delivery systems. Biodegradable, biocompatible polymers can be used, such as collagen, ethylene vinyl acetate, polyanhydrides (e.g., poly[1,3-bis(carboxyphenoxy)propane-co-sebacic-acid] (PCPP-SA) matrix, fatty acid

dimer-sebacic acid (FAD-SA) copolymer, poly(lactide-co-glycolide)), polyglycolic acid, collagen, polyorthoesters, polyethylene glycol-coated liposomes, hyaluronic acid and polylactic acid. Such formulations can be prepared using standard techniques, or obtained commercially, e.g., from Alza Corporation and Nova Pharmaceuticals, Inc. Liposomal suspensions (including liposomes targeted to selected cells with monoclonal antibodies to cellular antigens) can also be used as pharmaceutically acceptable carriers. These can be prepared according to methods known to those skilled in the art, for example, as described in U.S. Pat. No. 4,522,811. Semisolid, gelling, soft-gel, or other formulations (including controlled release) can be used, e.g., when administration to a surgical site is desired. Methods of making such formulations are known in the art and can include the use of biodegradable, biocompatible polymers. See, e.g., Sawyer et al., Yale J Biol Med. 2006 December; 79(3-4): 141-152.

[00777] The pharmaceutical compositions described herein may be included in a container, kit, pack, or dispenser together with instructions for administration.

A. Systemic administration

[00778] In some embodiments, a pharmaceutical composition comprising a CRISPR gene-editing system is administered systemically to a mammal in need thereof. In some embodiments, the composition is formulated for intravenous injection. In some embodiments, the composition is formulated for oral administration. In some embodiments, the composition is formulated for parenteral administration.

B. Local administration

[00779] In some embodiments, a pharmaceutical composition comprising a CRISPR gene-editing system is administered locally to a mammal in need thereof. In some embodiments, the local administration is an intra-articular injection. In some embodiments, the composition is formulated for intradiscal injection. In some embodiments, the composition is formulated for epidural injection. In some embodiments, the composition is formulated for peridiscal injection. In some embodiments, the composition is formulated for perivertebral injection. In some embodiments, composition is formulated for administration to the facet joints of the spine.

[00780] In some embodiments, a pharmaceutical composition comprising a CRISPR gene-editing system is administered locally to a mammal in need thereof during a surgical

procedure. In some embodiments, a pharmaceutical composition comprising a CRISPR gene-editing system is administered locally to a mammal in need thereof 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 20, or 30 days after a surgical procedure.

Examples

[00781] The embodiments encompassed herein are now described with reference to the following examples. These examples are provided for the purpose of illustration only and the disclosure encompassed herein should in no way be construed as being limited to these examples, but rather should be construed to encompass any and all variations which become evident as a result of the teachings provided herein.

EXAMPLE 1: DESIGN AND SELECTION OF GUIDES FOR EDITING THE IL1 RECEPTOR (IL1R1)

[00782] A pipeline of in silico and in vitro screening was developed to identify candidate CRISPR-Cas guides for gene editing. The pipeline was applied to identify guides that effectively edit the canine IL1R1 receptor gene (cIL1R1), thereby disrupting IL1α / IL1β signaling in vivo. The first step in the pipeline was to identify all possible crRNA sequences for a particular CRISPR-Cas protein in the coding portions of the cIL1R1. Many algorithms for identifying such sequences are known in the art. Generally, these algorithms function by identifying a protospacer adjacent motif (PAM) sequence for the particular CRISPR-Cas protein and then locate the sequence spaced according to the requirements of the particular Cas protein, typically directly 5' of the PAM site. For example, the S. pyogenes Cas9 (SpCas9) protein, which was used in this Example, recognizes a 5'-NGG-3' PAM sequence. Thus, all sequences directly 5' of an NGG trinucleotide are possible crRNA sequences. crRNA sequences identified in this fashion as shown in Figure 27, along with biographical information about the crRNA sequence.

[00783] Next, each identified crRNA sequence was evaluated across three different metrics: possible off-target editing at locations in the genome other than the target gene, on-target editing efficiency, and the likelihood of editing causing frameshift mutations, using multiple algorithms for each metric, as illustrated in Figure 11A. The basis of the combinatorial approach used lies in the assumption that every model has blind spots that may skew the

fitness of a particular guide RNA. Weighting these scores to obtain a consensus score for each of these properties allows for much better prediction of sgRNA fitness.

[00784] Off-target editing effects were predicted by averaging scores generated by the MIT , CFD and Elevation (human only) model. The MIT algorithm, also known as Hsu-Zhang score. Hsu, P. D. et al. DNA targeting specificity of RNA-guided Cas9 nucleases. *Nature Biotechnology* 31, 827–832 (2013). This model is based on a positional penalty matrix (1x20) generated from 15 EMX1 sgRNA libraries with mismatches against target at every position. The CFD algorithm (Cutting Frequency Determination) is based on threat matrix (12x20) considering both position and mismatch type and PAM integrity (27,897 'CD33' sgRNAs + 10,618 negative control sgRNAs). Doench, J. G. et al. Optimized sgRNA design to maximize activity and minimize off-target effects of CRISPR-Cas9. Nature Biotechnology 34, 184–191 (2016). The Elevation score using machine learning algorithms trained by genome-wide (GUIDE-Seq) and other aggregated off-target profiling data. Listgarten, J. et al. Prediction of off-target activities for the end-to-end design of CRISPR guide RNAs. Nature Biomedical Engineering 2, 38-47 (2018). The column labelled "OFF" shows the mean of the scores provided by the two or three models, respectively. The column labelled "OffTarget #" shows the number of potential off-targets with up to four mismatches as calculated by CRISPOR. *See*, Haeussler, M. et al. Evaluation of off-target and on-target scoring algorithms and integration into the guide RNA selection tool CRISPOR. *Genome Biology* 17, 148 (2016).

[00785] On-target editing efficiencies were predicted by averaging scores generated by the Azimuth model, the DeepSpCas9 model, and the CrisprScan model. The Azimuth model is a boosted regression tree model, trained with 881 sgRNAs (MOLM13/NB4/TF1 cells and additional unpublished data) delivered by lentivirus. Doench, J. G. et al. Optimized sgRNA design to maximize activity and minimize off-target effects of CRISPR-Cas9. Nature Biotechnology 34, 184–191 (2016). DeepSpCas9 is a deep learning model trained using editing data from 12,832 sgRNA. Kim, H. K. et al. SpCas9 activity prediction by DeepSpCas9, a deep learning–based model with high generalization performance. Science Advances 5(11) (2019). CrisprScan is a linear regression model, trained using editing data from 1000 sgRNAs injected into zebrafish embryos targeting >100 genes. Moreno-Mateos, M. A. *et al.* CRISPRscan: designing highly efficient sgRNAs for CRISPR-Cas9 targeting in vivo. *Nature Methods* 12, 982–988 (2015). The column labelled "ON" shows the mean of the scores provided by the three models.

[00786] The putative guides' potential to generate frameshift mutations were predicted by averaging scores generated by the Lindel model and the InDelphi model. Lindel is a machine learning model trained using profile data of 1.16 million independent mutational events triggered by CRISPR/Cas9-mediated cleavage and non-homologous end joining-mediated double strand break repair of 6872 synthetic target sequences, introduced into a human cell line via lentiviral infection. Chen, W. *et al.* Massively parallel profiling and predictive modeling of the outcomes of CRISPR/Cas9-mediated double-strand break repair. *Nucleic Acids Research* 47, 7989–8003 (2019). InDelphi is machine learning model trained with indels generated by 1872 sgRNAs. Shen, M. W. et al. Predictable and precise template-free CRISPR editing of pathogenic variants. Nature 563, 646–651 (2018). The column labelled "Frameshift" shows the mean of the scores provided by the two models. The column labelled "Precision" shows the frequency distribution of indels estimated by inDelphi. High precision is closer to 100 and represents sgRNAs that are characterised by one or a very low number of repair outcomes.

[00787] The candidate crRNA sequences were then evaluated for the presence of Graf motifs, TT or GCC present in the 4 PAM proximal bases of the crRNA sequence, as indicated in, e.g., Figures 26-42, as either TT or GCC. Graf, R. et al. sgRNA Sequence Motifs Blocking Efficient CRISPR/Cas9-Mediated Gene Editing. Cell Reports, 26(5), 1098-103 (2019). Graf et al. reported that TT- and GCC-motifs are a hallmark of inefficient sgRNAs. If possible, crRNA with Graf motifs and in particular the GCC motif were avoided. In contrast to the TT motif, the GCC motif remains critical if sgRNAs are synthesized de novo rather than by transcription.

[00788] As shown in, e.g., Figures 26-42, three consensus scores were then calculated for each crRNA sequence. The "ON-OFF" score represents the mean of the "ON" and "OFF" score. The "OFF-FS" score represents the mean of the "OFF" and "Frameshift" score. The OVERALL score represents the mean of the "ON", "OFF" and "Frameshift" score. Additionally, for human only, VBC's Bioscore was used to predict whether a possible in-frame mutation could disturb protein function. This is more likely to occur in conserved genomic DNA sequences coding for critical protein domains. Thus, Bioscore is based on protein domain annotations, phylogenetic conservation, amino acid identities and exon size. Michlits, G. et al. Multilayered VBC score predicts sgRNAs that efficiently generate loss-of-function alleles. Nature Methods 17, 708-716 (2020). The final criteria for selecting candidates is mainly based on the OVERALL score (in most cases >70), the relative low

counts of potential off-targets (in most cases <200 off-targets), the absence of Graf motifs (if possible) and the genomic cut position within the coding sequence to produce knockouts or truncated proteins with reduced functionality (e.g. decoy receptors),

[00789] Finally, the IL1R1 domain in which each crRNA guides editing was determined based on the nucleotide position in the gene. The domain location is used to predict whether the edit will result in a wild-type like protein (edits in the sequence encoding the extreme C-terminus of a receptor that are unlikely to disrupt receptor-mediated signaling), complete knock-out of any functional protein (edits in the sequence encoding the N-terminus and/or essential functional domains), a soluble decoy receptor (edits in the sequence encoding the transmembrane domain of the receptor), or a membrane-bound decoy receptor (edits in the sequence encoding the intracellular signaling domain of the receptor).

[00790] Indeed, this in silico analysis established that several candidate sgRNAs were predicted to yield genomic edits that would create a dominant negative (DN) IL1R1, thereby impacting intracellular pro-inflammatory signaling (Fig. 11A). In support of the robustness of these analyses, structural predictions also demonstrated that editing with these particular sgRNAs would yield an expressible form of IL1R1 protein (either soluble or membrane-bound) that cannot induce the ligand's signal (Fig. 11B). Taken together, these predictive studies demonstrated the feasibility of inducing a dominant negative canine IL1 receptor as a unique approach to tamping down inflammation in cells and provided a high-throughput method for validating candidates without the need for time- and resource-intensive brute force methods.

EXAMPLE 2: VALIDATION OF DN IL1R1 IN CANINE CELLS

[00791] Having designed and analyzed numerous sgRNA candidates that were predicted to edit IL1 receptor to produce a dominant negative reception, the next step was to assess their ability to act *in* vitro. Of particular interest is whether the preferred (i.e., on-target) edit would be observed in edited cells.

[00792] To test this, 80 pmoles of sgRNA candidates were introduced into canine DH82 monocytes via electroporation as part of a ribonucleoprotein (i.e., pre-assembled with 25 pmoles of Cas9 protein at room temperature for at least 5 min). In brief, around 600,000 cells resuspended in 20 µl PKM buffer (2.7 mM KCl, 137 mM NaCl, 10 mM Na2HPO4 / 1.8 mM NaH2PO4 (pH 7.4) and 50 mM D-Mannitol) were added to the pre-assembled Cas9 ribonucleoprotein complex, transferred into 16-well nucleocuvettes and electroporated with

pulse code CM-137 using the 4D nucleofector (Lonza). Electroporated cells were kept in PKM buffer for about 10 min before transferring them into 6-well tissue culture plates with complete culture media. After 2-5 days in culture, cells were dissociated for genomic DNA extraction using the DNeasy Blood & Tissue Kit (Qiagen). sgRNA target regions were amplified by PCR and editing efficacy was then deduced from Sanger sequencing traces using Inference of CRISPR Edits (ICE v1.2). See, Conant, D. et al. (2022). *The CRISPR Journal*, 5(1), 123-130.

[00793] While multiple candidates were indeed able to induce mutation in the IL1R1 gene at high efficiency—including several exhibiting frequencies above 95%—two lead candidates exhibited the ability to consistently induce the same on-target edit in a high percentage of cells (Fig. 12). These results confirmed the robustness of the *in silico* analysis and suggested that at least OCR13 (SEQ ID NO: 3403) and OCR14 (SEQ ID NO: 3336) are able to produced DN IL1 receptors in canine cells.

EXAMPLE 3: IMPACT OF CAS9 MUTANTS WITH ENHANCED SPECIFICITY

[00794] With the ultimate aim to eliminate off-target editing without sacrifizing on-target activity, the lead candidate sgRNAs were assembled with different high-fidelity Cas9 variants (i.e. mutated Cas9 nucleases with enhanced specificity; *see generally*, Slaymaker, I. M. et al (2016). Science, 351(6268):84-88; Vakulskas, C. A. et al. (2018). Nature Medicine, 24(8):1216-1224) and assessed for frameshift efficacy and precision (i.e. the primacy for single or low number of repair outcomes) in canine DH82 monocytes.

[00795] Among the high-fidelity Cas9 nucleases, AR-Cas9 (IDT, Catalogue #1081060; Vakulskas, C. A. et al. (2018). Nature Medicine, 24(8):1216-1224) performed best overall with the lead candidate sgRNAs. In comparison to wild-type Cas9 (WT-Cas9), AR-Cas9 reached similarly high frameshift efficacy (>97%) and precision (>83%) when paired with OCR13 (Fig. 13A) and OCR14 (Fig. 13B). The other high-fidelity Cas9 nucleases tested were ES-Cas9 (Growth Factory, eSpCas9 (1.1); Slaymaker, I. M. et al (2016). Science, 351(6268):84-88), HF-Cas9 (Invitrogen, Catalogue #A50576) and PE-Cas9 (Merck Life Science, Catalogue # PECAS9-250).

[00796] However, AR-Cas9 like all other high-fidelity Cas9 nucleases (ES-Cas9, PE-Cas9 and HF-Cas9) showed decreased editing efficacy with OCR06, as compared to a combination with WT-Cas9 (Fig. 13C). Also, OCR10, which exhibits high precision with WT-Cas9, gives rise to a second frameshift edit at frequency 20-30% with all tested high-fidelity Cas9

nucleases (Fig. 13D). These results, taken as a whole, suggested that pairings between high-fidelity RNA-dependent nuclease and sgRNA would likely need to be done on a case-by-case basis.

EXAMPLE 4: DESIGN FOR IL1RAP/IL1RAP DECOY PROTEINS

[00797] IL1RAP is the co-receptor of all IL1 ligands, including IL33, which activates the IL1RL1/IL1RAP receptor dimer rather than the IL1A/B-specific IL1R1/IL1RAP. Thus, like other IL1R complex proteins, IL1RAP may be another potent mediator of inflammation that can be exploited for therapeutic purposes.

[00798] To test this, 10 candidate sgRNAs were designed to target different exons of canine IL1RAP with the objective to either ablate IL1RAP expressing (OCP01 to OCP06) or generate decoy IL1RAP proteins that will not transduce a pro-inflammatory signal (OCP07 to OCP10) (Fig. 14A). For example, OCP07 is predicted to predominantly produce an A duplication in exon 9 of IL1RAP, which shifts the open reading frame at position 355. At the protein level, this causes a Threonine (T) to Asparagine (N) amino acid change and prematurely terminates translation at position 395. Based on AlphaFold2-generated models, this +1 frameshift converts IL1RAP into a soluble IL1RAP decoy ($IL1RAP_{T355NfsTer41}$) missing the transmembrane and the cytoplasmic TIR domain (Fig. 14B).

[00799] Having done the predictive analysis, the next step was to assess performance in vitro. Candidate sgRNAs were paired with WT-Cas9 and introduced into canine DH82 monocytes via electroporation and editing efficacy and precision assessed by ICE. As predicted with an OVERALL score of 82, OCP02 performed best among the knockout candidates with virtually 100% KO rate due to a single C deletion introducing a premature stop codon at position 32 (M32*) (Fig. 15). All decoy-producing sgRNA candidates exhibited strong editing efficacy (greater than 95%). OCP09 and OCP10 demonstrated the strongest editing primacy with the top edit reaching 89% and 95%, respectively.

EXAMPLE 5: EDITING OF IL1RAP/IL1RAP IN VARIOUS CANINE CELL TYPES WITH HIGH FIDELITY NUCLEASES

[00800] Having designed and validated numerous guides targeting IL1RAP, the next step was to validate them with high-fidelity Cas9 nuclease to mitigate potential off-target effects during the editing process. To do this, one or two sgRNAs with the strongest frameshift scores (Fig. 16A) for each type of interference (e.g., knockout or decoy receptor) were

selected and paired with different high-fidelity Cas9 nucleases to see which, if any, would show similar on-target activity to WT-Cas9, while potentially reducing undesirable off-target effects.

[00801] Indeed, for each selected sgRNA, the editing efficacy in canine DH82 monocytes remained strongly dependent upon which high-fidelity Cas9 nuclease was used (Fig. 16B). Notably, AR-Cas9 most consistently showed high frequency of the desired edit in canine IL1RAP. This was particularly true in the case of OCP02, OCP07, and OCP10. However, this was effect was not universal, as the frameshift score for OCP09 was decreased when paired with AR-Cas9. OCP02, OCP07 and OCP10 also performed well in a head-to-head comparison of WT-Cas9 and AR-Cas9 in canine synovial fibroblasts (Fig. 16C). As such, high-fidelity RNA-dependent nucleases appeared to generally impact editing efficiency, though the magnitude of such effects will likely vary depending upon the nuclease used and to a lesser extent the cell type to be edited.

[00802] Having observed strong on-target activity when pairing sgRNA with high-fidelity Cas9 nucleases, the next step involved expansion of the assay to include numerous relevant canine cell types, such as DH82 monocytes, chondrocytes, and synovial fibroblasts. Specifically, the same select sgRNAs were used with AR-Cas9 in DH82 monocytes, where a strong preference for each desired edit was again observed (Fig. 17A). Similar editing efficacies were also observed in chondrocytes (Fig. 17B) and synovial fibroblasts (Fig. 17C). This result demonstrated that consistently high editing efficacies and precision for a given sgRNA and high-fidelity RNA-dependent nuclease pairing was achieved across various cell types.

EXAMPLE 6: EDITING OF IL1R1 RENDERS CANINE SYNOVIOCYTES UNRESPONSIVE TO IL1β TREATMENT

[00803] Having designed and validated numerous guides targeting IL1R1, the next step involved functional testing of edited cells. As part of this testing, around 300,000 edited canine synoviocytes were treated with 100 pM human recombinant IL1β for 4 hours. Reverse transcription followed by quantitative PCR (RT-qPCR) on extracted total RNA was carried out to verify whether human recombinant IL1β can stimulate the transcription of the inflammatory marker prostaglandin-endoperoxide synthase 2 (PTGS2/COX-2). No observable transcriptional upregulation of PTGS2/COX-2 was detected, likely because canine IL1R1 does not have a high enough affinity for human IL1β at 100 pM. Indeed, upon

repeating of the protocol with recombinant canine IL1β (R&D Systems, 3747-CL), robust upregulation was observed (Fig. 18). However, edited canine cells exhibited no such upregulation, suggesting that IL1β signaling had been disrupted. Both types of IL1R1 interference, knockout (OCR06/OCR10) or decoy receptor conversion (OCR13/OCR14), repressed PTGS2 transcription by 97% or more, which was line with the observed genetic frameshift score.

[00804] Because of the well-established relationship between IL1 receptor activation and additional pro-inflammatroy transcriptional responses, such as the upregulation of IL6 (see, Attur, M. G. et al. (1998). Proceedings of the Association of American Physicians, 110(1):65-72), the same assay was used to determine the effect of IL1R1 editing on this pro-inflammatory response following IL1β treatment. Similar to PTGS2/COX-2, unedited cells exhibited robust upregulation of IL6 after treatment, while no edited cells exhibited this response (Fig. 19). Taken together, these results showed that edited cells had lost the ability to respond to IL1β treatment.

EXAMPLE 7: EDITING OF IL1RAP/IL1RAP REDUCES COX-2 UPREGULATION IN CANINE MONOCYTES FOLLOWING EXPOSURE TO MULTIPLE INFLAMMATORY TRIGGERS

[00805] To understand the potential nexus between a dysfunctional IL1RAP and reductions in pro-inflammatory signaling, the transcriptional response to various inflammatory triggers, such as bacterial lipopolysaccharides (LPS), monosodium urate (MSU) crystals and IL1β, were investigated in canine control and IL1RAP-edited DH82 monocytes (biological triplicates, N=3) using bulk RNA-Seq and differential expression analysis DESeq2 (Fig. 20). All edited cell lines were genotyped, and all CRISPR-induced frameshift scores perfectly aligned with previous efficacy readings. Cells were exposed to saline solution PBS (negative control), 1 μg/ml LPS, 100 pM IL1β or 400 μg/ml MSU crystals, and total RNA was extracted after 4 and 24 hours. IL1RAP genotypes and inflammatory induction of PTGS2 were verified in control and edited cells (Fig. 21).

[00806] Prior to performing RNA-Seq, the transcriptional effect of inflammatory triggers was validated by RT-qPCR. Stimulation with LPS resulted in strong PTGS2 upregulation at both 4 hours (Fig. 21A) and 24 hours (Fig. 21B). The edited canine cells exhibited similar levels of upregulation, particularly at 24 hours, suggesting that the loss of IL1RAP did not impact LPS-mediated inflammatory signaling, which canonically occurs through engagement

of Toll-like receptors, such as TLR2 (*see generally*, Erridge, C. (2010). *Journal of Leukocyte Biology*, 87(6):989-999.). By contrast, while treatment with either IL1β or MSU also stimulated upregulation in control cells, the edited cells demonstrated abrogation at 4h and, in particular, at 24h with PTGS2 induction being repressed by 93% or more. Under control conditions (i.e., PBS treatment) no induction was observed at either time point, and, as observed for IL1R1, similar levels of abrogation of inflammatory signaling were observed whether the cells were edited to generate a knockout (OCP02) or a decoy receptor (OCP07).

EXAMPLE 8: EDITING OF IL1RAP/IL1RAP REDUCES RESPONSIVENESS OF VARIOUS CANINE CELL TYPES TO IL1β TREATMENT

[00807] Having designed and validated numerous sgRNAs targeting IL1RAP and having observed reductions in pro-inflammatory signaling at the transcriptional level in canine monocytes, the functional assays continued, this time in edited canine chondrocyte and synoviocytes. As part of this testing, around 300,000 edited canine synoviocytes were treated with 100 pM recombinant canine IL1β for 4 hours. Reverse transcription followed by quantitative PCR (RT-qPCR) on extracted total RNA was carried out to assess the transcriptional impacts of IL1β. Indeed, robust upregulation of PTGS2 was observed in control chondrocytes (Fig. 22A). However, edited canine chondrocytes exhibited no such upregulation, suggesting that IL1β signaling had been disrupted by the interference of IL1RAP, whether the cells were edited to generate a knockout or a decoy receptor. Similarly, control synoviocytes responded to treatment (Fig. 22B). However, the edited canine synoviocytes exhibited differential upregulation, with strong abrogation of IL1β signaling observed when the cells were edited to generate a knockout or a soluble decoy receptor (OCP07). Interestingly, generation of a membrane-bound decoy (OCP10) IL1RAP had little impact on this transcriptional upregulation in synoviocytes. This was likely due to inefficient IL1RAP editing in canine synoviocytes (see Fig. 17C). Repeat experiments are currently underway. These results demonstrated that editing of IL1RAP in various cell types can impact function in response to IL1β exposure.

EXAMPLE 9: LNP-BASED DELIVERY OF mRNA IN VARIOUS CANINE CELL TYPES

[00808] To this point, nearly all validation experiments had been conducted via electroporation of cell cultures to introduce RNA-dependent nucleases and sgRNAs.

However, to assess the suitability of using lipid nanoparticle (LNP) to deliver mRNA to mammalian cells, LNPs from PNI containing Trilink Firefly Luciferase mRNA were exposed to canine synovial fibroblasts for 8 hours and canine chondrocytes for 24 hours at increasing concentrations (based on a stock 0.1 mg/mL solution). At each time point, a luciferase and Bradford assay were conducted to detect and normalize cellular luciferase activity.

[00809] For synovial fibroblasts, increasing luciferase activity was observed with an increase in LNP concentrations from 1% (v/v) to 4% (v/v); however, no statistically significant difference was observed between 4% (v/v) and 8% (v/v) (Fig. 23A). For chondrocytes, similar dose dependency was observed (Fig. 23B). These results showed that the LNP formulation is competent in delivering its cargo in the form of mRNA into therapeutically relevant cells.

[00810] Further tests were also conducted to show the safety of these LNP formulations in an organism, particularly in dogs. Low doses (0.025 mg/ml) of LNP compositions (or saline control) were injected into healthy joints of dogs after performing baseline cytology studies on synovial fluid to determine the baseline counts of monocytes, neutrophils, and lymphocytes (Fig. 24A). The same cytology tests were undertaken again four weeks after injection and showed no appreciable differences from the baseline results in the canine synovial fluid (Fig. 24B). Further, no changes in relative counts for any one cell type were observed post injection. Together, these results demonstrated that LNPs can be used to introduce mRNA into multiple canine cell types, while canine injection studies showed that use of these LNPs do not stimulate in vivo inflammatory responses in mammals.

EXAMPLE 10: DIFFERENTIAL TRANSCRIPTIONAL RESPONSES IN IL1RAP/IL1RAP-EDITED CANINE MONOCYTES ARE ATTRIBUTABLE TO THE INTERFERENCE OF THE GENE

[00811] Functional assays had shown that IL1RAP knockouts or decoys made cells less responsive to some inflammatory triggers. However, how IL1 signaling contributes to the inflammatory response such as gout-like MSU crystals and whether the various strategies to interfere with it shows any differences on a genome-wide scale remained unclear. To test this, transcriptome-wide analysis was undertaken in either control or edited cells treated with various pro-inflammatory triggers for either 4 or 24 hours as previously described. The transcriptomes of these cells were then subjected to principal component analysis (PCA) to obtain a first view about their relationships to each other (Fig. 25A). This PCA (covering

77% of transcriptional variance across all samples) found that IL1RAP knockout and decoys were similarly effective in preventing differential transcription in cells treated with IL1β (both after 4 and 24 hrs) and MSU crystals (after 24 hrs), as noted by the distance between the control and IL1RAP-edited cells on the plot. However, LPS treatment was largely unaffected by the editing of IL1RAP, as noted by the clustering of control and edited cells on the plot. As expected, in the absence of an inflammatory trigger, genetic IL1RAP interference did not substantially change transcription as shown by the tight clustering of control and edited cells treated with PBS.

[00812] The results of the PCA were further supported by a more detailed analysis of differentially expressed genes. For instance, unedited cells exhibited strong transcriptional induction of numerous inflammatory markers upon stimulation with IL1β for 24 hours, including IL1B, IL6, PTGS2, and TNF (Fig. 25B). Similar results were observed with MSU treatment (Fig. 25C). However, cells with edited IL1RAP genes exhibited dramatically reduced induction of each of these genes. Notably, this reduction occurred regardless of the type of interference to IL1RAP (i.e., knockout or decoy receptor), and this reduction did not impact induction of the IL1R antagonist (IL1R2) or the housekeeping gene GAPDH.

[00813] A Venn diagram was generated for differentially expressed genes (fold change >2; FDR <10%) to show uniquely upregulated or downregulated in response to 24 hours of IL1β or MSU treatment in control and IL1RAP-edited cells. More than half of the surveyed transcripts—733 in total—were upregulated by IL1β treatment in unedited cells only (Fig. 25D). By contrast, no more than 72 upregulated genes were unique to each IL1RAP-edited cell pool. Similarly for non-shared downregulated genes, unedited cells showed more than half of the surveyed transcripts, while IL1RAP-edited cells were largely inert (Fig. 25E). A similar profile, albeit with less robust up- and downregulation of genes was observed with MSU treatment (Figs. 25F, G). Taken together, these results demonstrated that (1) IL1RAP edits were the root cause of the functional differences observed between edited and control cells, (2) all types of gene interference demonstrated similar transcriptional profiles in being refractory to IL1β treatment, and (3) that IL1RAP interference could mitigate the inflammatory response to MSU crystals, which indicates a promising avenue to treat gout.

EXAMPLE 11: VALIDATION OF TGFBR1 EDITING IN HUMAN CELLS

[00814] Having designed and analyzed numerous sgRNAs that were predicted to edit the TGFBR1 receptor to produce either a knockout or (soluble or membrane-bound) dominant

negative decoy by bioinformatic methods described in Example 1 (*see*, Fig. 34), the next step was to assess their ability to act in vitro. Of particular interest was whether the one preferred, on-target edit would be observed in any of the candidates.

[00815] To test this, the sgRNA candidates were complexed with a Cas9 nuclease to form a ribonucleoprotein (RNP) complex before electroporating human THP-1 monocytes to introduce the RNPs to the cells as previously described above. Editing efficiency was then measured via sequencing. While multiple candidates were able to induce mutations in the hTGFBR1 gene at high efficiency, with several exhibiting frequencies above 50% with wtCas9 (Fig. 45A), this efficacy was universally reduced with use of the AR-Cas9 variant (Fig. 46B). Notably, pairing AR-Cas9 with OHTIR04 (SEQ ID NO: 1455) resulted in greater edit primacy (i.e., only the single, on-target edit was observed), albeit at a lower editing efficiency. These results generally confirmed the *in silico* analysis and suggested that several sgRNA candidates, including OHTIR04, were able to efficiently edit TGFBR1 in human cells at some frequency.

EXAMPLE 12: VALIDATION OF TGFBR2 EDITING IN HUMAN CELLS

[00816] Having designed and analyzed numerous sgRNAs that were predicted to edit the TGFBR2 receptor to produce either a knockout or (soluble or membrane-bound) dominant negative decoy by bioinformatic methods described in Example 1 (*see*, Fig. 35), the next step was to assess their ability to act in vitro. Of particular interest was whether the one preferred edit would be observed in any of the candidates.

[00817] To test this, the sgRNA candidates were complexed with a Cas9 nuclease to form a ribonucleoprotein (RNP) complex before electroporating human THP-1 monocytes to introduce the RNPs to the cells as previously described above. Editing efficiency was then measured via sequencing. While multiple candidates were able to induce mutations in the hTGFBR2 gene at high efficiency, with several exhibiting frequencies near or above 50% with wtCas9 (Fig. 46A), this efficacy was universally reduced with use of the AR-Cas9 variant (Fig. 46B). Notably, pairing AR-Cas9 with OHTIIR11 (SEQ ID NO: 1466) resulted in increased editing primacy (i.e., proportion of the editing comprised by the desired on-target edit), albeit at a lower editing efficiency than with wtCas9. These results generally confirmed the *in silico* analysis and suggested that several sgRNA candidates, including OHTIIR11, were able to efficiently edit TGFBR2 in human cells at some frequency.

EXAMPLE 13: EDITING OF TGFBR1 OR TGFBR2 RENDERS HUMAN MONOCYTES UNRESPONSIVE TO TGF-BETA STIMULI

[00818] Having designed and validated numerous guides targeting the TGF-beta pathway, the next step involved functional testing of edited cells. As part of this testing, around 300,000 edited human THP-1 monocytes were treated with either 1 μg/ml LPS or 20 ng/μl recombinant TGF-beta for 6 hours. Reverse transcription of total cellular RNA was followed by quantitative PCR (RT-qPCR) was carried out to verify whether human either LPS or TGF-beta can stimulate the transcription of TGFB1 as has been previously reported (*see generally*, Yan, X., et al. (2018). *Acta Biochimica et Biophysica Sinica*, *50*(1), 37-50.). LPS treatment did not induce robust expression of TGFB1 in control cells as compared to those treated with PBS (Fig. 47A). Despite this lack of response, TGFB1 levels were reduced as much as five-fold for TGFBR1-edited cells compared to the unedited control, while TGFBR2-edited cells exhibited a more modest two-fold reduction.

[00819] As an additional test, the same cellular RNA was assayed for induction of TIMP1, which canonically is upregulated by TGF-beta signaling via the SMAD proteins (*see generally*, Hall, M. C., et al. (2003). *Journal of Biological Chemistry*, 278(12), 10304-10313.). In the LPS-treated cells, robust induction of TIMP1 was observed in the unedited control as compared to the PBS-treated cells (Fig. 47B). TGFBR1-edited monocytes demonstrated a two-fold decrease in TIMP1 induction as compared to the unedited control. There was no change for TGFBR2-edited cells

[00820] Results were even more striking following treatment with the natural ligand. In response to TGF-beta treatment, TGFB1 induction was more robust, and edits to either TGFBR1 or TGFBR2 reduced this response by two-fold (Fig. 47C). These results were similar to those observed for TIMP1 induction following TGF-beta treatment (Fig. 47D). These results collectively showed that the edited cells did not respond to TGF-beta treatment, as their levels of TGFB1 remained well below the PBS-treated control. Taken together, these results demonstrated that TGF-beta positive feedback (TGFB1 induction) and downstream signaling (TIMP1 induction) were both impaired in cells with edited TGFBR1 and TGFBR2.

EXAMPLE 14: VALIDATION OF IL1R1 EDITING IN HUMAN CELLS

[00821] Having designed and analyzed numerous sgRNA candidates that were predicted to edit the human IL1 receptor to produce either a knockout or a dominant negative receptor (see Fig. 48A), the next step is to assess their ability to act in vitro. Of particular interest is whether the preferred (i.e., on-target) edit will be observed in edited cells.

[00822] To test this, 80 pmoles of sgRNA candidates (SEQ ID NOs: 3491-3513) are introduced into human THP-1 monocytes via electroporation as part of a ribonucleoprotein (i.e., pre-assembled with 25 pmoles or either wtCas9 or AR-Cas9 protein at room temperature for at least 5 min). In brief, around 600,000 cells resuspended in 20 µl PKM buffer (2.7 mM KCl, 137 mM NaCl, 10 mM Na2HPO4 / 1.8 mM NaH2PO4 (pH 7.4) and 50 mM D-Mannitol) are added to the pre-assembled Cas9 ribonucleoprotein complex, transferred into 16-well nucleocuvettes and electroporated with pulse code CM-137 using the 4D nucleofector (Lonza). Electroporated cells are kept in PKM buffer for about 10 min before transferring them into 6-well tissue culture plates with complete culture media. After 2-5 days in culture, cells are dissociated for genomic DNA extraction using the DNeasy Blood & Tissue Kit (Qiagen). sgRNA target regions are amplified by PCR and editing efficacy is then deduced from Sanger sequencing traces using Inference of CRISPR Edits (ICE v1.2). Conant, D. et al. (2022). *The CRISPR Journal*, 5(1), 123-130 (2022).

[00823] It is anticipated that results of these studies will confirm the robustness of the *in silico* analysis and identify multiple candidates are indeed able to induce mutation in the IL1R1 gene at high efficacy. It is further expected that use of AR-Cas9 will improve editing efficacy (i.e., increase on-target editing) as compared to wtCas9.

EXAMPLE 15: IN VITRO DELIVERY OF IL1R1-EDITING GUIDE RNA TO HUMAN CELLS VIA LIPID NANOPARTICLES

[00824] Because all validation experiments are to be conducted via electroporation of cell cultures to introduce RNA-dependent nucleases and sgRNAs, additional experiments will assess the suitability of using lipid nanoparticle (LNP) to deliver mRNA to human cells. 0.025 mg/mL of LNPs from PNI containing either 80 pmoles of sgRNA (SEQ ID NOs: 3491-3513) or 80 pmoles of Cas9 mRNA (alternatively, sgRNA may be pre-assembled with 25 pmoles or either wtCas9 or AR-Cas9 protein at room temperature for at least 5 min and encapsulated as an RNP) are exposed to THP-1 monocytes for 8 to 24 hours under typical

cell culture conditions. Sanger sequencing as described in Example 14 will be used to validate editing. Upon confirmation of editing various functional assays as described in Example 13 will be performed.

EXAMPLE 16: IN VITRO DELIVERY OF IL1R1-EDITING GUIDE RNA TO HUMAN CELLS VIA ADENO-ASSOCIATED VIRUS

[00825] Because all validation experiments are to be conducted via electroporation of cell cultures to introduce RNA-dependent nucleases and sgRNAs, additional experiments will assess the suitability of using adeno-associated virus (AAV) vectors to deliver sgRNA to human cells.

TABLE 2. Exemplary AAV vectors for introduction of sgRNA to human cells.

AAVPrimeTM Adeno-Associated Virus - Serotype6 (AAV-6) Particles for sgRNA (GeneCopoeia™, catalog No. AA06-MCP001682-AD01-2-200-a, lot No. GC03182K2001)
AAVPrimeTM Adeno-Associated Virus - Serotype6 (AAV-6) Particles for sgRNA (GeneCopoeia™, catalog No. AA06-MCP001682-AD01-2-200-b, lot No. GC03202K2001)
AAVPrimeTM Adeno-Associated Virus - Serotype6 (AAV-6) Particles for sgRNA (GeneCopoeia™, catalog No. AA06-CCPCTR01-AD01-200, lot No. GC03112K2002)
AAVPrimeTM Adeno-Associated Virus – Serotype5 (AAV-5) Particles for sgRNA (GeneCopoeia™, catalogue No. AA05-MCP001682-AD01-2-200A, lot No. GC-03182K2002)
AAVPrimeTM Adeno-Associated Virus – Serotype5 (AAV-5) Particles for sgRNA (GeneCopoeia™, catalogue No. AA05-MCP001682-AD01-2-200B, lot No. GC03182K2003)
AAVPrimeTM Adeno-Associated Virus – Serotype5 (AAV-5) Particles for sgRNA (GeneCopoeiaTM, catalogue No. AA05-CCPCTR01-AD01-200, lot No. GC03032K2003)

[00826] Exemplary AAV vectors are shown in Table 2. After being prepared according to manufacturer specifications, such that one or more of the sgRNAs containing SEQ ID NOs: 3491-3513 are integrated into the viral vector, said vectors are incubated (MOI=0.1 to 10) with approximately 500,000 U2OS cells that have been stably transfected with Cas9 (*see, e.g.*, Rojas-Fernandez, A., et al. (2015). *Scientific Reports*, 5(1), 1-6.). At 2-7 days post-

infection, Sanger sequencing as described in Example 14 will be used to validate editing. Upon confirmation of editing, various functional assays as described in Example 13 will be performed.

EXAMPLE 17: VALIDATION OF IL1RAP EDITING IN HUMAN CELLS

[00827] Having designed and analyzed numerous sgRNA candidates that were predicted to edit the human IL1 receptor accesory protein to produce either a knockout or a dominant negative receptor (see Fig. 48B), the next step is to assess their ability to act in vitro. Of particular interest is whether the preferred (i.e., on-target) edit will be observed in edited cells.

[00828] To test this, 80 pmoles of sgRNA candidates (SEQ ID NOs: 3514-3543) are introduced into human THP-1 monocytes via electroporation as part of a ribonucleoprotein as previously described in Example 14.

[00829] It is anticipated that results of these studies will confirm the robustness of the *in silico* analysis and identify multiple candidates are indeed able to induce mutation in the IL1RAP gene at high efficacy. It is further expected that use of AR-Cas9 will improve editing efficacy (i.e., increase on-target editing) as compared to wtCas9.

EXAMPLE 18: IN VITRO DELIVERY OF IL1RAP-EDITING GUIDE RNA TO HUMAN CELLS VIA LIPID NANOPARTICLES

[00830] Because all validation experiments are to be conducted via electroporation of cell cultures to introduce RNA-dependent nucleases and sgRNAs, additional experiments will assess the suitability of using lipid nanoparticle (LNP) to deliver mRNA to human cells. LNPs containing either sgRNA (SEQ ID NOs: 3514-3543) or Cas9 mRNA are incubated with THP-1 monocytes, followed by validation of editing as described in Example 15. Upon confirmation of editing various functional assays as described in Example 13 will be performed.

EXAMPLE 19: IN VITRO DELIVERY OF IL1RAP-EDITING GUIDE RNA TO HUMAN CELLS VIA ADENO-ASSOCIATED VIRUS

[00831] Because all validation experiments are to be conducted via electroporation of cell cultures to introduce RNA-dependent nucleases and sgRNAs, additional experiments will

assess the suitability of using adeno-associated virus (AAV) vectors to deliver sgRNA to human cells. Exemplary AAV vectors are shown in Table 2. After being prepared according to manufacturer specifications, such that one or more of the sgRNAs containing SEQ ID NOs: 3514-3543 are integrated into the viral vector, said vectors are introduced to human U2OS cells and editing is validated as previously described in Example 16. Upon confirmation of editing, various functional assays as described in Example 13 will be performed.

EXAMPLE 20: VALIDATION OF IL6R EDITING IN HUMAN CELLS

[00832] Having designed and analyzed numerous sgRNA candidates that were predicted to edit the human IL6 receptor protein to produce either a knockout or a dominant negative receptor (see Fig. 48C), the next step is to assess their ability to act in vitro. Of particular interest is whether the preferred (i.e., on-target) edit will be observed in edited cells.

[00833] To test this, 80 pmoles of sgRNA candidates (SEQ ID NOs: 3544-3566) are introduced into human THP-1 monocytes via electroporation as part of a ribonucleoprotein as previously described in Example 14.

[00834] It is anticipated that results of these studies will confirm the robustness of the *in silico* analysis and identify multiple candidates are indeed able to induce mutation in the IL6R gene at high efficacy. It is further expected that use of AR-Cas9 will improve editing efficacy (i.e., increase on-target editing) as compared to wtCas9.

EXAMPLE 21: IN VITRO DELIVERY OF IL6R-EDITING GUIDE RNA TO HUMAN CELLS VIA LIPID NANOPARTICLES

[00835] Because all validation experiments are to be conducted via electroporation of cell cultures to introduce RNA-dependent nucleases and sgRNAs, additional experiments will assess the suitability of using lipid nanoparticle (LNP) to deliver mRNA to human cells. LNPs containing either sgRNA (SEQ ID NOs: 3544-3566) or Cas9 mRNA are incubated with THP-1 monocytes, followed by validation of editing as described in Example 15. Upon confirmation of editing various functional assays as described in Example 13 will be performed.

EXAMPLE 22: IN VITRO DELIVERY OF IL6R-EDITING GUIDE RNA TO HUMAN CELLS VIA ADENO-ASSOCIATED VIRUS

[00836] Because all validation experiments are to be conducted via electroporation of cell cultures to introduce RNA-dependent nucleases and sgRNAs, additional experiments will assess the suitability of using adeno-associated virus (AAV) vectors to deliver sgRNA to human cells. Exemplary AAV vectors are shown in Table 2. After being prepared according to manufacturer specifications, such that one or more of the sgRNAs containing SEQ ID NOs: 3544-3566 are integrated into the viral vector, said vectors are introduced to human U2OS cells and editing is validated as previously described in Example 16. Upon confirmation of editing, various functional assays as described in Example 13 will be performed.

EXAMPLE 23: VALIDATION OF IL6ST EDITING IN HUMAN CELLS

[00837] Having designed and analyzed numerous sgRNA candidates that were predicted to edit the human IL6 Cytokine Family Signal Transducer protein to produce either a knockout or a dominant negative receptor (see Fig. 48D), the next step is to assess their ability to act in vitro. Of particular interest is whether the preferred (i.e., on-target) edit will be observed in edited cells.

[00838] To test this, 80 pmoles of sgRNA candidates (SEQ ID NOs: 3567-3606) are introduced into human THP-1 monocytes via electroporation as part of a ribonucleoprotein as previously described in Example 14.

[00839] It is anticipated that results of these studies will confirm the robustness of the *in silico* analysis and identify multiple candidates are indeed able to induce mutation in the IL6ST gene at high efficacy. It is further expected that use of AR-Cas9 will improve editing efficacy (i.e., increase on-target editing) as compared to wtCas9.

EXAMPLE 24: IN VITRO DELIVERY OF IL6ST-EDITING GUIDE RNA TO HUMAN CELLS VIA LIPID NANOPARTICLES

[00840] Because all validation experiments are to be conducted via electroporation of cell cultures to introduce RNA-dependent nucleases and sgRNAs, additional experiments will assess the suitability of using lipid nanoparticle (LNP) to deliver mRNA to human cells. LNPs containing either sgRNA (SEQ ID NOs: 3567-3606) or Cas9 mRNA are incubated

with THP-1 monocytes, followed by validation of editing as described in Example 15. Upon confirmation of editing various functional assays as described in Example 13 will be performed.

EXAMPLE 25: IN VITRO DELIVERY OF IL6ST-EDITING GUIDE RNA TO HUMAN CELLS VIA ADENO-ASSOCIATED VIRUS

[00841] Because all validation experiments are to be conducted via electroporation of cell cultures to introduce RNA-dependent nucleases and sgRNAs, additional experiments will assess the suitability of using adeno-associated virus (AAV) vectors to deliver sgRNA to human cells. Exemplary AAV vectors are shown in Table 2. After being prepared according to manufacturer specifications, such that one or more of the sgRNAs containing SEQ ID NOs: 3567-3606 are integrated into the viral vector, said vectors are introduced to human U2OS cells and editing is validated as previously described in Example 16. Upon confirmation of editing, various functional assays as described in Example 13 will be performed.

EXAMPLE 26: VALIDATION OF TNFRSF1A EDITING IN HUMAN CELLS

[00842] Having designed and analyzed numerous sgRNA candidates that were predicted to edit the human Tumor Necrosis Factor Receptor 1 protein to produce either a knockout or a dominant negative receptor (see Fig. 48E), the next step is to assess their ability to act in vitro. Of particular interest is whether the preferred (i.e., on-target) edit will be observed in edited cells.

[00843] To test this, 80 pmoles of sgRNA candidates (SEQ ID NOs: 3607-3647) are introduced into human THP-1 monocytes via electroporation as part of a ribonucleoprotein as previously described in Example 14.

[00844] It is anticipated that results of these studies will confirm the robustness of the *in silico* analysis and identify multiple candidates are indeed able to induce mutation in the TNFRSF1A gene at high efficacy. It is further expected that use of AR-Cas9 will improve editing efficacy (i.e., increase on-target editing) as compared to wtCas9.

EXAMPLE 27: IN VITRO DELIVERY OF TNFRSF1A-EDITING GUIDE RNA TO HUMAN CELLS VIA LIPID NANOPARTICLES

[00845] Because all validation experiments are to be conducted via electroporation of cell cultures to introduce RNA-dependent nucleases and sgRNAs, additional experiments will assess the suitability of using lipid nanoparticle (LNP) to deliver mRNA to human cells. LNPs containing either sgRNA (SEQ ID NOs: 3607-3647) or Cas9 mRNA are incubated with THP-1 monocytes, followed by validation of editing as described in Example 15. Upon confirmation of editing various functional assays as described in Example 13 will be performed.

EXAMPLE 28: IN VITRO DELIVERY OF TNFRSF1A-EDITING GUIDE RNA TO HUMAN CELLS VIA ADENO-ASSOCIATED VIRUS

[00846] Because all validation experiments are to be conducted via electroporation of cell cultures to introduce RNA-dependent nucleases and sgRNAs, additional experiments will assess the suitability of using adeno-associated virus (AAV) vectors to deliver sgRNA to human cells. Exemplary AAV vectors are shown in Table 2. After being prepared according to manufacturer specifications, such that one or more of the sgRNAs containing SEQ ID NOs: 3607-3647 are integrated into the viral vector, said vectors are introduced to human U2OS cells and editing is validated as previously described in Example 16. Upon confirmation of editing, various functional assays as described in Example 13 will be performed.

EXAMPLE 29: VALIDATION OF TNFRSF1B EDITING IN HUMAN CELLS

[00847] Having designed and analyzed numerous sgRNA candidates that were predicted to edit the human Tumor Necrosis Factor Receptor 2 protein to produce either a knockout or a dominant negative receptor (see Fig. 48F), the next step is to assess their ability to act in vitro. Of particular interest is whether the preferred (i.e., on-target) edit will be observed in edited cells.

[00848] To test this, 80 pmoles of sgRNA candidates (SEQ ID NOs: 3648-3692) are introduced into human THP-1 monocytes via electroporation as part of a ribonucleoprotein as previously described in Example 14.

[00849] It is anticipated that results of these studies will confirm the robustness of the *in silico* analysis and identify multiple candidates are indeed able to induce mutation in the TNFRSF1B gene at high efficacy. It is further expected that use of AR-Cas9 will improve editing efficacy (i.e., increase on-target editing) as compared to wtCas9.

EXAMPLE 30: IN VITRO DELIVERY OF TNFRSF1B-EDITING GUIDE RNA TO HUMAN CELLS VIA LIPID NANOPARTICLES

[00850] Because all validation experiments are to be conducted via electroporation of cell cultures to introduce RNA-dependent nucleases and sgRNAs, additional experiments will assess the suitability of using lipid nanoparticle (LNP) to deliver mRNA to human cells. LNPs containing either sgRNA (SEQ ID NOs: 3648-3692) or Cas9 mRNA are incubated with THP-1 monocytes, followed by validation of editing as described in Example 15. Upon confirmation of editing various functional assays as described in Example 13 will be performed.

EXAMPLE 31: IN VITRO DELIVERY OF TNFRSF1B-EDITING GUIDE RNA TO HUMAN CELLS VIA ADENO-ASSOCIATED VIRUS

[00851] Because all validation experiments are to be conducted via electroporation of cell cultures to introduce RNA-dependent nucleases and sgRNAs, additional experiments will assess the suitability of using adeno-associated virus (AAV) vectors to deliver sgRNA to human cells. Exemplary AAV vectors are shown in Table 2. After being prepared according to manufacturer specifications, such that one or more of the sgRNAs containing SEQ ID NOs: 3648-3692 are integrated into the viral vector, said vectors are introduced to human U2OS cells and editing is validated as previously described in Example 16. Upon confirmation of editing, various functional assays as described in Example 13 will be performed.

EXAMPLE 32: VALIDATION OF TNFRSF3 EDITING IN HUMAN CELLS

[00852] Having designed and analyzed numerous sgRNA candidates that were predicted to edit the human Lymphotoxin Beta Receptor protein to produce either a knockout or a dominant negative receptor (see Fig. 48G), the next step is to assess their ability to act in vitro. Of particular interest is whether the preferred (i.e., on-target) edit will be observed in edited cells.

[00853] To test this, 80 pmoles of sgRNA candidates (SEQ ID NOs: 3693-3713) are introduced into human THP-1 monocytes via electroporation as part of a ribonucleoprotein as previously described in Example 14.

[00854] It is anticipated that results of these studies will confirm the robustness of the *in silico* analysis and identify multiple candidates are indeed able to induce mutation in the TNFRSF3 gene at high efficacy. It is further expected that use of AR-Cas9 will improve editing efficacy (i.e., increase on-target editing) as compared to wtCas9.

EXAMPLE 33: IN VITRO DELIVERY OF TNFRSF3-EDITING GUIDE RNA TO HUMAN CELLS VIA LIPID NANOPARTICLES

[00855] Because all validation experiments are to be conducted via electroporation of cell cultures to introduce RNA-dependent nucleases and sgRNAs, additional experiments will assess the suitability of using lipid nanoparticle (LNP) to deliver mRNA to human cells. LNPs containing either sgRNA (SEQ ID NOs: 3693-3713) or Cas9 mRNA are incubated with THP-1 monocytes, followed by validation of editing as described in Example 15. Upon confirmation of editing various functional assays as described in Example 13 will be performed.

EXAMPLE 34: IN VITRO DELIVERY OF TNFRSF3-EDITING GUIDE RNA TO HUMAN CELLS VIA ADENO-ASSOCIATED VIRUS

[00856] Because all validation experiments are to be conducted via electroporation of cell cultures to introduce RNA-dependent nucleases and sgRNAs, additional experiments will assess the suitability of using adeno-associated virus (AAV) vectors to deliver sgRNA to human cells. Exemplary AAV vectors are shown in Table 2. After being prepared according to manufacturer specifications, such that one or more of the sgRNAs containing SEQ ID NOs: 3693-3713 are integrated into the viral vector, said vectors are introduced to human U2OS cells and editing is validated as previously described in Example 16. Upon confirmation of editing, various functional assays as described in Example 13 will be performed.

EXAMPLE 35: VALIDATION OF TNFRSF4 EDITING IN HUMAN CELLS

[00857] Having designed and analyzed numerous sgRNA candidates that were predicted to edit the human OX40 Receptor protein to produce either a knockout or a dominant negative

receptor (see Fig. 48H), the next step is to assess their ability to act in vitro. Of particular interest is whether the preferred (i.e., on-target) edit will be observed in edited cells.

[00858] To test this, 80 pmoles of sgRNA candidates (SEQ ID NOs: 3714-3740) are introduced into human THP-1 monocytes via electroporation as part of a ribonucleoprotein as previously described in Example 14.

[00859] It is anticipated that results of these studies will confirm the robustness of the *in silico* analysis and identify multiple candidates are indeed able to induce mutation in the TNFRSF4 gene at high efficacy. It is further expected that use of AR-Cas9 will improve editing efficacy (i.e., increase on-target editing) as compared to wtCas9.

EXAMPLE 36: IN VITRO DELIVERY OF TNFRSF4-EDITING GUIDE RNA TO HUMAN CELLS VIA LIPID NANOPARTICLES

[00860] Because all validation experiments are to be conducted via electroporation of cell cultures to introduce RNA-dependent nucleases and sgRNAs, additional experiments will assess the suitability of using lipid nanoparticle (LNP) to deliver mRNA to human cells. LNPs containing either sgRNA (SEQ ID NOs: 3714-3740) or Cas9 mRNA are incubated with THP-1 monocytes, followed by validation of editing as described in Example 15. Upon confirmation of editing various functional assays as described in Example 13 will be performed.

EXAMPLE 37: IN VITRO DELIVERY OF TNFRSF4-EDITING GUIDE RNA TO HUMAN CELLS VIA ADENO-ASSOCIATED VIRUS

[00861] Because all validation experiments are to be conducted via electroporation of cell cultures to introduce RNA-dependent nucleases and sgRNAs, additional experiments will assess the suitability of using adeno-associated virus (AAV) vectors to deliver sgRNA to human cells. Exemplary AAV vectors are shown in Table 2. After being prepared according to manufacturer specifications, such that one or more of the sgRNAs containing SEQ ID NOs: 3714-3740 are integrated into the viral vector, said vectors are introduced to human U2OS cells and editing is validated as previously described in Example 16. Upon confirmation of editing, various functional assays as described in Example 13 will be performed.

EXAMPLE 38: VALIDATION OF TNFRSF11A EDITING IN HUMAN CELLS

[00862] Having designed and analyzed numerous sgRNA candidates that were predicted to edit the human Tumor Necrosis Factor Receptor Superfamily Member 11A protein to produce either a knockout or a dominant negative receptor (see Fig. 48I), the next step is to assess their ability to act in vitro. Of particular interest is whether the preferred (i.e., on-target) edit will be observed in edited cells.

[00863] To test this, 80 pmoles of sgRNA candidates (SEQ ID NOs: 3741-3788) are introduced into human THP-1 monocytes via electroporation as part of a ribonucleoprotein as previously described in Example 14.

[00864] It is anticipated that results of these studies will confirm the robustness of the *in silico* analysis and identify multiple candidates are indeed able to induce mutation in the TNFRSF11A gene at high efficacy. It is further expected that use of AR-Cas9 will improve editing efficacy (i.e., increase on-target editing) as compared to wtCas9.

EXAMPLE 39: IN VITRO DELIVERY OF TNFRSF11A-EDITING GUIDE RNA TO HUMAN CELLS VIA LIPID NANOPARTICLES

[00865] Because all validation experiments are to be conducted via electroporation of cell cultures to introduce RNA-dependent nucleases and sgRNAs, additional experiments will assess the suitability of using lipid nanoparticle (LNP) to deliver mRNA to human cells. LNPs containing either sgRNA (SEQ ID NOs: 3741-3788) or Cas9 mRNA are incubated with THP-1 monocytes, followed by validation of editing as described in Example 15. Upon confirmation of editing various functional assays as described in Example 13 will be performed.

EXAMPLE 40: IN VITRO DELIVERY OF TNFRSF11A-EDITING GUIDE RNA TO HUMAN CELLS VIA ADENO-ASSOCIATED VIRUS

[00866] Because all validation experiments are to be conducted via electroporation of cell cultures to introduce RNA-dependent nucleases and sgRNAs, additional experiments will assess the suitability of using adeno-associated virus (AAV) vectors to deliver sgRNA to human cells. Exemplary AAV vectors are shown in Table 2. After being prepared according to manufacturer specifications, such that one or more of the sgRNAs containing SEQ ID NOs: 3741-3788 are integrated into the viral vector, said vectors are introduced to human

U2OS cells and editing is validated as previously described in Example 16. Upon confirmation of editing, various functional assays as described in Example 13 will be performed.

EXAMPLE 41: VALIDATION OF TGFBR1 EDITING IN HUMAN CELLS

[00867] Having designed and analyzed numerous sgRNA candidates that were predicted to edit the human Transforming Growth Factor Beta Receptor 1 protein to produce either a knockout or a dominant negative receptor (see Fig. 48J), the next step is to assess their ability to act in vitro. Of particular interest is whether the preferred (i.e., on-target) edit will be observed in edited cells.

[00868] To test this, 80 pmoles of sgRNA candidates (SEQ ID NOs: 3789-3813) are introduced into human THP-1 monocytes via electroporation as part of a ribonucleoprotein as previously described in Example 14.

[00869] It is anticipated that results of these studies will confirm the robustness of the *in silico* analysis and identify multiple candidates are indeed able to induce mutation in the TGFBR1 gene at high efficacy. It is further expected that use of AR-Cas9 will improve editing efficacy (i.e., increase on-target editing) as compared to wtCas9.

EXAMPLE 42: IN VITRO DELIVERY OF TGFBR1-EDITING GUIDE RNA TO HUMAN CELLS VIA LIPID NANOPARTICLES

[00870] Because all validation experiments are to be conducted via electroporation of cell cultures to introduce RNA-dependent nucleases and sgRNAs, additional experiments will assess the suitability of using lipid nanoparticle (LNP) to deliver mRNA to human cells. LNPs containing either sgRNA (SEQ ID NOs: 3789-3813) or Cas9 mRNA are incubated with THP-1 monocytes, followed by validation of editing as described in Example 15. Upon confirmation of editing various functional assays as described in Example 13 will be performed.

EXAMPLE 43: IN VITRO DELIVERY OF TGFBR1-EDITING GUIDE RNA TO HUMAN CELLS VIA ADENO-ASSOCIATED VIRUS

[00871] Because all validation experiments are to be conducted via electroporation of cell cultures to introduce RNA-dependent nucleases and sgRNAs, additional experiments will

assess the suitability of using adeno-associated virus (AAV) vectors to deliver sgRNA to human cells. Exemplary AAV vectors are shown in Table 2. After being prepared according to manufacturer specifications, such that one or more of the sgRNAs containing SEQ ID NOs: 3789-3813 are integrated into the viral vector, said vectors are introduced to human U2OS cells and editing is validated as previously described in Example 16. Upon confirmation of editing, various functional assays as described in Example 13 will be performed.

EXAMPLE 44: VALIDATION OF TGFBR2 EDITING IN HUMAN CELLS

[00872] Having designed and analyzed numerous sgRNA candidates that were predicted to edit the human Transforming Growth Factor Beta Receptor 2 protein to produce either a knockout or a dominant negative receptor (see Fig. 48K), the next step is to assess their ability to act in vitro. Of particular interest is whether the preferred (i.e., on-target) edit will be observed in edited cells.

[00873] To test this, 80 pmoles of sgRNA candidates (SEQ ID NOs: 3814-3865) are introduced into human THP-1 monocytes via electroporation as part of a ribonucleoprotein as previously described in Example 14.

[00874] It is anticipated that results of these studies will confirm the robustness of the *in silico* analysis and identify multiple candidates are indeed able to induce mutation in the TGFBR2 gene at high efficacy. It is further expected that use of AR-Cas9 will improve editing efficacy (i.e., increase on-target editing) as compared to wtCas9.

EXAMPLE 45: IN VITRO DELIVERY OF TGFBR2-EDITING GUIDE RNA TO HUMAN CELLS VIA LIPID NANOPARTICLES

[00875] Because all validation experiments are to be conducted via electroporation of cell cultures to introduce RNA-dependent nucleases and sgRNAs, additional experiments will assess the suitability of using lipid nanoparticle (LNP) to deliver mRNA to human cells. LNPs containing either sgRNA (SEQ ID NOs: 3814-3865) or Cas9 mRNA are incubated with THP-1 monocytes, followed by validation of editing as described in Example 15. Upon confirmation of editing various functional assays as described in Example 13 will be performed.

EXAMPLE 46: IN VITRO DELIVERY OF TGFBR2-EDITING GUIDE RNA TO HUMAN CELLS VIA ADENO-ASSOCIATED VIRUS

[00876] Because all validation experiments are to be conducted via electroporation of cell cultures to introduce RNA-dependent nucleases and sgRNAs, additional experiments will assess the suitability of using adeno-associated virus (AAV) vectors to deliver sgRNA to human cells. Exemplary AAV vectors are shown in Table 2. After being prepared according to manufacturer specifications, such that one or more of the sgRNAs containing SEQ ID NOs: 3814-3865 are integrated into the viral vector, said vectors are introduced to human U2OS cells and editing is validated as previously described in Example 16. Upon confirmation of editing, various functional assays as described in Example 13 will be performed.

[00877] The examples set forth above are provided to give those of ordinary skill in the art a complete disclosure and description of how to make and use the embodiments of the compositions, systems and methods of the disclosure, and are not intended to limit the scope of what the inventors regard as their invention. Modifications of the above-described modes for carrying out the embodiments of the disclosure that are obvious to persons of skill in the art are intended to be within the scope of the following claims. All patents and publications mentioned in the specification are indicative of the levels of skill of those skilled in the art to which the disclosure pertains.

[00878] All headings and section designations are used for clarity and reference purposes only and are not to be considered limiting in any way. For example, those of skill in the art will appreciate the usefulness of combining various aspects from different headings and sections as appropriate according to the spirit and scope of the disclosure described herein.

[00879] It is to be understood that the methods described herein are not limited to the particular methodology, protocols, subjects, and sequencing techniques described herein and as such can vary. It is also to be understood that the terminology used herein is for the purpose of describing particular embodiments only, and is not intended to limit the scope of the methods and compositions described herein, which will be limited only by the appended claims. While some embodiments of the present disclosure have been shown and described herein, it will be obvious to those skilled in the art that such embodiments are provided by way of example only. Numerous variations, changes, and substitutions will now occur to those skilled in the art without departing from the disclosure. It should be understood that various alternatives to the embodiments of the disclosure described herein can be employed

in practicing the disclosure. It is intended that the following claims define the scope of the disclosure and that methods and structures within the scope of these claims and their equivalents be covered thereby.

[00880] The examples set forth above are provided to give those of ordinary skill in the art a complete disclosure and description of how to make and use the embodiments of the compositions, systems and methods of the disclosure, and are not intended to limit the scope of what the inventors regard as their invention. Modifications of the above-described modes for carrying out the embodiments of the disclosure that are obvious to persons of skill in the art are intended to be within the scope of the following claims. All patents and publications mentioned in the specification are indicative of the levels of skill of those skilled in the art to which the disclosure pertains.

[00881] All headings and section designations are used for clarity and reference purposes only and are not to be considered limiting in any way. For example, those of skill in the art will appreciate the usefulness of combining various aspects from different headings and sections as appropriate according to the spirit and scope of the disclosure described herein.

[00882] It is to be understood that the methods described herein are not limited to the particular methodology, protocols, subjects, and sequencing techniques described herein and as such can vary. It is also to be understood that the terminology used herein is for the purpose of describing particular embodiments only, and is not intended to limit the scope of the methods and compositions described herein, which will be limited only by the appended claims. While some embodiments of the present disclosure have been shown and described herein, it will be obvious to those skilled in the art that such embodiments are provided by way of example only. Numerous variations, changes, and substitutions will now occur to those skilled in the art without departing from the disclosure. It should be understood that various alternatives to the embodiments of the disclosure described herein can be employed in practicing the disclosure. It is intended that the following claims define the scope of the disclosure and that methods and structures within the scope of these claims and their equivalents be covered thereby.

[00883] Several aspects are described with reference to example applications for illustration. Unless otherwise indicated, any embodiment can be combined with any other embodiment. It should be understood that numerous specific details, relationships, and methods are set forth to provide a full understanding of the features described herein. A skilled artisan, however, will readily recognize that the features described herein can be practiced without one or more of the specific details or with other methods. The features described herein are not limited by

the illustrated ordering of acts or events, as some acts can occur in different orders and/or concurrently with other acts or events. Furthermore, not all illustrated acts or events are required to implement a methodology in accordance with the features described herein.

[00884] While some embodiments have been shown and described herein, it will be obvious to those skilled in the art that such embodiments are provided by way of example only. It is not intended that the disclosure be limited by the specific examples provided within the specification. While the disclosure has been described with reference to the aforementioned specification, the descriptions and illustrations of the embodiments herein are not meant to be construed in a limiting sense. Numerous variations, changes, and substitutions will now occur to those skilled in the art without departing from the disclosure.

[00885] Furthermore, it shall be understood that all aspects of the disclosure are not limited to the specific depictions, configurations or relative proportions set forth herein which depend upon a variety of conditions and variables. It should be understood that various alternatives to the embodiments of the disclosure described herein can be employed in practicing the disclosure. It is therefore contemplated that the disclosure shall also cover any such alternatives, modifications, variations or equivalents. It is intended that the following claims define the scope of the disclosure and that methods and structures within the scope of these claims and their equivalents be covered thereby.

[00886] All publications, patents, and patent applications herein are incorporated by reference to the same extent as if each individual publication, patent, or patent application was specifically and individually indicated to be incorporated by reference. In the event of a conflict between a term herein and a term in an incorporated reference, the term herein controls.

WHAT IS CLAIMED IS:

1. A pharmaceutical composition for treating a disorder having a symptom caused, at least in part, by intercellular signaling mediated through a transmembrane receptor, the composition comprising:

(i) an RNA-guided nuclease or a nucleic acid encoding an RNA-guided nuclease; and

(ii) at least one guide RNA or a nucleic acid encoding at least one guide RNA targeting a gene encoding the transmembrane receptor.

2. The pharmaceutical composition of claim 1, wherein the disorder is a musculoskeletal disorder.

3. The pharmaceutical composition of claim 2, wherein the musculoskeletal disorder is selected from the group consisting of Rheumatoid Arthritis, Gout, Osteoarthritis, Osteoporosis, Intervertebral disc disease (IVDD), Psoriatic arthritis (PsA), Arthritis, Polymyositis, Proliferative synovitis, Malignant bone neoplasm, Sarcoid Myopathy, Cortex Bone Disorders, Idiopathic Scoliosis, Tendinopathy, Myofibrillar Myopathy, Enthesis-Related Arthritis, Ankylosing spondylitis, Degenerative, polyarthritis, Arthropathy, Osteitis Deformans, Prolapsed Lumbar Disc, Polymyositis Ossificans, Idiopathic Polymyositis, Luft Disease, Adult-onset Still's Disease, Osteoarthrosis Deformans, and Bachet's Disease.

4. The pharmaceutical composition of claim 2, wherein the musculoskeletal disorder is selected from the group consisting of Rheumatoid arthritis, Idiopathic osteoporosis, Post-menopausal osteoporosis, Paget's disease, Osteoarthritis, Juvenile idiopathic arthritis (JIA), Still's disease, Ankylosing spondylitis, Polymyalgia rheumatica, Arthritis, Secondary malignant neoplasm of bone, Type II, Mucolipidosis, Sjogren's Syndrome, Psoriatic arthritis, Rheumatism, Castleman's disease, Degenerative Polyarthritis, Arthropathy, Bone neoplasm, Osteoporosis, Massive osteolysis, Bone fracture healing, Systemic sclerosis, Systemic Juvenile Idiopathic, Arthritis, and Synovitis.

5. The pharmaceutical composition of claim 2, wherein the musculoskeletal disorder is selected from the group consisting of Arthritis, Infectious Intermittent joint effusion, Ankylosing spondylitis, Arthritis, Osteoarthritis, Spondylarthritis, Plantar fasciitis, Degenerative polyarthritis, Hemophilic arthropathy, Inflammatory myopathy with abundant

macrophages, Polymyositis, Tendinosis, Malignant Bone Neoplasm, Osteoporosis, Psoriatic arthritis, Rheumatism, Rheumatoid arthritis, Adult Still's disease, Juvenile arthritis, Early rheumatoid arthritis, Palindromic rheumatism, Gout, Infectious Arthritis, Myotonic dystrophy, Dermatomyositis, Hemophilic arthropathy, Osteopenia, Sjogren's syndrome, Juvenile Idiopathic Arthritis, Myasthenia gravis, Osteolysis, Inflammation, Degenerative polyarthritis, Osteitis deformans, Pigmented villonodular synovitis, or Hyperphosphatasemia with bone disease.

6. The pharmaceutical composition of claim 2, wherein the musculoskeletal disorder is selected from the group consisting of Loeys-Dietz Syndrome, Osteoarthrosis, Marfan Syndrome, Aortic aneurysm (familial thoracic 3), and a Craniofacial abnormality.

7. The pharmaceutical composition of claim 1, wherein the disorder is a neoplasia.

8. The pharmaceutical composition of claim 7, wherein the neoplasia is selected from the group consisting of Osteosarcoma, Colon Cancer, Metastasis (General), Lung Cancer, Multiple Myeloma. Breast Cancer, Solid Tumors, Lymphoma, Pancreatic Cancer, Stomach Cancer, Epithelial Ovarian Cancer, Mammary Neoplasms, Oropharyngeal Carcinoma, Renal Cell Carcinoma, Chondrosarcoma, Esophageal Neoplasms, B-Cell Lymphoma, Cutaneous Lymphoma T-Cell, Leukemia, Thyroid Carcinoma, Skin carcinogenesis, Cholectoral Cancer, Glioma, Liver Cancer, Melanoma, Neuroblastoma, Polycystic Ovary Syndrome, Glioblastoma, Prostate Cancer, Cervical Cancer, Ovarian Cancer, Bladder Cancer, Squamous cell carcinoma, Kaposi Sarcoma, Oral Cavity Cancer, Leiomyosarcoma, Malignant Peripheral Nerve Sheath Tumor, and Ewing's Sarcoma.

9. The pharmaceutical composition of claim 7, wherein the neoplasia is selected from the group consisting of Multiple myeloma, Lung Cancer, Stomach Cancer, Breast Cancer, Kidney Cancer, Neoplasm Metastasis, Colorectal Neoplasms, Ovarian cancer, Osteosarcoma, Cholangiocarcinoma, Leukemia, Prostate cancer, Plasmacytoma, Pancreatic cancer, Cervical cancer, Lymphoma, Liver neoplasms, Neuroblastoma, Melanoma, Mastocytosis, Endometrial cancer, Bladder Cancer, Squamous cell carcinoma, Gallbladder carcinoma, Adenocarcinoma, Thyroid Cancer, prostate neoplasms, stomach cancer, liver carcinoma, pituitary neoplasms, hepatoblastoma, multiple myeloma, hepatocellular adenoma, breast carcinoma, carcinogenesis, leukemia, colon carcinoma, melanoma, metastasis (general), lung cancer,

pancreatic cancer, Kaposi sarcoma, medulloblastoma, carcinoma of bladder, squamous cell carcinoma, mast cell neoplasm, glioma, mastocytoma, brain neoplasms, ovarian neoplasms, bone neoplasm, rhabdomyosarcoma, solid tumors, metastatic kidney cancer, and metastatic renal cell carcinoma

10. The pharmaceutical composition of claim 7, wherein the neoplasia is selected from the group consisting of a Neoplasm, Glioblastoma, Astrocytoma, Adenocarcinoma, Osteosarcoma, Squamous cell carcinoma, Metastasis, Ameloblastoma, Cholangiocarcinoma, Choriocarcinoma, Ovarian cancer, Prostate cancer, Lung Cancer, Larynx Cancer, Breast Cancer, Lip and Oral Cavity Carcinoma, Squamous intraepithelial lesion, Neuroblastoma, Non-Hodgkin lymphomas, Malignant Neoplasms, Skin Neoplasms, Neuroblastoma, Neoplasm Metastasis, Colorectal Cancer, Fibrosarcoma, Myeloid Leukemia, Myelofibrosis, Hodgkin Lymphomas, Non-Small Cell Lung Carcinoma, Cervical Cancer, Liver cancer, Extrapulmonary small cell carcinoma, Basal cell carcinoma, Kidney cancer, Pancreatic carcinoma, Mesothelioma, Gastric cancer, Polycystic Ovary Syndrome, Chordoma, Cholangiocarcinoma, Malignant ascites, Nasopharyngeal carcinoma, Head and Neck Carcinoma, Cancer metastasis, Prostate carcinoma, Fibrosarcoma, Liver carcinoma, Carcinoma of bladder, T-Cell Lymphoblastic Leukemia, Bladder Neoplasm, melanoma, Leukemia, acute myeloid leukemia, Hepatocellular carcinoma, Colorectal cancer, a Lymphoma, Mycosis fungoides, and Sézary syndrome.

11. The pharmaceutical composition of claim 7, wherein the neoplasia is selected from the group consisting of Pancreatic cancer, Multiple self-healing squamous epithelioma (Ferguson-Smith disease), Pancreatic cancer, Gastrointestinal Stromal Tumors (GIST), Hereditary Nonpolyposis Colorectal Cancer (Lynch Syndrome), Metastasis, Colorectal Carcinoma, Bone neoplasms, Anaplastic carcinoma, Spindle-Cell carcinoma, Malignant Bone Neoplasm, Lung neoplasms, and Malignant brain neoplasm.

12. The pharmaceutical composition of claim 1, wherein the disorder is a neurological disorder.

13. The pharmaceutical composition of claim 12, wherein the neurological disorder is selected from the group consisting of Acute Thrombotic Stroke, Epilepsy, Multiple Sclerosis, and Alzheimer's Disease.

14. The pharmaceutical composition of claim 1, wherein the disorder is a cardiac disorder.

15. The pharmaceutical composition of claim 14, wherein the cardiac disorder is selected from the group consisting of Acute Myocardial Infarction, refractory heart failure, arrhythmias, pericarditis, myocarditis, sepsis-induced cardiomyopathy, Acute Decompensated Heart Failure, Refractory Idiopathic Pericarditis, Atherosclerosis, coronary artery disease, myocardial infarction, and cardiac remodeling.

16. The pharmaceutical composition of claim 14, wherein the cardiac disorder is atherosclerosis or abdominal aortic aneurism.

17. The pharmaceutical composition of claim 1, wherein the disorder is an inflammatory disorder.

18. The pharmaceutical composition of claim 17, wherein the inflammatory disorder is selected from the group consisting of Autoinflammatory Disease (AID), Cryopyrin Associated Periodic syndrome (CAPS), Familial Mediterranean Fever (FMF), TNF-Receptor Associated Periodic Syndrome (TRAPS), Hyper-IgD Syndrome (HIDS), Systemic Lupus Erythematosus (SLE), and Fibrosis.

19. The pharmaceutical composition of claim 17, wherein the inflammatory disorder is selected from the group consisting of a cytokine storm, acute local inflammation, inflammatory bowel disease, Crohn's disease, sepsis, Experimental sepsis, and Castleman's disease

20. The pharmaceutical composition of claim 1, wherein the disorder is a digestive disorder.

21. The pharmaceutical composition of claim 20, wherein the digestive disorder is selected from the group consisting of Inflammatory Bowel Disease (IBD), Gastroesophageal reflux disease (GERD), and Non-HP-associated Peptic Ulcer Disease.

22. The pharmaceutical composition of claim 1, wherein the disorder is a respiratory disorder.

23. The pharmaceutical composition of claim 22, wherein the respiratory disorder is Asthma or Pulmonary Fibrosis.

24. The pharmaceutical composition of claim 1, wherein the disorder is a renal, metabolic, or ophthalmic disorder.

25. The pharmaceutical composition of claim 24, wherein the renal, metabolic, or ophthalmic disorder is selected from the group consisting of Chronic Kidney Disease, Type 2 Diabetes, an Eye Disease, Uveitis, Scleritis, Sjogren asthenia, and dry eye.

26. The pharmaceutical composition of claim 1, wherein the disorder is an autoimmune disorder.

27. The pharmaceutical composition of claim 26, wherein the autoimmune disorder is Systemic Lupus Erythematosus.

28. The pharmaceutical composition of claim 1, wherein the disorder is acute synovitis, chronic synovitis, inflammatory arthritis, or immune-mediated arthritides.

29. The pharmaceutical composition of claim 1, wherein the disorder is an autoimmune or inflammatory disorder.

30. The pharmaceutical composition of claim 28, wherein the autoimmune or inflammatory disorder is selected from the group consisting of an Allergy, Asthma, Multiple sclerosis, Psoriasis, Inflammatory bowel disease, Autoimmune experimental uveitis, Colitis, Hypersensitivity reaction disease, Diabetes, Crohn's disease, Systemic lupus erythematosus, Pulmonary sarcoidosis, Leishmaniasis, Experimental autoimmune encephalomyelitis, HTLV-1-associated myelopathy, Tropical spastic paraparesis, Scleroderma, an Idiopathic inflammatory myopathy, polymyositis, and dermatomyositis.

31. The pharmaceutical composition of any one of claims 1-30, wherein the transmembrane receptor is an interleukin-1 receptor.

32. The pharmaceutical composition of claim 31, wherein the at least one guide RNA targets a gene selected from the group consisting of IL1R1, IL1RAP, IL1R5, IL1R6, IL1R7, and IL1R9.

33. The pharmaceutical composition of claim 31, wherein the at least one guide RNA targets an IL1R1 gene.

34. The pharmaceutical composition of claim 33, wherein the at least one guide RNA comprises a crRNA sequence selected from the group consisting of SEQ ID NOS: 680-811.

35. The pharmaceutical composition of claim 33, wherein the at least one guide RNA comprises a crRNA sequence selected from the group consisting of SEQ ID NOS: 825-892 and 3336-3405.

36. The pharmaceutical composition of claim 33, wherein the at least one guide RNA comprises a crRNA sequence selected from the group consisting of SEQ ID NOS: 893-967.

37. The pharmaceutical composition of claim 33, wherein the at least one guide RNA comprises a crRNA sequence selected from the group consisting of SEQ ID NOS: 968-1039.

38. The pharmaceutical composition of claim 33, wherein the at least one guide RNA comprises a crRNA sequence selected from the group consisting of SEQ ID NOS: 3491-3513.

39. The pharmaceutical composition of claim 31, wherein the at least one guide RNA targets an IL1RAP gene.

40. The pharmaceutical composition of claim 39, wherein the at least one guide RNA comprises a crRNA sequence selected from the group consisting of SEQ ID NOS: 1040-1194.

41. The pharmaceutical composition of claim 39, wherein the at least one guide RNA comprises a crRNA sequence selected from the group consisting of SEQ ID NOS: 1204-1271 and 3421-3490.

42. The pharmaceutical composition of claim 39, wherein the at least one guide RNA comprises a crRNA sequence selected from the group consisting of SEQ ID NOS: 1272-1348.

43. The pharmaceutical composition of claim 39, wherein the at least one guide RNA comprises a crRNA sequence selected from the group consisting of SEQ ID NOS: 1349-1424.

44. The pharmaceutical composition of claim 39, wherein the at least one guide RNA comprises a crRNA sequence selected from the group consisting of SEQ ID NOS: 3514-3543.

45. The pharmaceutical composition of any one of claims 1-30, wherein the transmembrane receptor is an interleukin-6 receptor.

46. The pharmaceutical composition of claim 45, wherein the at least one guide RNA targets an IL6R gene.

47. The pharmaceutical composition of claim 46, wherein the at least one guide RNA comprises a crRNA sequence selected from the group consisting of SEQ ID NOS: 1746-1920.

48. The pharmaceutical composition of claim 46, wherein the at least one guide RNA comprises a crRNA sequence selected from the group consisting of SEQ ID NOS: 3544-3566.

49. The pharmaceutical composition of claim 45, wherein the at least one guide RNA targets an IL6ST gene.

50. The pharmaceutical composition of claim 49, wherein the at least one guide RNA comprises a crRNA sequence selected from the group consisting of SEQ ID NOS: 1969-2176.

51. The pharmaceutical composition of claim 49, wherein the at least one guide RNA comprises a crRNA sequence selected from the group consisting of SEQ ID NOS: 3567-3606.

52. The pharmaceutical composition of any one of claims 1-30, wherein the transmembrane receptor is a tumor necrosis factor receptor.

53. The pharmaceutical composition of claim 52, wherein the at least one guide RNA targets a TNFRSF1A gene.

54. The pharmaceutical composition of claim 53, wherein the at least one guide RNA comprises a crRNA sequence selected from the group consisting of SEQ ID NOS: 2179-2383.

55. The pharmaceutical composition of claim 53, wherein the at least one guide RNA comprises a crRNA sequence selected from the group consisting of SEQ ID NOS: 3607-3647.

56. The pharmaceutical composition of claim 52, wherein the at least one guide RNA targets a TNFRSF1B gene.

57. The pharmaceutical composition of claim 56, wherein the at least one guide RNA comprises a crRNA sequence selected from the group consisting of SEQ ID NOS: 2396-2622.

58. The pharmaceutical composition of claim 56, wherein the at least one guide RNA comprises a crRNA sequence selected from the group consisting of SEQ ID NOS: 3648-3692.

59. The pharmaceutical composition of claim 52, wherein the at least one guide RNA targets a TNFRSF3 gene.

60. The pharmaceutical composition of claim 59, wherein the at least one guide RNA comprises a crRNA sequence selected from the group consisting of SEQ ID NOS: 2643-2852.

61. The pharmaceutical composition of claim 59, wherein the at least one guide RNA comprises a crRNA sequence selected from the group consisting of SEQ ID NOS: 3693-3713.

62. The pharmaceutical composition of claim 52, wherein the at least one guide RNA targets a TNFRSF4 gene.

63. The pharmaceutical composition of claim 62, wherein the at least one guide RNA comprises a crRNA sequence selected from the group consisting of SEQ ID NOS: 2867-3035.

64. The pharmaceutical composition of claim 62, wherein the at least one guide RNA comprises a crRNA sequence selected from the group consisting of SEQ ID NOS: 3714-3740.

65. The pharmaceutical composition of claim 52, wherein the at least one guide RNA targets a TNFRSF11A gene.

66. The pharmaceutical composition of claim 65, wherein the at least one guide RNA comprises a crRNA sequence selected from the group consisting of SEQ ID NOS: 3042-3331.

67. The pharmaceutical composition of claim 65, wherein the at least one guide RNA comprises a crRNA sequence selected from the group consisting of SEQ ID NOS: 3741-3788.

68. The pharmaceutical composition of any one of claims 1-30, wherein the transmembrane receptor is a transforming growth factor beta receptor.

69. The pharmaceutical composition of claim 68, wherein the at least one guide RNA targets a TGFBR1 gene.

70. The pharmaceutical composition of claim 69, wherein the at least one guide RNA comprises a crRNA sequence selected from the group consisting of SEQ ID NOS: 1425-1544.

71. The pharmaceutical composition of claim 69, wherein the at least one guide RNA comprises a crRNA sequence selected from the group consisting of SEQ ID NOS: 3789-3813.

72. The pharmaceutical composition of claim 68, wherein the at least one guide RNA targets a TGFBR2 gene.

73. The pharmaceutical composition of claim 72, wherein the at least one guide RNA comprises a crRNA sequence selected from the group consisting of SEQ ID NOS: 1547-1734.

74. The pharmaceutical composition of claim 72, wherein the at least one guide RNA comprises a crRNA sequence selected from the group consisting of SEQ ID NOS: 3814-3865.

75. The pharmaceutical composition of any one of claims 1-73, wherein the RNA-guided nuclease or a nucleic acid encoding an RNA-guided nuclease is the RNA-guided nuclease.

76. The pharmaceutical composition of any one of claims 1-73, wherein the RNA-guided nuclease or a nucleic acid encoding an RNA-guided nuclease is DNA encoding the RNA-guided nuclease.

77. The pharmaceutical composition of any one of claims 1-73, wherein the RNA-guided nuclease or a nucleic acid encoding an RNA-guided nuclease is mRNA encoding the RNA-guided nuclease.

78. The pharmaceutical composition of any one of claims 1-77, wherein the RNA-guided nuclease is a Cas protein.

79. The pharmaceutical composition of claim 78, wherein the Cas protein is a Cas9 protein.

80. The pharmaceutical composition of claim 78, wherein the Cas9 protein is an *S. pyogenes* Cas9 polypeptide.

81. The pharmaceutical composition of claim 78, wherein the Cas9 protein is selected from the group consisting of esCas9, hfCas9, peCas9, and ARCas9.

82. The pharmaceutical composition of any one of claims 1-81, wherein the at least one guide RNA or a nucleic acid encoding at least one guide RNA is the at least one guide RNA.

83. The pharmaceutical composition of any one of claims 1-81, wherein the at least one guide RNA or a nucleic acid encoding at least one guide RNA is DNA encoding the at least one guide RNA.

84. The pharmaceutical composition of any one of claims 1-81, comprising a nucleic acid encoding both the RNA-guided nuclease and the at least one guide RNA.

85. The pharmaceutical composition of any one of claims 1-84, wherein the at least one guide RNA is a single guide RNA (sgRNA).

86. The pharmaceutical composition of any one of claims 1-85, wherein the at least one guide RNA targets a human gene.

87. The pharmaceutical composition of any one of claims 1-85, wherein the at least one guide RNA targets a canine gene.

88. The pharmaceutical composition of any one of claims 1-85, wherein the at least one guide RNA targets an equine gene.

89. The pharmaceutical composition of any one of claims 1-85, wherein the at least one guide RNA targets a feline gene.

90. The pharmaceutical composition of any one of claims 1-85, wherein the at least one guide RNA targets a mammalian gene.

91. The pharmaceutical composition of any one of claims 1-90, wherein the composition comprises one or more viral vectors collectively comprising the (i) RNA-guided nuclease or a nucleic acid encoding an RNA-guided nuclease, and (ii) at least one guide RNA or a nucleic acid encoding at least one guide RNA targeting a gene encoding the transmembrane receptor.

92. The pharmaceutical composition of claim 91, wherein the one of more viral vectors comprise a recombinant virus selected from a retrovirus, an adenovirus, an adeno-associated virus, a lentivirus, and a herpes simplex virus-1.

93. The pharmaceutical composition of claim 91, wherein the one of more viral vectors comprise a recombinant adeno-associated virus (AAV).

94. The pharmaceutical composition of claim 93, wherein the recombinant AAV is of serotype 5 (AAV5).

95. The pharmaceutical composition of claim 93, wherein the recombinant AAV is of serotype 6 (AAV6).

96. The pharmaceutical composition of any one of claims 1-90, wherein the composition comprises one or more lipid nanoparticles (LNP) collectively comprising the (i) RNA-guided nuclease or a nucleic acid encoding an RNA-guided nuclease, and (ii) at least one guide RNA or a nucleic acid encoding at least one guide RNA targeting a gene encoding the transmembrane receptor.

97. The pharmaceutical composition of claim 96, wherein the one or more LNP comprises:

a first plurality of LNP encapsulating the RNA-guided nuclease or a nucleic acid encoding an RNA-guided nuclease; and

a second plurality of LNP encapsulating the at least one guide RNA or a nucleic acid encoding at least one guide RNA.

98. The pharmaceutical composition of claim 96, wherein the one or more LNP comprises a plurality of LNP encapsulating both the (i) RNA-guided nuclease or a nucleic acid encoding an RNA-guided nuclease, and (ii) at least one guide RNA or a nucleic acid encoding at least one guide RNA targeting a gene encoding the transmembrane receptor.

99. The pharmaceutical composition of any one of claims 96-98, wherein the one or more LNP comprises a component selected from the group consisting of 3-(didodecylamino)-N1,N1,4-tridodecyl-1-piperazineethanamine (KL10), N1-[2-(didodecylamino)ethyl]-

N1,N4,N4-tridodecyl-1,4-piperazinediethanamine (KL22), 14,25-ditridecyl-15,18,21,24-tetraaza-octatriacontane (KL25), 1,2-dilinoleyloxy-N,N-dimethylaminopropane (DLin-DMA), 2,2-dilinoleyl-4-dimethylaminomethyl-[1,3]-dioxolane (DLin-K-DMA), heptatriaconta-6,9,28,31-tetraen-19-yl 4-(dimethylamino)butanoate (DLin-MC3-DMA), 2,2-dilinoleyl-4-(2-dimethylaminoethyl)-[1,3]-dioxolane (DLin-KC2-DMA), 1,2-dioleyloxy-N,N-dimethylaminopropane (DODMA), 2-({8-[(3.beta.)-cholest-5-en-3-yloxy]octyl}oxy)-N,N-dimethyl-3-[(9Z,12Z)- -octadeca-9,12-dien-1-yloxy]propan-1-amine (Octyl-CLinDMA), (2R)-2-({8-[(3.beta.)-cholest-5-en-3-yloxy]octyl}oxy)-N,N-dimethyl-3-[(9Z- ,12Z)-octadeca-9,12-dien-1-yloxy]propan-1-amine (Octyl-CLinDMA (2R)), (2S)-2-({8-[(3.beta.)-cholest-5-en-3-yloxy]octyl}oxy)-N,N-dimethyl-3-[(9Z- ,12Z)-octadeca-9,12-dien-1-yloxy]propan-1-amine (Octyl-CLinDMA (2S)), a lipid including a cyclic amine group, and a mixture thereof.

100. The pharmaceutical composition of any one of claims 96-99, wherein the LNP comprises a component selected from the group consisting of 1,2-dilinoleoyl-sn-glycero-3-phosphocholine (DLPC), 1,2-dimyristoyl-sn-glycero-phosphocholine (DMPC), 1,2-dioleoyl-sn-glycero-3-phosphocholine (DOPC), 1,2-dipalmitoyl-sn-glycero-3-phosphocholine (DPPC), 1,2-distearoyl-sn-glycero-3-phosphocholine (DSPC), 1,2-diundecanoyl-sn-glycero-phosphocholine (DUPC), 1-palmitoyl-2-oleoyl-sn-glycero-3-phosphocholine (POPC), 1,2-di-O-octadecenyl-sn-glycero-3-phosphocholine (18:0 Diether PC), 1-oleoyl-2-cholesterylhemisuccinoyl-sn-glycero-3-phosphocholine (OChemsPC), 1-hexadecyl-sn-glycero-3-phosphocholine (C16 Lyso PC), 1,2-dilinolenoyl-sn-glycero-3-phosphocholine, 1,2-diarachidonoyl-sn-glycero-3-phosphocholine, 1,2-didocosahexaenoyl-sn-glycero-3-phosphocholine, 1,2-dioleoyl-sn-glycero-3-phosphoethanolamine (DOPE), 1,2-diphytanoyl-sn-glycero-3-phosphoethanolamine (ME 16.0 PE), 1,2-distearoyl-sn-glycero-3-phosphoethanolamine, 1,2-dilinoleoyl-sn-glycero-3-phosphoethanolamine, 1,2-dilinolenoyl-sn-glycero-3-phosphoethanolamine, 1,2-diarachidonoyl-sn-glycero-3-phosphoethanolamine, 1,2-didocosahexaenoyl-sn-glycero-3-phosphoethanolamine, 1,2-dioleoyl-sn-glycero-3-phospho-rac-(1-glycerol) sodium salt (DOPG), sphingomyelin (SM), and a mixture thereof.

101. The pharmaceutical composition of any one of claims 96-296, wherein the LNP comprises a component selected from the group consisting of PEG-modified phosphatidylethanolamines, PEG-modified phosphatidic acids, PEG-modified ceramides, PEG-modified dialkylamines, PEG-modified diacylglycerols, PEG-modified dialkylglycerols, and mixtures thereof. For example, a PEG lipid may be PEG-c-DOMG,

PEG-DMG, PEG-DLPE, PEG-DMPE, PEG-DPPC, PEG-DMA, a PEG-DSPE lipid, and a mixture thereof.

102. The pharmaceutical composition of any one of claims 96-100, wherein the LNP comprises a component selected from the group consisting of a cholesterol, fecosterol, stigmasterol, stigmastanol, sitosterol, β-sitosterol, lupeol, betulin, ursolic acid, oleanolic acid, campesterol, fucosterol, brassicasterol, ergosterol, 9, 11-dehydroergosterol, tomatidine, tomatine, α-tocopherol, and a mixture thereof.

103. The pharmaceutical composition of any one of claims 1-90, wherein the composition comprises one or more liposomes collectively comprising the (i) RNA-guided nuclease or a nucleic acid encoding an RNA-guided nuclease, and (ii) at least one guide RNA or a nucleic acid encoding at least one guide RNA targeting a gene encoding the transmembrane receptor.

104. The pharmaceutical composition of claim 103, wherein the one or more liposomes comprises:

a first plurality of liposomes encapsulating the RNA-guided nuclease or a nucleic acid encoding an RNA-guided nuclease; and

a second plurality of liposomes encapsulating the at least one guide RNA or a nucleic acid encoding at least one guide RNA.

105. The pharmaceutical composition of claim 103, wherein the one or more liposomes comprises a plurality of liposomes encapsulating both the (i) RNA-guided nuclease or a nucleic acid encoding an RNA-guided nuclease, and (ii) at least one guide RNA or a nucleic acid encoding at least one guide RNA targeting a gene encoding the transmembrane receptor.

106. The pharmaceutical composition of any one of claims 1-90, wherein the composition comprises one or more virus-like particles collectively comprising the (i) RNA-guided nuclease or a nucleic acid encoding an RNA-guided nuclease, and (ii) at least one guide RNA or a nucleic acid encoding at least one guide RNA targeting a gene encoding the transmembrane receptor.

107. The pharmaceutical composition of claim 106, wherein the one or more virus-like particles comprises:

a first plurality of virus-like particles encapsulating the RNA-guided nuclease or a nucleic acid encoding an RNA-guided nuclease; and

a second plurality of virus-like particles encapsulating the at least one guide RNA or a nucleic acid encoding at least one guide RNA.

108. The pharmaceutical composition of claim 106, wherein the one or more virus-like particles comprises a plurality of virus-like particles encapsulating both the (i) RNA-guided nuclease or a nucleic acid encoding an RNA-guided nuclease, and (ii) at least one guide RNA or a nucleic acid encoding at least one guide RNA targeting a gene encoding the transmembrane receptor.

109. The pharmaceutical composition of any one of claims 1-108, wherein the composition is formulated for parenteral administration.

110. The pharmaceutical composition of any one of claims 1-108, wherein the composition is formulated for intra-articular injection within a joint of the subject.

111. The pharmaceutical composition of any one of claims 1-108, wherein the composition is formulated for intradiscal injection.

112. The pharmaceutical composition of any one of claims 1-108, wherein the composition is formulated for peridiscal injection.

113. The pharmaceutical composition of any one of claims 1-108, wherein the composition is formulated for intravertebral injection.

114. A method for treating a disorder having a symptom caused, at least in part, by intracellular signaling mediated through a transmembrane receptor in a subject in need thereof, comprising:

administering a therapeutically effective amount of a composition, wherein the composition comprises:

(i) an RNA-guided nuclease or a nucleic acid encoding an RNA-guided nuclease; and

(ii) at least one guide RNA or a nucleic acid encoding at least one guide RNA targeting a gene encoding the transmembrane receptor.

115. The method of claim 114, wherein the at least one guide RNA targets a gene selected from the group consisting of IL1R1, IL1RAP, IL1R5, IL1R6, IL1R7, and IL1R9.

116. The method of claim 114, wherein the at least one guide RNA targets an IL1R1 gene.

117. The method of claim 116, wherein the at least one guide RNA comprises a crRNA sequence selected from the group consisting of SEQ ID NOS: 680-758.

118. The method of claim 116, wherein the at least one guide RNA comprises a crRNA sequence selected from the group consisting of SEQ ID NOS: 825-864.

119. The method of claim 116, wherein the at least one guide RNA comprises a crRNA sequence selected from the group consisting of SEQ ID NOS: 893-922.

120. The method of claim 116, wherein the at least one guide RNA comprises a crRNA sequence selected from the group consisting of SEQ ID NOS: 968-997.

121. The method of claim 116, wherein the at least one guide RNA comprises a crRNA sequence selected from the group consisting of SEQ ID NOS: 3491-3503.

122. The method of claim 114, wherein the at least one guide RNA targets an IL1RAP gene.

123. The method of claim 122, wherein the at least one guide RNA comprises a crRNA sequence selected from the group consisting of SEQ ID NOS: 1040-1122.

124. The method of claim 122, wherein the at least one guide RNA comprises a crRNA sequence selected from the group consisting of SEQ ID NOS: 1204-1271 and 3421-3458.

125. The method of claim 122, wherein the at least one guide RNA comprises a crRNA sequence selected from the group consisting of SEQ ID NOS: 1272-1301.

126. The method of claim 122, wherein the at least one guide RNA comprises a crRNA sequence selected from the group consisting of SEQ ID NOS: 1349-1378.

127. The method of claim 122, wherein the at least one guide RNA comprises a crRNA sequence selected from the group consisting of SEQ ID NOS: 3514-3529.

128. The method of claim 114, wherein the transmembrane receptor is an interleukin-6 receptor.

129. The method of claim 128, wherein the at least one guide RNA targets an IL6R gene.

130. The method of claim 129, wherein the at least one guide RNA comprises a crRNA sequence selected from the group consisting of SEQ ID NOS: 1746-1834.

131. The method of claim 129, wherein the at least one guide RNA comprises a crRNA sequence selected from the group consisting of SEQ ID NOS: 3544-3553.

132. The method of claim 128, wherein the at least one guide RNA targets an IL6ST gene.

133. The method of claim 132, wherein the at least one guide RNA comprises a crRNA sequence selected from the group consisting of SEQ ID NOS: 1969-2037.

134. The method of claim 132, wherein the at least one guide RNA comprises a crRNA sequence selected from the group consisting of SEQ ID NOS: 3567-3574.

135. The method of claim 114, wherein the transmembrane receptor is a tumor necrosis factor receptor.

136. The method of claim 135, wherein the at least one guide RNA targets a TNFRSF1A gene.

137. The method of claim 136, wherein the at least one guide RNA comprises a crRNA sequence selected from the group consisting of SEQ ID NOS: 2179-2247.

138. The method of claim 136, wherein the at least one guide RNA comprises a crRNA sequence selected from the group consisting of SEQ ID NOS: 3607-3621.

139. The method of claim 135, wherein the at least one guide RNA targets a TNFRSF1B gene.

140. The method of claim 139, wherein the at least one guide RNA comprises a crRNA sequence selected from the group consisting of SEQ ID NOS: 2396-2482.

141. The method of claim 139, wherein the at least one guide RNA comprises a crRNA sequence selected from the group consisting of SEQ ID NOS: 3648-3673.

142. The method of claim 135, wherein the at least one guide RNA targets a TNFRSF3 gene.

143. The method of claim 142, wherein the at least one guide RNA comprises a crRNA sequence selected from the group consisting of SEQ ID NOS: 2643-2737.

144. The method of claim 142, wherein the at least one guide RNA comprises a crRNA sequence selected from the group consisting of SEQ ID NOS: 3693-3698.

145. The method of claim 135, wherein the at least one guide RNA targets a TNFRSF4 gene.

146. The method of claim 145, wherein the at least one guide RNA comprises a crRNA sequence selected from the group consisting of SEQ ID NOS: 2867-2950.

147. The method of claim 145, wherein the at least one guide RNA comprises a crRNA sequence selected from the group consisting of SEQ ID NOS: 3714-3734.

148. The method of claim 135, wherein the at least one guide RNA targets a TNFRSF11A gene.

149. The method of claim 148, wherein the at least one guide RNA comprises a crRNA sequence selected from the group consisting of SEQ ID NOS: 3042-3106.

150. The method of claim 148, wherein the at least one guide RNA comprises a crRNA sequence selected from the group consisting of SEQ ID NOS: 3741-3754.

151. The method of claim 114, wherein the transmembrane receptor is a transforming growth factor beta receptor.

152. The method of claim 151, wherein the at least one guide RNA targets a TGFBR1 gene.

153. The method of claim 152, wherein the at least one guide RNA comprises a crRNA sequence selected from the group consisting of SEQ ID NOS: 1425-1454.

154. The method of claim 152, wherein the at least one guide RNA comprises a crRNA sequence selected from the group consisting of SEQ ID NOS: 3789-3791.

155. The method of claim 151, wherein the at least one guide RNA targets a TGFBR2 gene.

156. The method of claim 155, wherein the at least one guide RNA comprises a crRNA sequence selected from the group consisting of SEQ ID NOS: 1547-1580.

157. The method of claim 155, wherein the at least one guide RNA comprises a crRNA sequence selected from the group consisting of SEQ ID NOS: 3814-3819.

158. The method of claim 114, wherein editing of a genomic copy of the gene for the transmembrane receptor by the RNA-guided nuclease and at least one guide RNA results in a genomic sequence encoding a membrane-bound form of the transmembrane receptor lacking signaling function.

159. The method of claim 158, wherein the at least one guide RNA targets a gene selected from the group consisting of IL1R1, IL1RAP, IL1R5, IL1R6, IL1R7, and IL1R9.

160. The method of claim 158, wherein the at least one guide RNA targets an IL1R1 gene.

161. The method of claim 160, wherein the at least one guide RNA comprises a crRNA sequence selected from the group consisting of SEQ ID NOS: 759-808.

162. The method of claim 160, wherein the at least one guide RNA comprises a crRNA sequence selected from the group consisting of SEQ ID NOS: 3336-3401.

163. The method of claim 160, wherein the at least one guide RNA comprises a crRNA sequence selected from the group consisting of SEQ ID NOS: 942-967.

164. The method of claim 160, wherein the at least one guide RNA comprises a crRNA sequence selected from the group consisting of SEQ ID NOS: 1010-1039.

165. The method of claim 160, wherein the at least one guide RNA comprises a crRNA sequence selected from the group consisting of SEQ ID NOS: 3505-3513.

166. The method of claim 158, wherein the at least one guide RNA targets an IL1RAP gene.

167. The method of claim 166, wherein the at least one guide RNA comprises a crRNA sequence selected from the group consisting of SEQ ID NOS: 1123-1180.

168. The method of claim 166, wherein the at least one guide RNA comprises a crRNA sequence selected from the group consisting of SEQ ID NOS: 3459-3485.

169. The method of claim 166, wherein the at least one guide RNA comprises a crRNA sequence selected from the group consisting of SEQ ID NOS: 1323-1348.

170. The method of claim 166, wherein the at least one guide RNA comprises a crRNA sequence selected from the group consisting of SEQ ID NOS: 1397-1424.

171. The method of claim 166, wherein the at least one guide RNA comprises a crRNA sequence selected from the group consisting of SEQ ID NOS: 3533-3543.

172. The method of claim 158, wherein the transmembrane receptor is an interleukin-6 receptor.

173. The method of claim 172, wherein the at least one guide RNA targets an IL6ST gene.

174. The method of claim 173, wherein the at least one guide RNA comprises a crRNA sequence selected from the group consisting of SEQ ID NOS: 2038-2102.

175. The method of claim 173, wherein the at least one guide RNA comprises a crRNA sequence selected from the group consisting of SEQ ID NOS: 3595-3606.

176. The method of claim 158, wherein the transmembrane receptor is a tumor necrosis factor receptor.

177. The method of claim 176, wherein the at least one guide RNA targets a TNFRSF1A gene.

178. The method of claim 177, wherein the at least one guide RNA comprises a crRNA sequence selected from the group consisting of SEQ ID NOS: 2248-2369.

179. The method of claim 177, wherein the at least one guide RNA comprises a crRNA sequence selected from the group consisting of SEQ ID NOS: 3623-3647.

180. The method of claim 176, wherein the at least one guide RNA targets a TNFRSF1B gene.

181. The method of claim 180, wherein the at least one guide RNA comprises a crRNA sequence selected from the group consisting of SEQ ID NOS: 2483-2574.

182. The method of claim 180, wherein the at least one guide RNA comprises a crRNA sequence selected from the group consisting of SEQ ID NOS: 3681-3692.

183. The method of claim 176, wherein the at least one guide RNA targets a TNFRSF3 gene.

184. The method of claim 183, wherein the at least one guide RNA comprises a crRNA sequence selected from the group consisting of SEQ ID NOS: 2738-2846.

185. The method of claim 183, wherein the at least one guide RNA comprises a crRNA sequence selected from the group consisting of SEQ ID NOS: 3703-3713.

186. The method of claim 176, wherein the at least one guide RNA targets a TNFRSF4 gene.

187. The method of claim 186, wherein the at least one guide RNA comprises a crRNA sequence selected from the group consisting of SEQ ID NOS: 2951-2981.

188. The method of claim 186, wherein the at least one guide RNA comprises a crRNA sequence selected from the group consisting of SEQ ID NOS: 3738-3740.

189. The method of claim 176, wherein the at least one guide RNA targets a TNFRSF11A gene.

190. The method of claim 189, wherein the at least one guide RNA comprises a crRNA sequence selected from the group consisting of SEQ ID NOS: 3107-3322.

191. The method of claim 189, wherein the at least one guide RNA comprises a crRNA sequence selected from the group consisting of SEQ ID NOS: 3757-3788.

192. The method of claim 158, wherein the transmembrane receptor is a transforming growth factor beta receptor.

193. The method of claim 192, wherein the at least one guide RNA targets a TGFBR1 gene.

194. The method of claim 193, wherein the at least one guide RNA comprises a crRNA sequence selected from the group consisting of SEQ ID NOS: 1455-1534.

195. The method of claim 193, wherein the at least one guide RNA comprises a crRNA sequence selected from the group consisting of SEQ ID NOS: 3792-3813.

196. The method of claim 192, wherein the at least one guide RNA targets a TGFBR2 gene.

197. The method of claim 196, wherein the at least one guide RNA comprises a crRNA sequence selected from the group consisting of SEQ ID NOS: 1581-1724.

198. The method of claim 196, wherein the at least one guide RNA comprises a crRNA sequence selected from the group consisting of SEQ ID NOS: 3821-3865.

199. The method of claim 114, wherein editing of a genomic copy of the gene for the transmembrane receptor by the RNA-guided nuclease and at least one guide RNA results in a genomic sequence encoding a soluble form of the transmembrane receptor.

200. The method of claim 199, wherein the at least one guide RNA targets a gene selected from the group consisting of IL1R1, IL1RAP, IL1R5, IL1R6, IL1R7, and IL1R9.

201. The method of claim 200, wherein the at least one guide RNA targets an IL1R1 gene.

202. The method of claim 201, wherein the at least one guide RNA comprises a crRNA sequence selected from the group consisting of SEQ ID NOS: 809-811.

203. The method of claim 201, wherein the at least one guide RNA comprises a crRNA sequence selected from the group consisting of SEQ ID NOS: 3402-3405.

204. The method of claim 201, wherein the at least one guide RNA comprises a crRNA sequence selected from the group consisting of SEQ ID NOS: 923-941.

205. The method of claim 201, wherein the at least one guide RNA comprises a crRNA sequence selected from the group consisting of SEQ ID NOS: 998-1009.

206. The method of claim 201, wherein the at least one guide RNA comprises a crRNA sequence of SEQ ID NO 3504.

207. The method of claim 200, wherein the at least one guide RNA targets an IL1RAP gene.

208. The method of claim 207, wherein the at least one guide RNA comprises a crRNA sequence selected from the group consisting of SEQ ID NOS: 1181-1194.

209. The method of claim 207, wherein the at least one guide RNA comprises a crRNA sequence selected from the group consisting of SEQ ID NOS: 3481-3490.

210. The method of claim 207, wherein the at least one guide RNA comprises a crRNA sequence selected from the group consisting of SEQ ID NOS: 1302-1322.

211. The method of claim 207, wherein the at least one guide RNA comprises a crRNA sequence selected from the group consisting of SEQ ID NOS: 1379-1396.

212. The method of claim 207, wherein the at least one guide RNA comprises a crRNA sequence selected from the group consisting of SEQ ID NOS: 3530-3532.

213. The method of claim 199, wherein the transmembrane receptor is an interleukin-6 receptor.

214. The method of claim 213, wherein the at least one guide RNA targets an IL6R gene.

215. The method of claim 214, wherein the at least one guide RNA comprises a crRNA sequence selected from the group consisting of SEQ ID NOS: 1835-1920.

216. The method of claim 214, wherein the at least one guide RNA comprises a crRNA sequence selected from the group consisting of SEQ ID NOS: 3554-3566.

217. The method of claim 213, wherein the at least one guide RNA targets an IL6ST gene.

218. The method of claim 217, wherein the at least one guide RNA comprises a crRNA sequence selected from the group consisting of SEQ ID NOS: 2103-2176.

219. The method of claim 217, wherein the at least one guide RNA comprises a crRNA sequence selected from the group consisting of SEQ ID NOS: 3575-3594.

220. The method of claim 199, wherein the transmembrane receptor is a tumor necrosis factor receptor.

221. The method of claim 220, wherein the at least one guide RNA targets a TNFRSF1A gene.

222. The method of claim 221, wherein the at least one guide RNA comprises a crRNA sequence selected from the group consisting of SEQ ID NOS: 2370-2383.

223. The method of claim 221, wherein the at least one guide RNA comprises a crRNA sequence selected from the group consisting of SEQ ID NOS: 3621-3622.

224. The method of claim 220, wherein the at least one guide RNA targets a TNFRSF1B gene.

225. The method of claim 224, wherein the at least one guide RNA comprises a crRNA sequence selected from the group consisting of SEQ ID NOS: 2575-2622.

226. The method of claim 224, wherein the at least one guide RNA comprises a crRNA sequence selected from the group consisting of SEQ ID NOS: 3664-3680.

227. The method of claim 220, wherein the at least one guide RNA targets a TNFRSF3 gene.

228. The method of claim 227, wherein the at least one guide RNA comprises a crRNA sequence selected from the group consisting of SEQ ID NOS: 2847-2852.

229. The method of claim 227, wherein the at least one guide RNA comprises a crRNA sequence selected from the group consisting of SEQ ID NOS: 3699-3702.

230. The method of claim 220, wherein the at least one guide RNA targets a TNFRSF4 gene.

231. The method of claim 230, wherein the at least one guide RNA comprises a crRNA sequence selected from the group consisting of SEQ ID NOS: 2982-3035.

232. The method of claim 230, wherein the at least one guide RNA comprises a crRNA sequence selected from the group consisting of SEQ ID NOS: 3730-3737.

233. The method of claim 220, wherein the at least one guide RNA targets a TNFRSF11A gene.

234. The method of claim 233, wherein the at least one guide RNA comprises a crRNA sequence selected from the group consisting of SEQ ID NOS: 3323-3331.

235. The method of claim 233, wherein the at least one guide RNA comprises a crRNA sequence selected from the group consisting of SEQ ID NOS: 3749-3756.

236. The method of claim 199, wherein the transmembrane receptor is a transforming growth factor beta receptor.

237. The method of claim 236, wherein the at least one guide RNA targets a TGFBR1 gene.

238. The method of claim 237, wherein the at least one guide RNA comprises a crRNA sequence selected from the group consisting of SEQ ID NOS: 1535-1544.

239. The method of claim 237, wherein the at least one guide RNA comprises a crRNA sequence of 3792.

240. The method of claim 236, wherein the at least one guide RNA targets a TGFBR2 gene.

241. The method of claim 240, wherein the at least one guide RNA comprises a crRNA sequence selected from the group consisting of SEQ ID NOS: 1725-1734.

242. The method of claim 240, wherein the at least one guide RNA comprises a crRNA sequence selected from the group consisting of SEQ ID NOS: 3820-3822.

243. The method of any one of claims 114-242, wherein the disorder is a musculoskeletal disorder.

244. The method of claim 243, wherein the musculoskeletal disorder is selected from the group consisting of Rheumatoid Arthritis, Gout, Osteoarthritis, Osteoporosis, Intervertebral disc disease (IVDD), Psoriatic arthritis (PsA), Arthritis, Polymyositis, Proliferative synovitis, Malignant bone neoplasm, Sarcoid Myopathy, Cortex Bone Disorders, Idiopathic Scoliosis, Tendinopathy, Myofibrillar Myopathy, Enthesis-Related Arthritis, Ankylosing spondylitis,

Degenerative, polyarthritis, Arthropathy, Osteitis Deformans, Prolapsed Lumbar Disc, Polymyositis Ossificans, Idiopathic Polymyositis, Luft Disease, Adult-onset Still's Disease, Osteoarthrosis Deformans, and Bachet's Disease.

245. The method of claim 243, wherein the musculoskeletal disorder is selected from the group consisting of Rheumatoid arthritis, Idiopathic osteoporosis, Post-menopausal osteoporosis, Paget's disease, Osteoarthritis, Juvenile idiopathic arthritis (JIA), Still's disease, Ankylosing spondylitis, Polymyalgia rheumatica, Arthritis, Secondary malignant neoplasm of bone, Type II, Mucolipidosis, Sjogren's Syndrome, Psoriatic arthritis, Rheumatism, Castleman's disease, Degenerative Polyarthritis, Arthropathy, Bone neoplasm, Osteoporosis, Massive osteolysis, Bone fracture healing, Systemic sclerosis, Systemic Juvenile Idiopathic, Arthritis, and Synovitis.

246. The method of claim 243, wherein the musculoskeletal disorder is selected from the group consisting of Arthritis, Infectious Intermittent joint effusion, Ankylosing spondylitis, Arthritis, Osteoarthritis, Spondylarthritis, Plantar fasciitis, Degenerative polyarthritis, Hemophilic arthropathy, Inflammatory myopathy with abundant macrophages, Polymyositis, Tendinosis, Malignant Bone Neoplasm, Osteoporosis, Psoriatic arthritis, Rheumatism, Rheumatoid arthritis, Adult Still's disease, Juvenile arthritis, Early rheumatoid arthritis, Palindromic rheumatism, Gout, Infectious Arthritis, Myotonic dystrophy, Dermatomyositis, Hemophilic arthropathy, Osteopenia, Sjogren's syndrome, Juvenile Idiopathic Arthritis, Myasthenia gravis, Osteolysis, Inflammation, Degenerative polyarthritis, Osteitis deformans, Pigmented villonodular synovitis, or Hyperphosphatasemia with bone disease.

247. The method of claim 243, wherein the musculoskeletal disorder is selected from the group consisting of Loeys-Dietz Syndrome, Osteoarthrosis, Marfan Syndrome, Aortic aneurysm (familial thoracic 3), and a Craniofacial abnormality.

248. The method of any one of claims 114-242, wherein the disorder is a neoplasia.

249. The method of claim 248, wherein the neoplasia is selected from the group consisting of Osteosarcoma, Colon Cancer, Metastasis (General), Lung Cancer, Multiple Myeloma. Breast Cancer, Solid Tumors, Lymphoma, Pancreatic Cancer, Stomach Cancer, Epithelial Ovarian Cancer, Mammary Neoplasms, Oropharyngeal Carcinoma, Renal Cell Carcinoma,

Chondrosarcoma, Esophageal Neoplasms, B-Cell Lymphoma, Cutaneous Lymphoma T-Cell, Leukemia, Thyroid Carcinoma, Skin carcinogenesis, Cholectoral Cancer, Glioma, Liver Cancer, Melanoma, Neuroblastoma, Polycystic Ovary Syndrome, Glioblastoma, Prostate Cancer, Cervical Cancer, Ovarian Cancer, Bladder Cancer, Squamous cell carcinoma, Kaposi Sarcoma, Oral Cavity Cancer, Leiomyosarcoma, Malignant Peripheral Nerve Sheath Tumor, and Ewing's Sarcoma.

250. The method of claim 248, wherein the neoplasia is selected from the group consisting of Multiple myeloma, Lung Cancer, Stomach Cancer, Breast Cancer, Kidney Cancer, Neoplasm Metastasis, Colorectal Neoplasms, Ovarian cancer, Osteosarcoma, Cholangiocarcinoma, Leukemia, Prostate cancer, Plasmacytoma, Pancreatic cancer, Cervical cancer, Lymphoma, Liver neoplasms, Neuroblastoma, Melanoma, Mastocytosis, Endometrial cancer, Bladder Cancer, Squamous cell carcinoma, Gallbladder carcinoma, Adenocarcinoma, Thyroid Cancer, prostate neoplasms, stomach cancer, liver carcinoma, pituitary neoplasms, hepatoblastoma, multiple myeloma, hepatocellular adenoma, breast carcinoma, carcinogenesis, leukemia, colon carcinoma, melanoma, metastasis (general), lung cancer, pancreatic cancer, Kaposi sarcoma, medulloblastoma, carcinoma of bladder, squamous cell carcinoma, mast cell neoplasm, glioma, mastocytoma, brain neoplasms, ovarian neoplasms, bone neoplasm, rhabdomyosarcoma, solid tumors, metastatic kidney cancer, and metastatic renal cell carcinoma

251. The method of claim 248, wherein the neoplasia is selected from the group consisting of a Neoplasm, Glioblastoma, Astrocytoma, Adenocarcinoma, Osteosarcoma, Squamous cell carcinoma, Metastasis, Ameloblastoma, Cholangiocarcinoma, Choriocarcinoma, Ovarian cancer, Prostate cancer, Lung Cancer, Larynx Cancer, Breast Cancer, Lip and Oral Cavity Carcinoma, Squamous intraepithelial lesion, Neuroblastoma, Non-Hodgkin lymphomas, Malignant Neoplasms, Skin Neoplasms, Neuroblastoma, Neoplasm Metastasis, Colorectal Cancer, Fibrosarcoma, Myeloid Leukemia, Myelofibrosis, Hodgkin Lymphomas, Non-Small Cell Lung Carcinoma, Cervical Cancer, Liver cancer, Extrapulmonary small cell carcinoma, Basal cell carcinoma, Kidney cancer, Pancreatic carcinoma, Mesothelioma, Gastric cancer, Polycystic Ovary Syndrome, Chordoma, Cholangiocarcinoma, Malignant ascites, Nasopharyngeal carcinoma, Head and Neck Carcinoma, Cancer metastasis, Prostate carcinoma, Fibrosarcoma, Liver carcinoma, Carcinoma of bladder, T-Cell Lymphoblastic

Leukemia, Bladder Neoplasm, melanoma, Leukemia, acute myeloid leukemia, Hepatocellular carcinoma, Colorectal cancer, a Lymphoma, Mycosis fungoides, and Sézary syndrome.

252. The method of claim 248, wherein the neoplasia is selected from the group consisting of Pancreatic cancer, Multiple self-healing squamous epithelioma (Ferguson-Smith disease), Pancreatic cancer, Gastrointestinal Stromal Tumors (GIST), Hereditary Nonpolyposis Colorectal Cancer (Lynch Syndrome), Metastasis, Colorectal Carcinoma, Bone neoplasms, Anaplastic carcinoma, Spindle-Cell carcinoma, Malignant Bone Neoplasm, Lung neoplasms, and Malignant brain neoplasm.

253. The method of any one of claims 114-242, wherein the disorder is a neurological disorder.

254. The method of claim 253, wherein the neurological disorder is selected from the group consisting of Acute Thrombotic Stroke, Epilepsy, Multiple Sclerosis, and Alzheimer's Disease.

255. The method of any one of claims 114-242, wherein the disorder is a cardiac disorder.

256. The method of claim 255, wherein the cardiac disorder is selected from the group consisting of Acute Myocardial Infarction, refractory heart failure, arrhythmias, pericarditis, myocarditis, sepsis-induced cardiomyopathy, Acute Decompensated Heart Failure, Refractory Idiopathic Pericarditis, Atherosclerosis, coronary artery disease, myocardial infarction, and cardiac remodeling.

257. The method of claim 255, wherein the cardiac disorder is atherosclerosis or abdominal aortic aneurism.

258. The method of any one of claims 114-242, wherein the disorder is an inflammatory disorder.

259. The method of claim 258, wherein the inflammatory disorder is selected from the group consisting of Autoinflammatory Disease (AID), Cryopyrin Associated Periodic syndrome (CAPS), Familial Mediterranean Fever (FMF), TNF-Receptor Associated Periodic

Syndrome (TRAPS), Hyper-IgD Syndrome (HIDS), Systemic Lupus Erythematosus (SLE), and Fibrosis.

260. The method of claim 258, wherein the inflammatory disorder is selected from the group consisting of a cytokine storm, acute local inflammation, inflammatory bowel disease, Crohn's disease, sepsis, Experimental sepsis, and Castleman's disease

261. The method of any one of claims 114-242, wherein the disorder is a digestive disorder.

262. The method of claim 261, wherein the digestive disorder is selected from the group consisting of Inflammatory Bowel Disease (IBD), Gastroesophageal reflux disease (GERD), and Non-HP-associated Peptic Ulcer Disease.

263. The method of any one of claims 114-242, wherein the disorder is a respiratory disorder.

264. The method of claim 263, wherein the respiratory disorder is Asthma or Pulmonary Fibrosis.

265. The method of any one of claims 114-242, wherein the disorder is a renal, metabolic, or ophthalmic disorder.

266. The method of claim 265, wherein the renal, metabolic, or ophthalmic disorder is selected from the group consisting of Chronic Kidney Disease, Type 2 Diabetes, an Eye Disease, Uveitis, Scleritis, Sjogren asthenia, and dry eye.

267. The method of any one of claims 114-242, wherein the disorder is an autoimmune disorder.

268. The method of claim 267, wherein the autoimmune disorder is Systemic Lupus Erythematosus.

269. The method of any one of claims 114-242, wherein the disorder is an autoimmune or inflammatory disorder.

270. The method of claim 269, wherein the autoimmune or inflammatory disorder is selected from the group consisting of an Allergy, Asthma, Multiple sclerosis, Psoriasis, Inflammatory bowel disease, Autoimmune experimental uveitis, Colitis, Hypersensitivity reaction disease, Diabetes, Crohn's disease, Systemic lupus erythematosus, Pulmonary sarcoidosis, Leishmaniasis, Experimental autoimmune encephalomyelitis, HTLV-1-associated myelopathy, Tropical spastic paraparesis, Scleroderma, an Idiopathic inflammatory myopathy, polymyositis, and dermatomyositis.

271. The method of any one of claims 114-270, wherein the RNA-guided nuclease or a nucleic acid encoding an RNA-guided nuclease is the RNA-guided nuclease.

272. The method of any one of claims 114-270, wherein the RNA-guided nuclease or a nucleic acid encoding an RNA-guided nuclease is DNA encoding the RNA-guided nuclease.

273. The method of any one of claims 114-270, wherein the RNA-guided nuclease or a nucleic acid encoding an RNA-guided nuclease is mRNA encoding the RNA-guided nuclease.

274. The method of any one of claims 114-273, wherein the RNA-guided nuclease is a Cas protein.

275. The method of claim 274, wherein the Cas protein is a Cas9 protein.

276. The method of claim 274, wherein the Cas9 protein is an *S. pyogenes* Cas9 polypeptide.

277. The method of claim 274, wherein the Cas9 protein is selected from the group consisting of esCas9, hfCas9, peCas9, and ARCas9.

278. The method of any one of claims 114-277, wherein the at least one guide RNA or a nucleic acid encoding at least one guide RNA is the at least one guide RNA.

279. The method of any one of claims 114-277, wherein the at least one guide RNA or a nucleic acid encoding at least one guide RNA is DNA encoding the at least one guide RNA.

280. The method of any one of claims 114-277, comprising a nucleic acid encoding both the RNA-guided nuclease and the at least one guide RNA.

281. The method of any one of claims 114-280, wherein the at least one guide RNA is a single guide RNA (sgRNA).

282. The method of any one of claims 114-281, wherein the at least one guide RNA targets a human gene.

283. The method of any one of claims 114-281, wherein the at least one guide RNA targets a canine gene.

284. The method of any one of claims 114-281, wherein the at least one guide RNA targets an equine gene.

285. The method of any one of claims 114-281, wherein the at least one guide RNA targets a feline gene.

286. The method of any one of claims 114-281, wherein the at least one guide RNA targets a mammalian gene.

287. The method of any one of claims 114-286, wherein the composition comprises one or more viral vectors collectively comprising the (i) RNA-guided nuclease or a nucleic acid encoding an RNA-guided nuclease, and (ii) at least one guide RNA or a nucleic acid encoding at least one guide RNA targeting a gene encoding the transmembrane receptor.

288. The method of claim 287, wherein the one of more viral vectors comprise a recombinant virus selected from a retrovirus, an adenovirus, an adeno-associated virus, a lentivirus, and a herpes simplex virus-1.

289. The method of claim 287, wherein the one of more viral vectors comprise a recombinant adeno-associated virus (AAV).

290. The method of claim 289, wherein the recombinant AAV is of serotype 5 (AAV5).

291. The method of claim 289, wherein the recombinant AAV is of serotype 6 (AAV6).

292. The method of any one of claims 114-286, wherein the composition comprises one or more lipid nanoparticles (LNP) collectively comprising the (i) RNA-guided nuclease or a nucleic acid encoding an RNA-guided nuclease, and (ii) at least one guide RNA or a nucleic acid encoding at least one guide RNA targeting a gene encoding the transmembrane receptor.

293. The method of claim 292, wherein the one or more LNP comprises:

a first plurality of LNP encapsulating the RNA-guided nuclease or a nucleic acid encoding an RNA-guided nuclease; and

a second plurality of LNP encapsulating the at least one guide RNA or a nucleic acid encoding at least one guide RNA.

294. The method of claim 292, wherein the one or more LNP comprises a plurality of LNP encapsulating both the (i) RNA-guided nuclease or a nucleic acid encoding an RNA-guided nuclease, and (ii) at least one guide RNA or a nucleic acid encoding at least one guide RNA targeting a gene encoding the transmembrane receptor.

295. The method of any one of claims 292-294, wherein the one or more LNP comprises a component selected from the group consisting of 3-(didodecylamino)-N1,N1,4-tridodecyl-1-piperazineethanamine (KL10), N1-[2-(didodecylamino)ethyl]-N1,N4,N4-tridodecyl-1,4-piperazinediethanamine (KL22), 14,25-ditridecyl-15,18,21,24-tetraaza-octatriacontane (KL25), 1,2-dilinoleyloxy-N,N-dimethylaminopropane (DLin-DMA), 2,2-dilinoleyl-4-dimethylaminomethyl-[1,3]-dioxolane (DLin-K-DMA), heptatriaconta-6,9,28,31-tetraen-19-yl 4-(dimethylamino)butanoate (DLin-MC3-DMA), 2,2-dilinoleyl-4-(2-dimethylaminoethyl)-[1,3]-dioxolane (DLin-KC2-DMA), 1,2-dioleyloxy-N,N-dimethylaminopropane (DODMA), 2-({8-[(3.beta.)-cholest-5-en-3-yloxy]octyl}oxy)-N,N-dimethyl-3-[(9Z,12Z)- -octadeca-9,12-dien-1-yloxy]propan-1-amine (Octyl-CLinDMA), (2R)-2-({8-[(3.beta.)-cholest-5-en-3-yloxy]octyl}oxy)-N,N-dimethyl-3-[(9Z- ,12Z)-octadeca-9,12-dien-1-yloxy]propan-1-amine (Octyl-CLinDMA (2R)), (2S)-2-({8-[(3.beta.)-cholest-5-en-3-yloxy]octyl}oxy)-N,N-dimethyl-3-[(9Z- ,12Z)-octadeca-9,12-dien-1-yloxy]propan-1-amine (Octyl-CLinDMA (2S)), a lipid including a cyclic amine group, and a mixture thereof.

296. The method of any one of claims 292-295, wherein the LNP comprises a component selected from the group consisting of 1,2-dilinoleoyl-sn-glycero-3-phosphocholine (DLPC), 1,2-dimyristoyl-sn-glycero-phosphocholine (DMPC), 1,2-dioleoyl-sn-glycero-3-phosphocholine (DOPC), 1,2-dipalmitoyl-sn-glycero-3-phosphocholine (DPPC), 1,2-distearoyl-sn-glycero-3-phosphocholine (DSPC), 1,2-diundecanoyl-sn-glycero-phosphocholine (DUPC), 1-palmitoyl-2-oleoyl-sn-glycero-3-phosphocholine (POPC), 1,2-di-O-octadecenyl-sn-glycero-3-phosphocholine (18:0 Diether PC), 1-oleoyl-2-cholesterylhemisuccinoyl-sn-glycero-3-phosphocholine (OChemsPC), 1-hexadecyl-sn-glycero-3-phosphocholine (C16 Lyso PC), 1,2-dilinolenoyl-sn-glycero-3-phosphocholine, 1,2-diarachidonoyl-sn-glycero-3-phosphocholine, 1,2-didocosahexaenoyl-sn-glycero-3-phosphocholine, 1,2-dioleoyl-sn-glycero-3-phosphoethanolamine (DOPE), 1,2-diphytanoyl-sn-glycero-3-phosphoethanolamine (ME 16.0 PE), 1,2-distearoyl-sn-glycero-3-phosphoethanolamine, 1,2-dilinoleoyl-sn-glycero-3-phosphoethanolamine, 1,2-dilinolenoyl-sn-glycero-3-phosphoethanolamine, 1,2-diarachidonoyl-sn-glycero-3-phosphoethanolamine, 1,2-didocosahexaenoyl-sn-glycero-3-phosphoethanolamine, 1,2-dioleoyl-sn-glycero-3-phospho-rac-(1-glycerol) sodium salt (DOPG), sphingomyelin (SM), and a mixture thereof.

297. The method of any one of claims 292-296, wherein the LNP comprises a component selected from the group consisting of PEG-modified phosphatidylethanolamines, PEG-modified phosphatidic acids, PEG-modified ceramides, PEG-modified dialkylamines, PEG-modified diacylglycerols, PEG-modified dialkylglycerols, and mixtures thereof. For example, a PEG lipid may be PEG-c-DOMG, PEG-DMG, PEG-DLPE, PEG-DMPE, PEG-DPPC, PEG-DMA, a PEG-DSPE lipid, and a mixture thereof.

298. The method of any one of claims 96-100, wherein the LNP comprises a component selected from the group consisting of a cholesterol, fecosterol, stigmasterol, stigmastanol, sitosterol, β-sitosterol, lupeol, betulin, ursolic acid, oleanolic acid, campesterol, fucosterol, brassicasterol, ergosterol, 9, 11-dehydroergosterol, tomatidine, tomatine, α-tocopherol, and a mixture thereof.

299. The method of any one of claims 114-286, wherein the composition comprises one or more liposomes collectively comprising the (i) RNA-guided nuclease or a nucleic acid encoding an RNA-guided nuclease, and (ii) at least one guide RNA or a nucleic acid encoding at least one guide RNA targeting a gene encoding the transmembrane receptor.

300. The method of claim 299, wherein the one or more liposomes comprises:

a first plurality of liposomes encapsulating the RNA-guided nuclease or a nucleic acid encoding an RNA-guided nuclease; and

a second plurality of liposomes encapsulating the at least one guide RNA or a nucleic acid encoding at least one guide RNA.

301. The method of claim 299, wherein the one or more liposomes comprises a plurality of liposomes encapsulating both the (i) RNA-guided nuclease or a nucleic acid encoding an RNA-guided nuclease, and (ii) at least one guide RNA or a nucleic acid encoding at least one guide RNA targeting a gene encoding the transmembrane receptor.

302. The method of any one of claims 114-286, wherein the composition comprises one or more virus-like particles collectively comprising the (i) RNA-guided nuclease or a nucleic acid encoding an RNA-guided nuclease, and (ii) at least one guide RNA or a nucleic acid encoding at least one guide RNA targeting a gene encoding the transmembrane receptor.

303. The method of claim 302, wherein the one or more virus-like particles comprises:

a first plurality of virus-like particles encapsulating the RNA-guided nuclease or a nucleic acid encoding an RNA-guided nuclease; and

a second plurality of virus-like particles encapsulating the at least one guide RNA or a nucleic acid encoding at least one guide RNA.

304. The method of claim 302, wherein the one or more virus-like particles comprises a plurality of virus-like particles encapsulating both the (i) RNA-guided nuclease or a nucleic acid encoding an RNA-guided nuclease, and (ii) at least one guide RNA or a nucleic acid encoding at least one guide RNA targeting a gene encoding the transmembrane receptor.

305. The method of any one of claims 114-304, wherein the composition is formulated for parenteral administration.

306. The method of any one of claims 114-304, wherein the composition is formulated for intra-articular injection within a joint of the subject.

307. The method of any one of claims 114-304, wherein the composition is formulated for intradiscal injection.

308. The method of any one of claims 114-304, wherein the composition is formulated for peridiscal injection.

309. The method of any one of claims 114-304, wherein the composition is formulated for intravertebral injection.

310. The method of any one of claims 114-304, wherein the administering comprises parenteral administration.

311. The method of any one of claims 114-304, wherein the administering comprises intra-articular injection within a joint of the subject.

312. The method of any one of claims 114-304, wherein the administering comprises intradiscal injection.

313. The method of any one of claims 114-304, wherein the administering comprises peridiscal injection.

314. The method of any one of claims 114-304, wherein the administering comprises intravertebral injection.

315. The method of any one of claims 114-304, wherein the administering comprises intra-articular injection of the pharmaceutical composition into the joint of the subject.

316. The method of any one of claims 114-315, wherein the pharmaceutical composition is administered during surgery.

317. The method of any one of claims 114-316, wherein the pharmaceutical composition is administered after surgery.

318. The method of any one of claims 114-317, wherein the pharmaceutical composition is a controlled release pharmaceutical composition.

Receptor	Exon(s) targeted		
	Knockout	Sol. Decoy	TM Decoy
hIL1R1	3-9	9, 10	10-12
cIL1R1	3-9	6-10	10-12
eIL1R1	3-8	9, 10	10, 11
fIL1R1	4-8	9, 10	10, 11
hIL1R3	3-9	9, 10	10-12
cIL1R3	3-9	9, 10	10, 11
eIL1R3	3-6, 8	9, 10	10, 11
fIL1R3	4-9	9, 10	10, 11
hTGFBR1	1, 2	2, 3	3-9
hTGFBR2	1-3	4	4-7
hIL6R	1-6	4-9	n/a
hIL6ST	3-8	9-15	15-17
hTNFRSF1A	1-5	5-7	7-10
hTNFRSF1B	1-6	4-7	7-10
hTNFRSF3	1-6	4-7	7-10
hTNFRSF4	1-5	4-6	6, 7
hTNFRSF11A	1-6	6, 7	7-10

FIG. 1

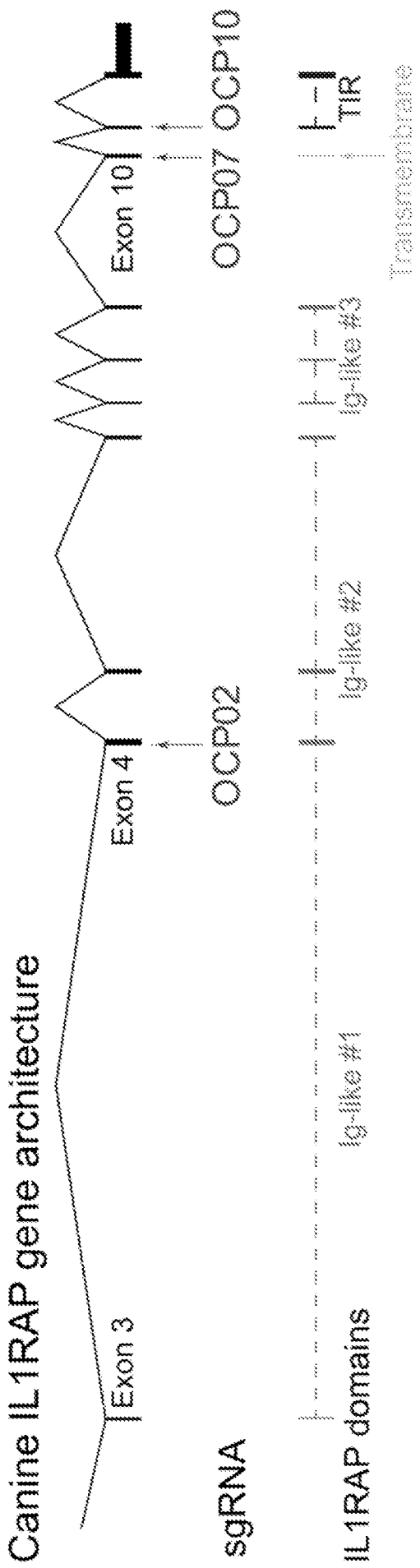

Canine IL1RAP gene architecture
Exon 3
Exon 4
Exon 10
OCP02
OCP07
OCP10
sgRNA
IL1RAP domains
Ig-like #1
Ig-like #2
Ig-like #3
TIR
Transmembrane

FIG. 2A

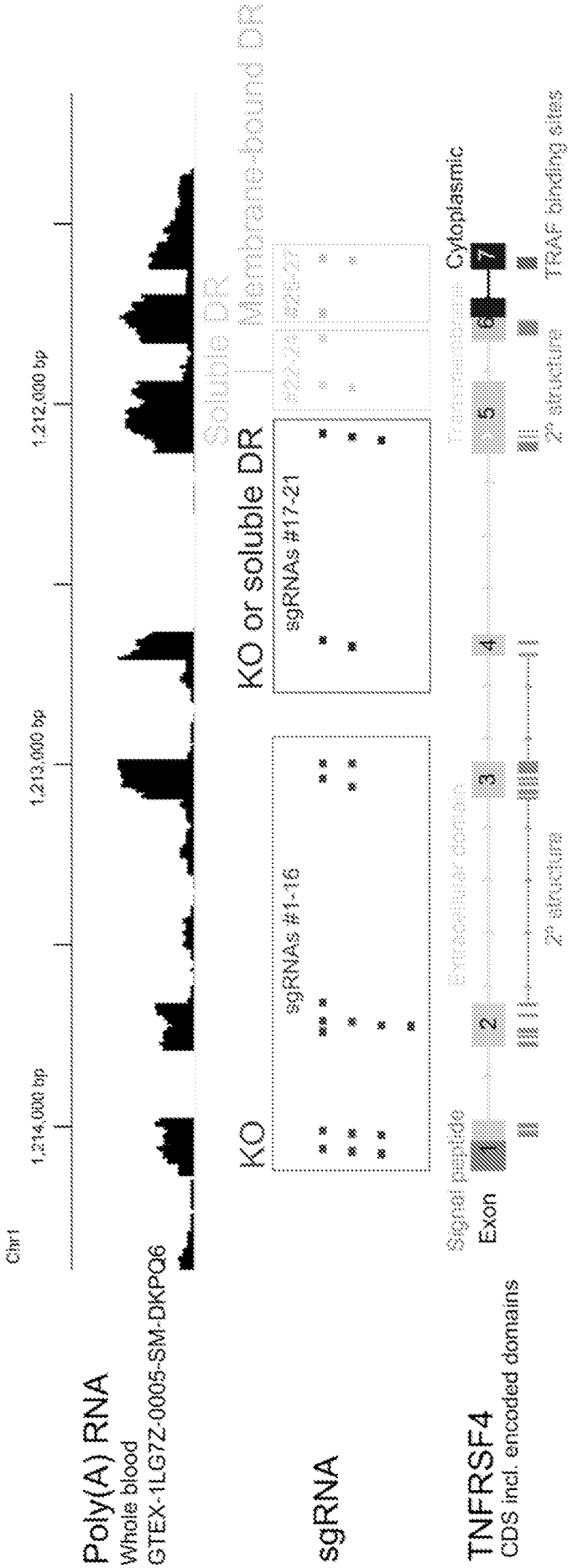

Chr1
1,214,000 bp
1,213,000 bp
1,212,000 bp
Poly(A) RNA
Whole blood
GTEX-1LG7Z-0005-SM-DKPQ6
Soluble DR
Membrane-bound DR
KO or soluble DR
sgRNAs #17-21
KO
sgRNAs #1-16
sgRNA
Signal peptide
Extracellular domain
Cytoplasmic
Exon
1
2
3
4
5
6
7
2° structure
TRAF binding sites
TNFRSF4
CDS incl. encoded domains

FIG. 2B

Receptor(s)	Ligand(s)	Disease Group	Associated Disease
IL1R1, IL1RAP, IL1R4	IL1α, IL1β, IL-33	Autoinflammatory	Fibrosis (general)
IL1R1, IL1RacP, IL1R5, IL1R7	IL1α, IL1β, IL18	Cardiac	Heart disease: Acute Myocardial Infarction, refractory heart failure, arrhythmias, pericarditis, myocarditis and sepsis-induced cardiomyopathy
IL1R1, IL1RAP	IL1β	Cardiac	Acute Decompensated Heart Failure
IL1R1	IL1β driven autoinflammation	Cardiac	Refractory Idiopathic Pericarditis
IL1R1, IL1RAP, IL1R5	IL1α, IL1β, IL-37	Cardiac	Atherosclerosis: coronary artery disease, myocardial infarction and remodelling
IL1R1, IL1RAP	IL1α, IL1β (esophageal mucosa)	Digestive	Gastroesophageal reflux disease (GERD)
IL1R1, IL1RAP	IL1β	Digestive	Non-HP-associated Peptic Ulcer Disease
IL1R1, IL1RAP, IL1R5, IL1R6, IL1R7, IL1R8, IL1R9	IL1β (tissue), IL18 (mucousa), IL-33 (mucousa), IL-36α, IL-36γ, IL-38	Digestive	Inflammatory Bowel Disease (IBD):
IL1R1, IL1RAP, IL1R5, IL1R7	IL1β, IL18	Inflammatory	Autoinflammatory Disease (AID):
IL1R1, IL1RAP	IL1α, IL1β	Inflammatory	Cryopyrin Associated Periodic syndrome (CAPS), Familial Mediterranean Fever (FMF), TNF-Receptor Associated Periodic Syndrome (TRAPS), Hyper-IgD Syndrome (HIDS)
IL1R1, IL1RAP, IL1R5, IL1R6, IL1R7, IL1R8, IL1R9	IL1α, IL18, IL-36α, IL-36γ, IL-37, IL-38	Inflammatory	Systemic Lupus Erythematosus (SLE):
IL1R1, IL1RAP	IL1β	Metabolic	Type 2 Diabietes
IL1R(1,3,5,6,7,9)	IL1α, IL1β, IL18, IL-33, IL-36β, IL-36γ, IL-37, IL-38	Musculoskeletal	Rheumatoid Arthritis
IL1R1, IL1RAP	IL1β	Musculoskeletal	Gout
IL1R1, IL1RAP	IL1α, IL1β	Musculoskeletal	Osteoarthritis
IL1R1, IL1RAP	IL1α, IL1β	Musculoskeletal	Osteoporosis
IL1R1, IL1RAP	IL1α, IL1β, IL1β-converting enzyme (ICE),	Musculoskeletal	Intervertebral disc disease (IVDD)
IL1R1, IL1RAP, IL1R6, IL1R9	IL1β, IL-38	Musculoskeletal	Psoriatic arthritis (PsA)
IL1R1, IL1RAP	IL1α, IL1β	Musculoskeletal	Arthritis
IL1R1, IL1RAP	IL1A	Musculoskeletal	Polymyositis
IL1R1, IL1RAP	IL1B	Musculoskeletal	Proliferative synovitis
IL1R1, IL1RAP	IL1B	Musculoskeletal	Malignant bone neoplasm
IL1R1, IL1RAP	IL1B	Musculoskeletal	Sarcoid Myopathy
IL1R1, IL1RAP	IL1B	Musculoskeletal	Cortex Bone Disorders
IL1R1, IL1RAP	IL1B	Musculoskeletal	Idiopathic Scoliosis
IL1R1, IL1RAP	IL1B	Musculoskeletal	Tendinopathy
IL1R1, IL1RAP	IL1B	Musculoskeletal	Myofibrillar Myopathy
IL1R1, IL1RAP	IL1B	Musculoskeletal	Enthesis-Related Arthritis
IL1R1,2	IL1A, IL1B	Musculoskeletal	Ankylosing spondylitis
IL1R1	IL1A, IL1B	Musculoskeletal	Degenerative polyarthritis
IL1R1	IL1A, IL1B	Musculoskeletal	Arthopathy
IL1R1	IL1A, IL1B	Musculoskeletal	Osteitis Deformans
IL1R1	IL1B	Musculoskeletal	Prolapsed Lumbar Disc
IL1R1	IL1A, IL1B	Musculoskeletal	Polymyositis Ossificans
IL1R1	IL1A	Musculoskeletal	Idiopathic Polymyositis
IL1R1	IL1A	Musculoskeletal	Luft Disease
IL1R1	IL1A, IL1B	Musculoskeletal	Adult-onset Still's Disease
IL1R1	IL1B	Musculoskeletal	Osteoarthrosis Deformans
IL1R1, IL1RAP	IL1A, IL1B	Musculoskeletal	Bachet's Disease

FIG. 3A

Receptor(s)	Ligand(s)	Disease Group	Associated Disease
IL1R1	IL1A, IL1B	Neoplasia	Osteosarcoma
IL1R1, IL1R2	IL1A, IL1B	Neoplasia	Colon Cancer
IL1R1, IL1RAP	IL1α, IL1β	Neoplasia	Metastasis (General)
IL1R1, IL1RAP	IL1α, IL1β	Neoplasia	Lung Cancer
IL1R1, IL1RAP	IL1α, IL1β	Neoplasia	Multiple Myeloma
IL1R1, IL1RAP	IL1α, IL1β	Neoplasia	Breast Cancer
IL1R1, IL1RAP	IL1α, IL1β	Neoplasia	Solid Tumors
IL1R1, IL1RAP	IL1A	Neoplasia	Lymphoma
IL1RAP	IL1A, IL1B	Neoplasia	Pancreatic Cancer
IL1R1	IL1A, IL1B	Neoplasia	Stomach Cancer
IL1R1	IL1A	Neoplasia	Epithelial Ovarian Cancer
IL1R1	IL1A	Neoplasia	Mammary Neoplasms
IL1R1	IL1A	Neoplasia	Oropharyngeal Carcinoma
IL1R1	IL1α, IL1β	Neoplasia	Renal Cell Carcinoma
IL1R1	IL1α, IL1β	Neoplasia	Chondrosarcoma
IL1R2	IL1A	Neoplasia	Esophageal Neoplasms
IL1R1	IL1A, IL1B	Neoplasia	B-Cell Lymphoma
IL1R1	IL1A, IL1B	Neoplasia	Lymphoma T-Cell, Cutaneous
IL1R1, IL1RAP	IL1A, IL1B	Neoplasia	Leukemia
IL1R1, IL1R2	IL1A, IL1B	Neoplasia	Thyroid Carcinoma
IL1R1	IL1A	Neoplasia	Skin carcinogenesis
IL1R1, IL1RAP	IL1B	Neoplasia	Cholectoral Cancer
IL1R1, IL1RAP	IL1B	Neoplasia	Glioma
IL1R1, IL1RAP	IL1B	Neoplasia	Liver Cancer
IL1R1, IL1RAP	IL1B	Neoplasia	Melanoma
IL1R1, IL1RAP	IL1B	Neoplasia	Neuroblastoma
IL1R1	IL1B	Neoplasia	Polycystic Ovary Syndrome
IL1R1, IL1RAP	IL1B	Neoplasia	Glioblastoma
IL1R1, IL1RAP	IL1B	Neoplasia	Prostate Cancer
IL1R1, IL1RAP	IL1B	Neoplasia	Cervical Cancer
IL1R1, IL1R2	IL1B	Neoplasia	Ovarian Cancer
IL1R1, IL1RAP	IL1B	Neoplasia	Bladder Cancer
IL1R1, IL1RAP	IL1B	Neoplasia	Squamous cell carcinoma
IL1R1, IL1RAP	IL1B	Neoplasia	Kaposi Sarcoma
IL1R1, IL1RAP	IL1B	Neoplasia	Oral Cavity Cancer
IL1R1	IL1B	Neoplasia	Leiomyosarcoma
IL1R1	IL1B	Neoplasia	Malignant Peripheral Nerve Sheath Tumour
IL1R1, IL1RAP	IL1B	Neoplasia	Ewing's Sarcoma
IL1R1, IL1RAP	IL1α, IL1β	Neuro	Acute Thrombotic Stroke
IL1R1, IL1RAP	IL1β	Neuro	Epilepsy
IL1R1, IL1RAP, IL1R4 IL1R5, IL1R7, IL1R6	IL1β (brain and CSF), IL18 (CSF mRNA and PBMC), IL-33 (circulation), IL-37	Neuro	Multiple Sclerosis
IL1R1, IL1RAP, IL1R4, IL1R5, IL1R7	IL1α, IL1β, IL18 (in CSF), IL-33, IL18BP	Neuro	Alzheimer's Disease
IL1R1, IL1RAP	IL1β	Opthalmic	Eye Diseases: Uveitis, Scleritis, Sjogren asthenia, dry eye
IL1R1, IL1RAP	IL1α	Renal	Chronic Kidney Disease
IL1R1, IL1RAP, IL1R4	IL1α, IL1β, IL-33	Respiratory	Pulmonary Fibrosis
IL1R1, IL1RAP	IL1α, IL1β	Respiratory	Asthma

FIG. 3B

Receptor	Ligand	Disease Group	Associated disease
IL6R	IL6	Musculoskeletal	Rheumatoid arthritis
IL6R	IL6	Musculoskeletal	Idiopathic osteoporosis
IL6R	IL6	Musculoskeletal	Post-menopaual osteoporosis
IL6R	IL6	Musculoskeletal	Paget's disease
IL6R	IL6	Musculoskeletal	Osteoarthritis
IL6R	IL6	Musculoskeletal	Juvenile idiopathic arthritis (JIA)
IL6R	IL6	Musculoskeletal	Still's disease
IL6R	IL6	Musculoskeletal	Ankylosing spondylitis
IL6R	IL6	Musculoskeletal	Polymyalgia rheumatica
IL6R	IL6	Musculoskeletal	Arthritis
IL6R	IL6	Musculoskeletal	Secondary malignant neoplasm of bone
IL6R	IL6	Musculoskeletal	Type II Mucolipidosis
IL6R	IL6	Musculoskeletal	Sjogren's Syndrome
IL6R	IL6	Musculoskeletal	Psoriatic arthritis
IL6R	IL6	Musculoskeletal	Rheumatism
IL6R	IL6	Inflammation	Inflammatory diseases (e.g. cytokine storm in COVID 19/post- CAR-T therapy)
IL6R	IL6	Neoplasia	Multiple myeloma
IL6R	IL6	Musculoskeletal	Castlemans disease
IL6R	IL6	Neoplasia	Lung Cancer
IL6R	IL6	Neoplasia	Stomach Cancer
IL6R	IL6	Neoplasia	Breast Cancer
IL6R	IL6	Neoplasia	Kidney Cancer
IL6R	IL6	Neoplasia	Neoplasm Metastasis
IL6R	IL6	Neoplasia	Colorectal Neoplasms
IL6R	IL6	Neoplasia	Ovarian cancer
IL6R	IL6	Neoplasia	Osteosarcoma
IL6R	IL6	Neoplasia	Cholangiocarcinoma
IL6R	IL6	Neoplasia	Leukemia
IL6R	IL6	Neoplasia	Prostate cancer
IL6R	IL6	Neoplasia	Plasmacytoma
IL6R	IL6	Neoplasia	Pancreatic cancer
IL6R	IL6	Neoplasia	Cervical cancer
IL6R	IL6	Neoplasia	Lymphoma
IL6R	IL6	Neoplasia	Liver neoplasms
IL6R	IL6	Neoplasia	Neuroblastoma
IL6R	IL6	Neoplasia	Melanoma
IL6R	IL6	Neoplasia	Mastocytosis
IL6R	IL6	Neoplasia	Endometrial cancer
IL6R	IL6	Neoplasia	Bladder Cancer
IL6R	IL6	Neoplasia	Squamous cell carcinoma
IL6R	IL6	Neoplasia	Gallbladder carcinoma
IL6R	IL6	Neoplasia	Adenocarcinoma
IL6R	IL6	Neoplasia	Thyroid Cancer

FIG. 4A

Receptor	Ligand	Disease Group	Associated disease
IL6ST	IL6	Musculoskeletal	degenerative polyarthritis
IL6ST	IL6	Musculoskeletal	arthritis
IL6ST	IL6	Musculoskeletal	rheumatoid arthritis
IL6ST	IL6	Musculoskeletal	arthropathy
IL6ST	IL6	Musculoskeletal	psoriatic arthritis
IL6ST	IL6	Musculoskeletal	ankylosing spondylitis
IL6ST	IL6	Musculoskeletal	bone neoplasm
IL6ST	IL6	Musculoskeletal	osteoporosis
IL6ST	IL6	Musculoskeletal	massive osteolyses
IL6ST	IL6	Musculoskeletal	bone fracture healing
IL6ST	IL6	Musculoskeletal	systemic sclerosis
IL6ST	IL6	Musculoskeletal	systemic Juvenile idiopathic arthritis
IL6ST	IL6	Musculoskeletal	still disease
IL6ST	IL6	Musculoskeletal	synovitis
IL6ST	IL6	Neoplasia	prostate neoplasms
IL6ST	IL6	Neoplasia	stomach cancer
IL6ST	IL6	Neoplasia	liver carcinoma
IL6ST	IL6	Neoplasia	pituitary neoplasms
IL6ST	IL6	Neoplasia	hepatoblastoma
IL6ST	IL6	Neoplasia	multiple myeloma
IL6ST	IL6	Neoplasia	hepatocellular adenoma
IL6ST	IL6	Neoplasia	breast carcinoma
IL6ST	IL6	Neoplasia	carcinogenesis
IL6ST	IL6	Neoplasia	leukemia
IL6ST	IL6	Neoplasia	colon carcinoma
IL6ST	IL6	Neoplasia	melanoma
IL6ST	IL6	Neoplasia	metastasis (general)
IL6ST	IL6	Neoplasia	lung
IL6ST	IL6	Neoplasia	pancreatic cancer
IL6ST	IL6	Neoplasia	kaposi sarcoma
IL6ST	IL6	Neoplasia	medulloblastoma
IL6ST	IL6	Neoplasia	carcinoma of bladder
IL6ST	IL6	Neoplasia	squamous cell carcinoma
IL6ST	IL6	Neoplasia	mast cell neoplasm
IL6ST	IL6	Neoplasia	glioma
IL6ST	IL6	Neoplasia	mastocytoma
IL6ST	IL6	Neoplasia	brain neoplasms
IL6ST	IL6	Neoplasia	ovarian neoplasms
IL6ST	IL6	Neoplasia	bone
IL6ST	IL6	Neoplasia	rhabdomyosarcoma
IL6ST	IL6	Neoplasia	solid tumors
IL6ST	IL6	Neoplasia	metastatic kidney cancer
IL6ST	IL6	Neoplasia	metastatic renal cell carcinoma
IL6ST	IL6	Inflammatory	acute local inflammation
IL6ST	IL6	Inflammatory	inflammatory bowel disease
IL6ST	IL6	Inflammatory	experimental sepsis
IL6ST	IL6	Inflammatory	castleman disease
IL6ST	IL6	Inflammatory/Digestive	crohn's disease
IL6ST	IL6	Cardiac	atherosclerosis
IL6ST	IL6	Cardiac	abdominal aortic aneurism
IL6ST	IL6	Autoimmune	systemic lupus erthematosus

FIG. 4B

Receptor	Ligands	Disease Group	Associated disease
TNFRSF1A	TNF, LTa (TNFb)	Musculoskeletal	Arthritis, Infectious
TNFRSF1A	TNF, LTa (TNFb)	Musculoskeletal	Intermittent joint effusion
TNFRSF1A	TNF, LTa (TNFb)	Musculoskeletal	Ankylosing spondylitis
TNFRSF1A	TNF, LTa (TNFb)	Musculoskeletal	Arthritis
TNFRSF1A	TNF, LTa (TNFb)	Musculoskeletal	Osteoarthritis
TNFRSF1A	TNF, LTa (TNFb)	Musculoskeletal	Spondylarthritis
TNFRSF1A	TNF, LTa (TNFb)	Musculoskeletal	Plantar fasciitis
TNFRSF1A	TNF, LTa (TNFb)	Musculoskeletal	Degenerative polyarthritis
TNFRSF1A	TNF, LTa (TNFb)	Musculoskeletal	Hemophilic arthropathy
TNFRSF1A	TNF, LTa (TNFb)	Musculoskeletal	Inflammatory myopathy with abundant macrophages
TNFRSF1A	TNF, LTa (TNFb)	Musculoskeletal	Polymyositis
TNFRSF1A	TNF, LTa (TNFb)	Musculoskeletal	Tendinosis
TNFRSF1A	TNF, LTa (TNFb)	Musculoskeletal	Malignant Bone Neoplasm
TNFRSF1A	TNF, LTa (TNFb)	Musculoskeletal	Osteonecrosis
TNFRSF1A	TNF, LTa (TNFb)	Musculoskeletal	Psoriatic arthritis
TNFRSF1A	TNF, LTa (TNFb)	Musculoskeletal	Rheumatism
TNFRSF1A	TNF, LTa (TNFb)	Musculoskeletal	Rheumatoid arthritis
TNFRSF1A	TNF, LTa (TNFb)	Musculoskeletal	Adult Still's disease
TNFRSF1A	TNF, LTa (TNFb)	Musculoskeletal	Juvenile arthritis
TNFRSF1A	TNF, LTa (TNFb)	Musculoskeletal	Early rheumatoid arthritis
TNFRSF1A	TNF, LTa (TNFb)	Musculoskeletal	Palindromic rheumatism
TNFRSF1A	TNF, LTa (TNFb)	Musculoskeletal	Gout
TNFRSF1A	TNF, LTa (TNFb)	Neoplasia	Neoplasms
TNFRSF1A	TNF, LTa (TNFb)	Neoplasia	Glioblastoma
TNFRSF1A	TNF, LTa (TNFb)	Neoplasia	Astrocytoma
TNFRSF1A	TNF, LTa (TNFb)	Neoplasia	Adenocarcinoma
TNFRSF1A	TNF, LTa (TNFb)	Neoplasia	Osteosarcoma
TNFRSF1A	TNF, LTa (TNFb)	Neoplasia	Squamous cell carcinoma
TNFRSF1A	TNF, LTa (TNFb)	Neoplasia	Metastasis
TNFRSF1A	TNF, LTa (TNFb)	Neoplasia	Ameloblastoma
TNFRSF1A	TNF, LTa (TNFb)	Neoplasia	Cholangiocarcinoma
TNFRSF1A	TNF, LTa (TNFb)	Neoplasia	Choriocarcinoma
TNFRSF1A	TNF, LTa (TNFb)	Neoplasia	Ovarian cancer
TNFRSF1A	TNF, LTa (TNFb)	Neoplasia	Prostate cancer
TNFRSF1A	TNF, LTa (TNFb)	Neoplasia	Lung Cancer
TNFRSF1A	TNF, LTa (TNFb)	Neoplasia	Larynx Cancer
TNFRSF1A	TNF, LTa (TNFb)	Neoplasia	Breast Cancer
TNFRSF1A	TNF, LTa (TNFb)	Neoplasia	Lip and Oral Cavity Carcinoma
TNFRSF1A	TNF, LTa (TNFb)	Neoplasia	Squamous intraepithelial lesion
TNFRSF1A	TNF, LTa (TNFb)	Neoplasia	Neuroblastoma

FIG. 5

Receptor	Ligands	Disease Group	Associated disease
TNFRSF1B	TNF, LTa	Musculoskeletal	Arthritis
TNFRSF1B	TNF, LTa	Musculoskeletal	Rheumatoid arthritis
TNFRSF1B	TNF, LTa	Musculoskeletal	Osteoarthritis
TNFRSF1B	TNF, LTa	Musculoskeletal	Arthritis, Infectious
TNFRSF1B	TNF, LTa	Musculoskeletal	Ankylosing spondylitis
TNFRSF1B	TNF, LTa	Musculoskeletal	Osteoporosis
TNFRSF1B	TNF, LTa	Musculoskeletal	Juvenile arthritis
TNFRSF1B	TNF, LTa	Musculoskeletal	Arthritis, Psoriatic
TNFRSF1B	TNF, LTa	Musculoskeletal	Myotonic dystrophy
TNFRSF1B	TNF, LTa	Musculoskeletal	Dermatomyositis
TNFRSF1B	TNF, LTa	Musculoskeletal	Hemophilic arthropathy
TNFRSF1B	TNF, LTa	Musculoskeletal	Osteopenia
TNFRSF1B	TNF, LTa	Musculoskeletal	Polymyositis
TNFRSF1B	TNF, LTa	Musculoskeletal	Palindromic rheumatism
TNFRSF1B	TNF, LTa	Neoplasia	Non-Hodgkin lymphomas
TNFRSF1B	TNF, LTa	Neoplasia	Breast Cancer
TNFRSF1B	TNF, LTa	Neoplasia	Malignant Neoplasms
TNFRSF1B	TNF, LTa	Neoplasia	Skin Neoplasms
TNFRSF1B	TNF, LTa	Neoplasia	Neuroblastoma
TNFRSF1B	TNF, LTa	Neoplasia	Squamous cell carcinoma
TNFRSF1B	TNF, LTa	Neoplasia	Neoplasm Metastasis
TNFRSF1B	TNF, LTa	Neoplasia	Colorectal Cancer
TNFRSF1B	TNF, LTa	Neoplasia	Lung cancer
TNFRSF1B	TNF, LTa	Neoplasia	Fibrosarcoma
TNFRSF1B	TNF, LTa	Neoplasia	Myeloid Leukemia
TNFRSF1B	TNF, LTa	Neoplasia	Myelofibrosis
TNFRSF1B	TNF, LTa	Neoplasia	Hodgkin Lymphomas
TNFRSF1B	TNF, LTa	Neoplasia	Non-Small Cell Lung Carcinoma
TNFRSF1B	TNF, LTa	Neoplasia	Ovarian cancer
TNFRSF1B	TNF, LTa	Neoplasia	Prostate cancer
TNFRSF1B	TNF, LTa	Neoplasia	Cervical Cancer
TNFRSF1B	TNF, LTa	Neoplasia	Liver cancer
TNFRSF1B	TNF, LTa	Neoplasia	Extrapulmonary small cell carcinoma
TNFRSF1B	TNF, LTa	Neoplasia	Basal cell carcinoma
TNFRSF1B	TNF, LTa	Neoplasia	Kidney cancer
TNFRSF1B	TNF, LTa	Neoplasia	Pancreatic carcinoma
TNFRSF1B	TNF, LTa	Neoplasia	Mesothelioma
TNFRSF1B	TNF, LTa	Neoplasia	Gastric cancer
TNFRSF1B	TNF, LTa	Neoplasia	Adenocarcinoma
TNFRSF1B	TNF, LTa	Neoplasia	Glioblastoma
TNFRSF1B	TNF, LTa	Neoplasia	Polycystic Ovary Syndrome
TNFRSF1B	TNF, LTa	Neoplasia	Chordoma
TNFRSF1B	TNF, LTa	Neoplasia	Cholangiocarcinoma
TNFRSF1B	TNF, LTa	Neoplasia	Malignant ascites

FIG. 6

Receptor	Ligands	Disease Group	Associated disease
TNFRSF3	LTa, LTb, LIGHT	Musculoskeletal	Ankylosing spondylitis
TNFRSF3	LTa, LTb, LIGHT	Musculoskeletal	Sjogren's Syndrome
TNFRSF3	LTa, LTb, LIGHT	Musculoskeletal	Rheumatoid arthritis
TNFRSF3	LTa, LTb, LIGHT	Musculoskeletal	Juvenile Idopathic Arthritis
TNFRSF3	LTa, LTb, LIGHT	Neoplasia	Nasopharyngeal carcinoma
TNFRSF3	LTa, LTb, LIGHT	Neoplasia	Head and Neck Carcinoma
TNFRSF3	LTa, LTb, LIGHT	Neoplasia	Ovarian Cancer
TNFRSF3	LTa, LTb, LIGHT	Neoplasia	Cancer metastasis
TNFRSF3	LTa, LTb, LIGHT	Neoplasia	adenocarcinoma
TNFRSF3	LTa, LTb, LIGHT	Neoplasia	Prostate carcinoma
TNFRSF3	LTa, LTb, LIGHT	Neoplasia	Fibrosarcoma
TNFRSF3	LTa, LTb, LIGHT	Neoplasia	Liver carcinoma
TNFRSF3	LTa, LTb, LIGHT	Neoplasia	Carcinoma of bladder
TNFRSF3	LTa, LTb, LIGHT	Neoplasia	Breast Cancer
TNFRSF3	LTa, LTb, LIGHT	Neoplasia	T-Cell Lymphoblastic Leukemia
TNFRSF3	LTa, LTb, LIGHT	Neoplasia	Glioblastoma
TNFRSF3	LTa, LTb, LIGHT	Neoplasia	Non-Small Cell Lung Carcinoma
TNFRSF3	LTa, LTb, LIGHT	Neoplasia	Bladder Neoplasm
TNFRSF3	LTa, LTb, LIGHT	Neoplasia	melanoma

FIG. 7

Receptor	Ligands	Disease Group	Associated disease	Notes
TNFRSF4	OX40L	Musculoskeletal	Rheumatoid arthritis	PMID: 32140389
TNFRSF4	OX40L	Musculoskeletal	Myasthenia gravis	PMID: 35265719
TNFRSF4	OX40L		Allergy	PMID: 33160971
TNFRSF4	OX40L		Asthma	PMID: 33160971
TNFRSF4	OX40L		Multiple sclerosis	PMID: 32140389
TNFRSF4	OX40L		Psoriasis	PMID: 34354596
TNFRSF4	OX40L		Inflammatory bowel disease	PMID: 34371056
TNFRSF5	OX40L		Autoimmune experimental uveitis	PMID: 32140389
TNFRSF4	OX40L		Colitis	PMID: 32140389
TNFRSF4	OX40L		Hypersensitivity reaction disease	PMID: 36121111
TNFRSF4	OX40L		Diabetes	PMID: 32140389
TNFRSF4	OX40L		Crohn's disease	PMID: 23181223
TNFRSF4	OX40L		Systemic lupus erythematosus	PMID: 32140389
TNFRSF4	OX40L		Pulmonary sarcoidosis	PMID: 33901497
TNFRSF4	OX40L		Leishmaniasis	PMID: 10637281
TNFRSF4	OX40L		Experimental autoimmune encephalomyelitis	PMID: 32140389
TNFRSF4	OX40L		HTLV-1-associated myelopathy	PMID: 23651542
TNFRSF4	OX40L		Tropical spastic paraparesis	PMID: 23651542
TNFRSF4	OX40L		Scleroderma	PMID: 27298374
TNFRSF4	OX40L		Idiopathic inflammatory myopathy (such as polymyositis and dermatomyositis)	PMID: 23469620
TNFRSF4	OX40L		Spondyloarthritis	PMID: 34907325
TNFRSF4	OX40L		Sjogren's syndrome	PMID: 34234777
TNFRSF4	OX40L	Neoplasia	Leukemia (such as acute myeloid leukemia)	PMID: 36151238
TNFRSF4	OX40L	Neoplasia	Squamous cell carcinoma	PMID: 34036015
TNFRSF4	OX40L	Neoplasia	Hepatocellular carcinoma	PMID: 36591653; PMID: 36148160
TNFRSF4	OX40L	Neoplasia	Colorectal cancer	PMID: 36504589
TNFRSF4	OX40L	Neoplasia	Lymphoma (such as Mycosis fungoides and Sézary syndrome)	PMID: 34830466

FIG. 8

Receptor	Ligands	Disease Group	Associated disease
TNFRSF11A	RANKL	Musculoskeletal	Osteoporosis
TNFRSF11A	RANKL	Musculoskeletal	Osteolysis
TNFRSF11A	RANKL	Musculoskeletal	Rheumatoid arthritis
TNFRSF11A	RANKL	Musculoskeletal	Inflammation
TNFRSF11A	RANKL	Musculoskeletal	Degenerative polyarthritis
TNFRSF11A	RANKL	Musculoskeletal	Osteitis deformans
TNFRSF11A	RANKL	Musculoskeletal	Ankylosing spondylitis
TNFRSF11A	RANKL	Musculoskeletal	Pigmented villonodular synovitis
TNFRSF11A	RANKL	Musculoskeletal	Hyperphosphatasemia with bone disease

FIG. 9

Receptor	Ligands	Disease Group	Associated disease
TGFBR1	TGFB1, TGFB2, TGFB3	Musculoskeletal	Loeys-Dietz Syndrome
TGFBR1	TGFB1, TGFB2, TGFB9	Musculoskeletal	Osteoarthrosis
TGFBR1	TGFB1, TGFB2, TGFB10	Musculoskeletal	Marfan Syndrome
TGFBR1	TGFB1, TGFB2, TGFB4	Neoplasia	Pancreatic cancer
TGFBR1	TGFB1, TGFB2, TGFB4	Neoplasia	Multiple self-healing squamous epithelioma (Ferguson-Smith disease)
TGFBR1	TGFB1, TGFB2, TGFB4	Neoplasia	Pancreatic cancer
TGFBR1	TGFB1, TGFB2, TGFB33	Neoplasia	Gastrointestinal Stromal Tumors (GIST)

FIG. 10A

Receptor	Ligands	Disease Group	Associated disease
TGFBR2	TGFB1, TGFB2, TGFB11	Musculoskeletal	Loeys-Dietz Syndrome
TGFBR2	TGFB1, TGFB2, TGFB12	Musculoskeletal	Aortic aneurysm, familial thoracic 3
TGFBR2	TGFB1, TGFB2, TGFB16	Musculoskeletal	Marfan Syndrome
TGFBR2	TGFB1, TGFB2, TGFB25	Musculoskeletal	Craniofacial abnormalities
TGFBR2	TGFB1, TGFB2, TGFB15	Neoplasia	Hereditary Nonpolyposis Colorectal Cancer (Lynch Syndrome)
TGFBR2	TGFB1, TGFB2, TGFB18	Neoplasia	Metastasis
TGFBR2	TGFB1, TGFB2, TGFB19	Neoplasia	Colorectal Carcinoma
TGFBR2	TGFB1, TGFB2, TGFB26	Neoplasia	Bone neoplasms
TGFBR2	TGFB1, TGFB2, TGFB27	Neoplasia	Anaplastic carcinoma
TGFBR2	TGFB1, TGFB2, TGFB28	Neoplasia	Carcinoma, Spindle-Cell
TGFBR2	TGFB1, TGFB2, TGFB31	Neoplasia	Malignant Bone Neoplasm
TGFBR2	TGFB1, TGFB2, TGFB32	Neoplasia	Lung neoplasms
TGFBR2	TGFB1, TGFB2, TGFB33	Neoplasia	Gastrointestinal Stromal Tumors (GIST)
TGFBR2	TGFB1, TGFB2, TGFB34	Neoplasia	Malignant neoplasm of brain

FIG. 10B

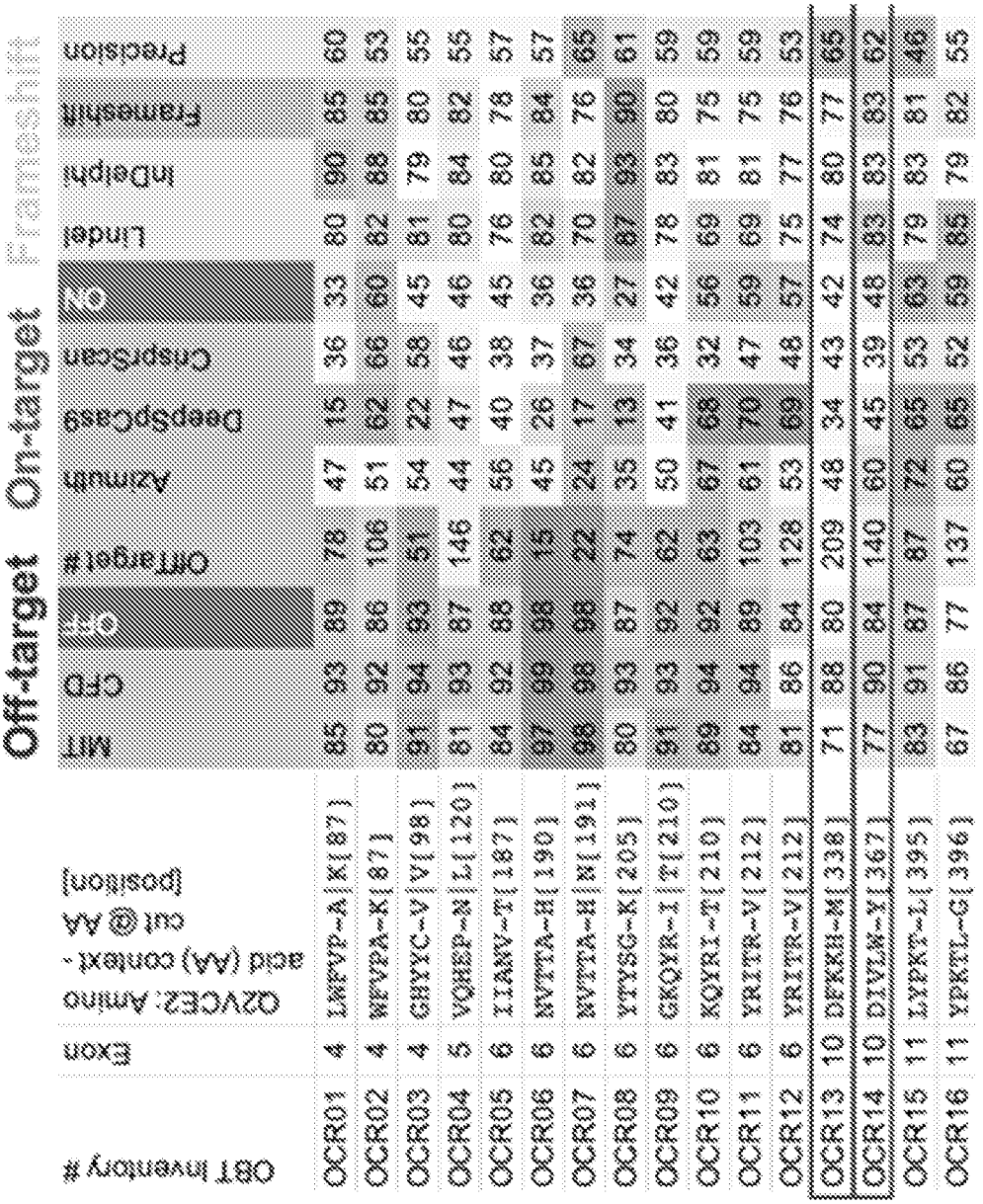

Off-target
On-target
Frameshift
OBT Inventory #
Exon
O2VCE2: Amino acid (AA) context - cut @ AA [position]
MIT
CFD
OT1
OffTarget #
Azimuth
DeepSpCas9
CnsprScan
OT3
Lindel
inDelphi
Frameshift
Precision
Fitness

FIG. 11A

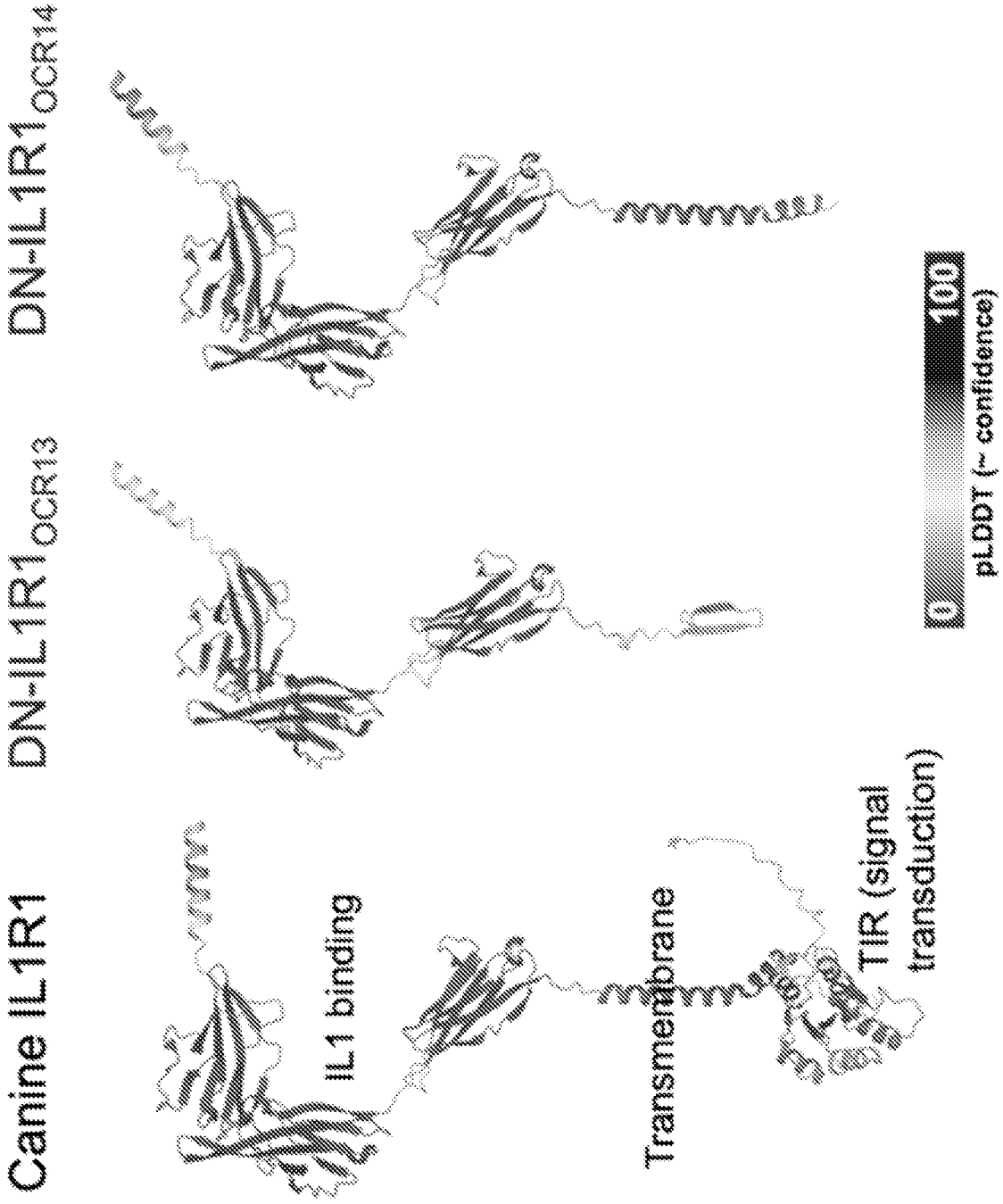

Canine IL1R1
DN-IL1R1OCR13
DN-IL1R1OCR14
IL1 binding
Transmembrane
TIR (signal transduction)
0
100
pLDDT (~ confidence)

FIG. 11B

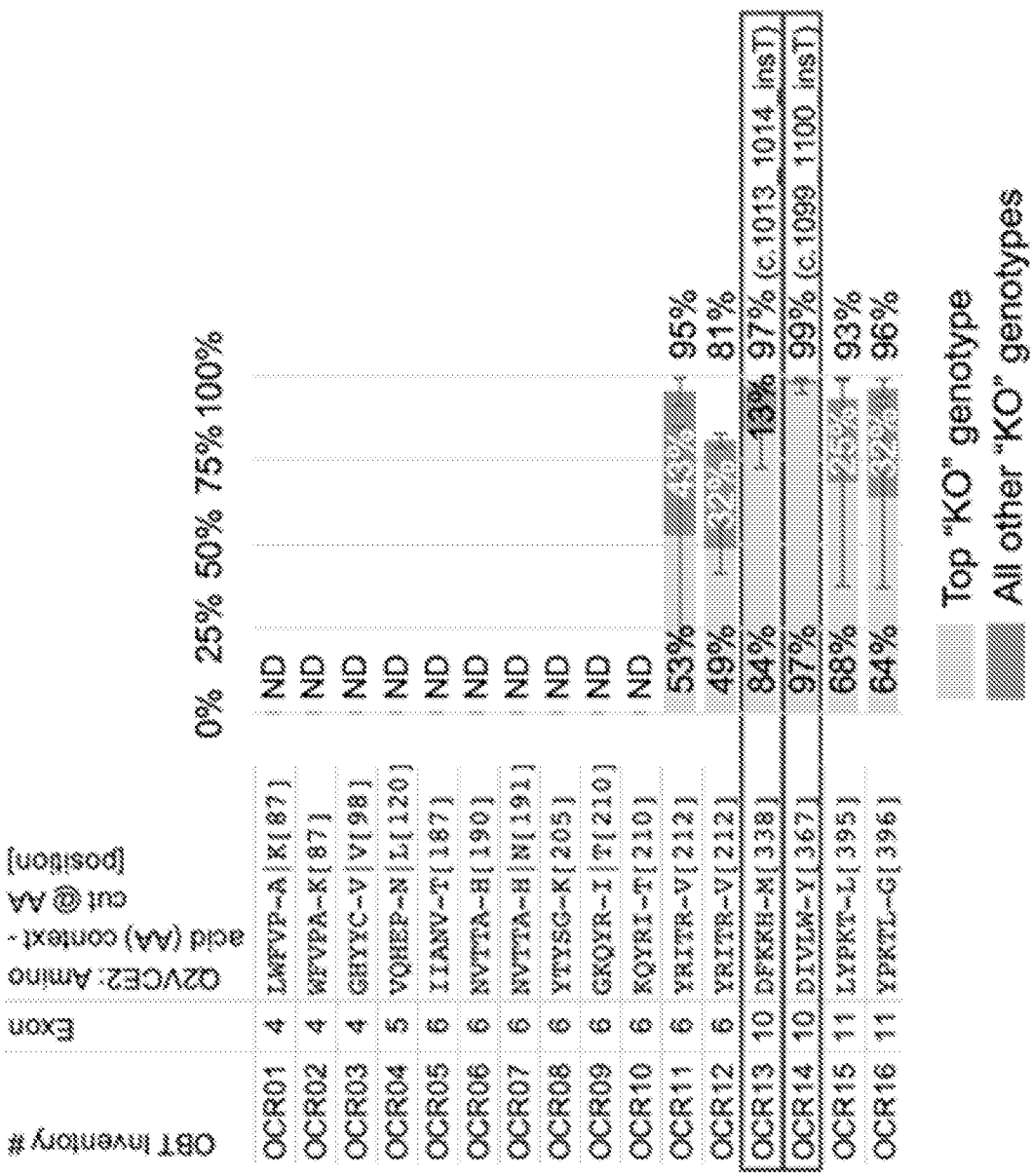

OBT Inventory #
Exon
OZYCE2: Amino acid (AA) context - cut @ AA [position]
0% 25% 50% 75% 100%
OCR01 4 LMPVP-A|K187]
OCR02 4 MPVPA-K|87]
OCR03 4 GPYYC-V|V198]
OCR04 5 VQHEA-N|L1120]
OCR05 6 IIAWV-T|1187]
OCR06 6 NVTLA-H|1901]
OCR07 6 NVTLA-H|N1191]
OCR08 6 YTYSC-K|2051]
OCR09 6 GKQYR-I|T1210]
OCR10 6 KQYRI-T|2101]
OCR11 6 YRITR-V|2121]
OCR12 6 YRITR-V|2121]
OCR13 10 DFKKH-M|338]
OCR14 10 DTVLW-Y|367]
OCR15 11 LYPKT-L|395]
OCR16 11 YPKTL-G|396]
ND
53%
49%
84%
97%
68%
64%
95%
81%
13%
97% (c.1013_1014 insT)
99% (c.1099_1100 insT)
93%
96%
Top "KO" genotype
All other "KO" genotypes

FIG. 12

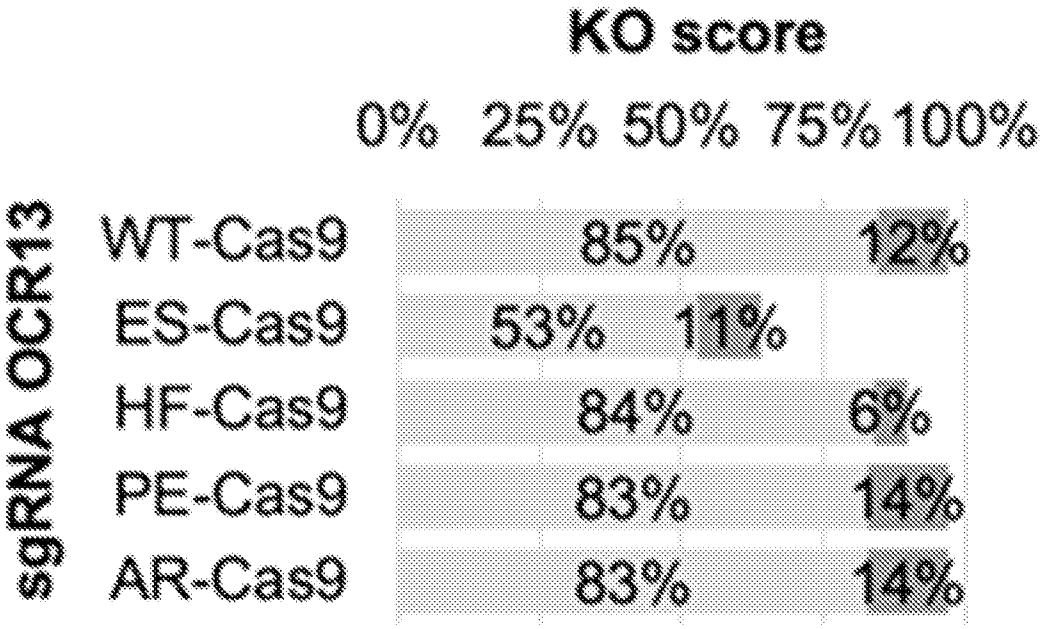


FIG. 13A

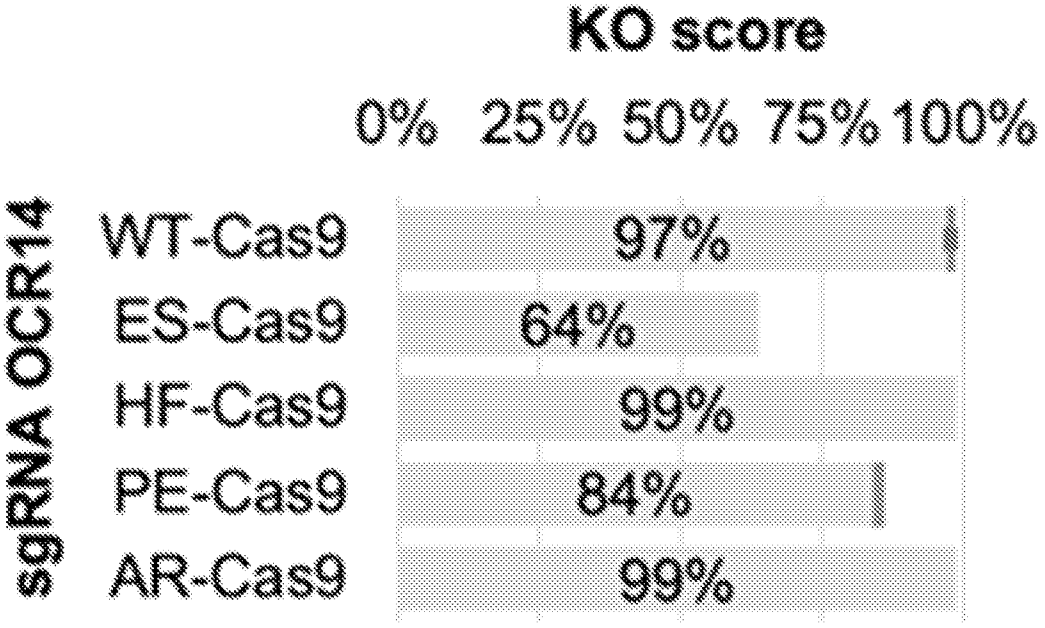


FIG. 13B

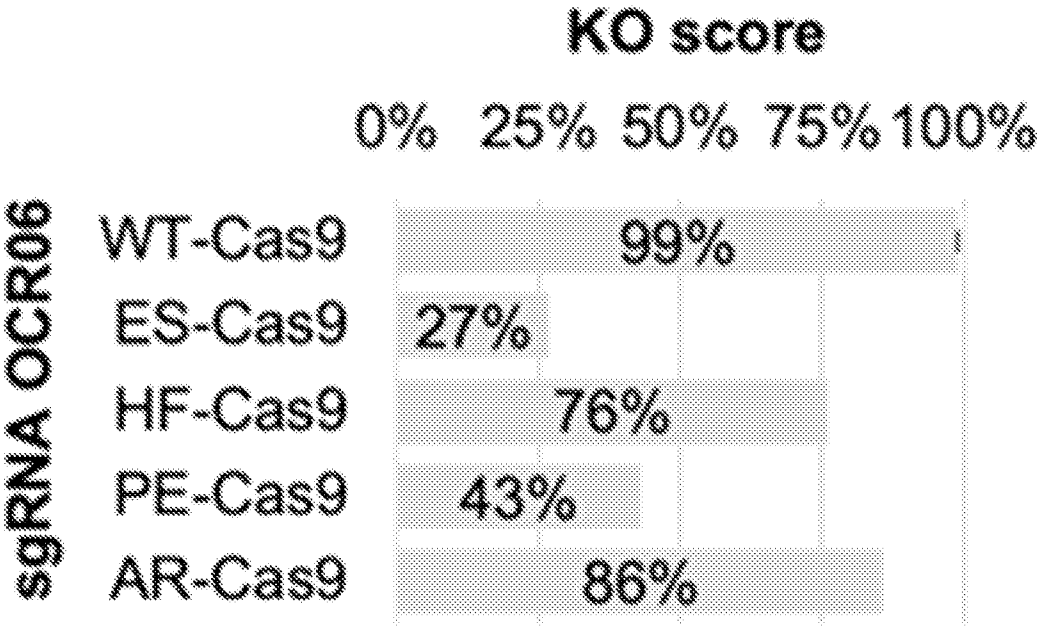


FIG. 13C

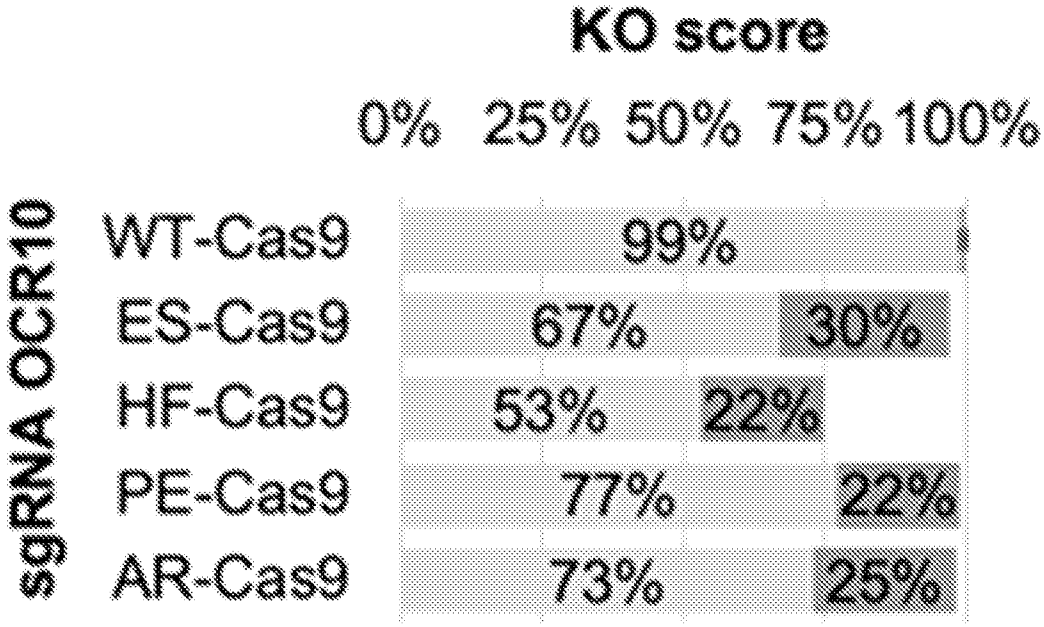
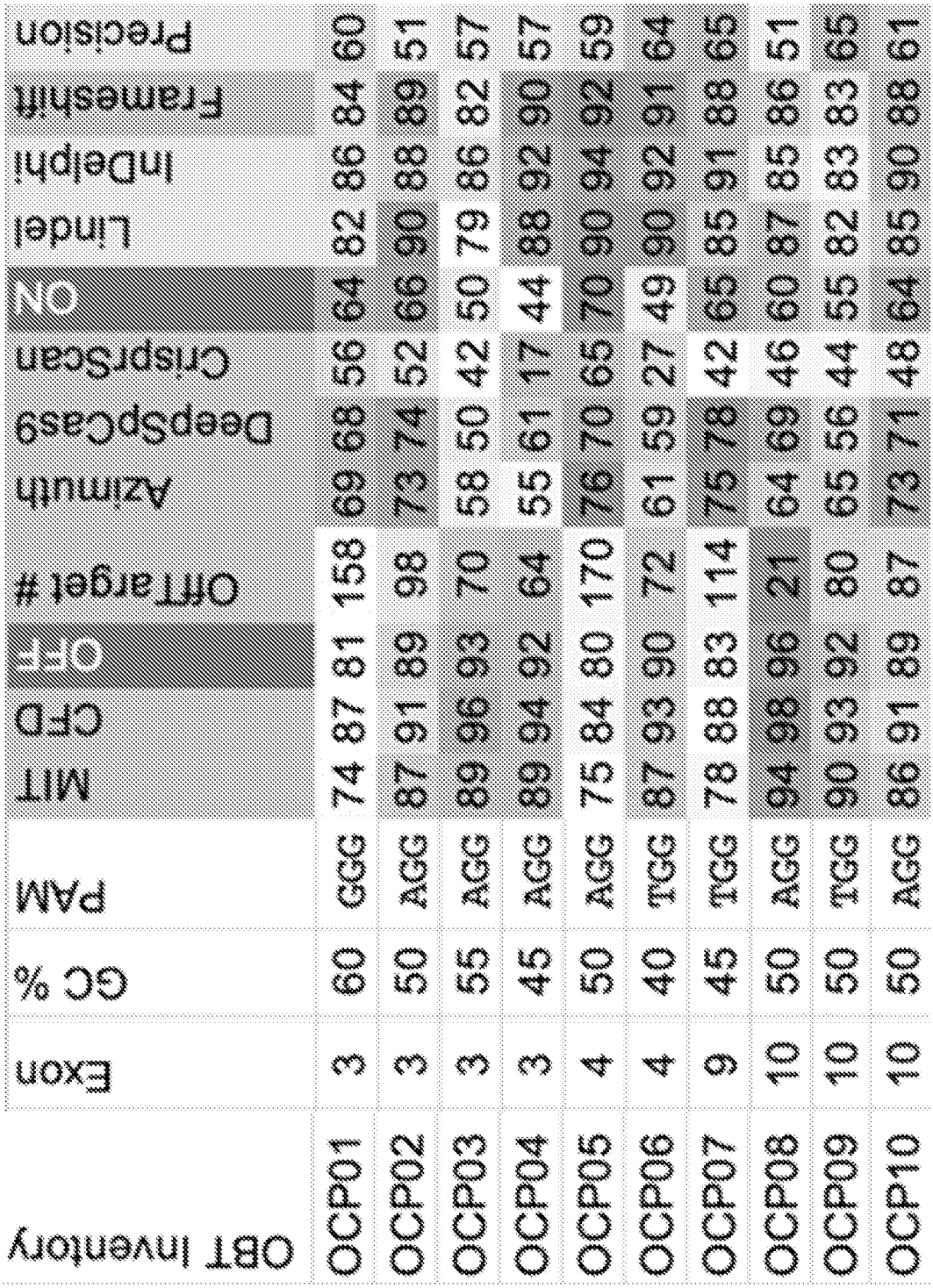


FIG. 13D



OBT inventory	Exon	GC %	PAM	MIT	CFD	OFF	OffTarget #	Azimuth	DeepSpCas9	CrisprScan	ON	Lindel	inDelphi	Frameshift	Precision
OCP01	3	60	CGG	74	87	81	158	69	68	56	64	82	86	84	60
OCP02	3	50	AGG	87	91	89	98	73	74	52	66	90	88	89	51
OCP03	3	55	AGG	89	96	93	70	58	50	42	50	79	86	82	57
OCP04	3	45	AGG	89	94	92	64	55	61	17	44	88	92	90	57
OCP05	4	50	AGG	75	84	80	170	76	70	65	70	90	94	92	59
OCP06	4	40	TGG	87	93	90	72	61	59	27	49	90	92	91	64
OCP07	9	45	TGG	78	88	83	114	75	78	42	65	85	91	88	65
OCP08	10	50	AGG	94	98	96	21	64	69	46	60	87	85	86	51
OCP09	10	50	TGG	90	93	92	80	65	56	44	55	82	83	83	65
OCP10	10	50	AGG	86	91	89	87	73	71	48	64	85	90	88	61

FIG. 14A



FIG. 14B

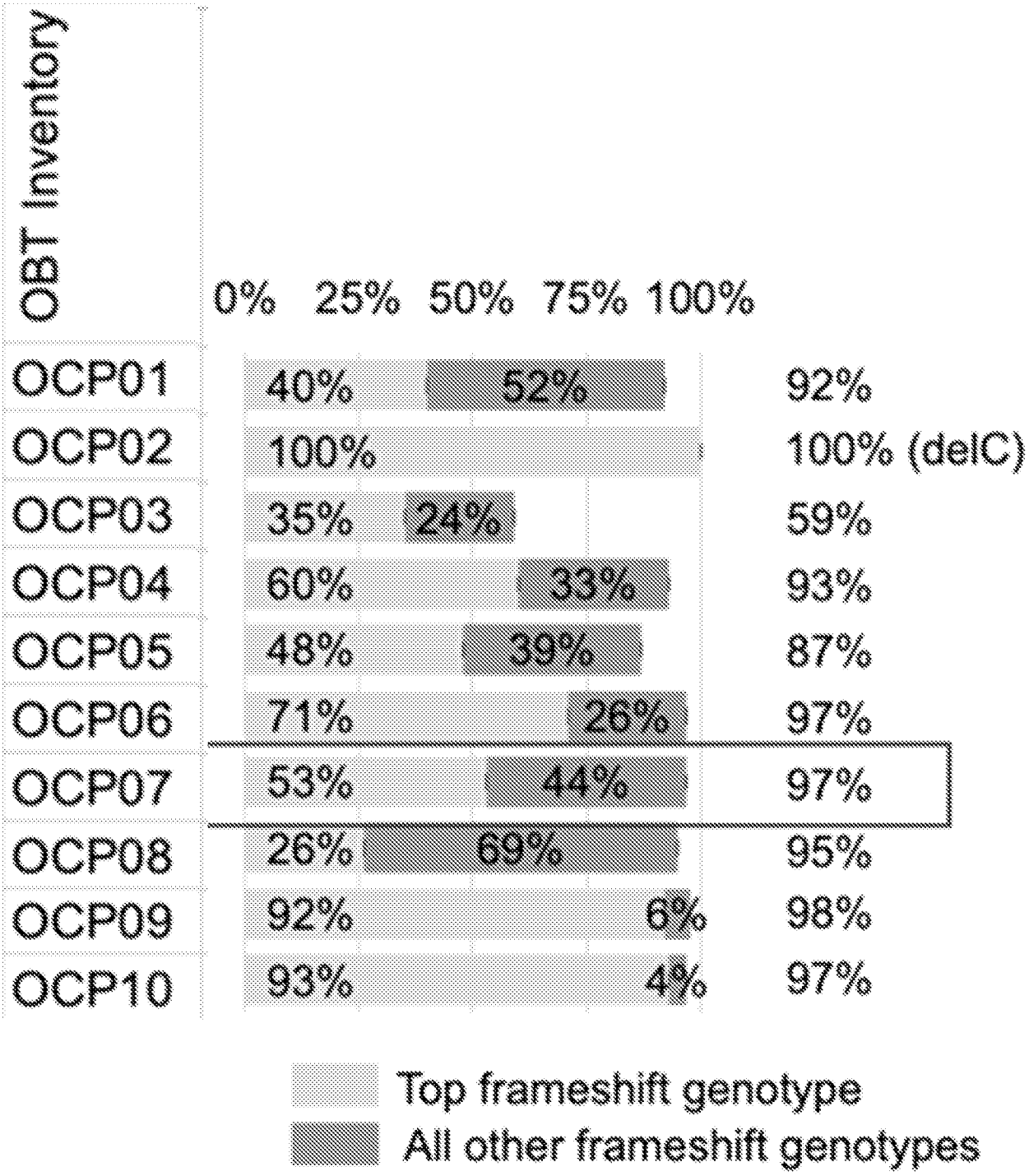

OBT Inventory
0%
25%
50%
75%
100%
OCP01
40%
52%
92%
OCP02
100%
100% (delC)
OCP03
35%
24%
59%
OCP04
60%
33%
93%
OCP05
48%
39%
87%
OCP06
71%
26%
97%
OCP07
53%
44%
97%
OCP08
26%
69%
95%
OCP09
92%
6%
98%
OCP10
93%
4%
97%
Top frameshift genotype
All other frameshift genotypes

FIG. 15

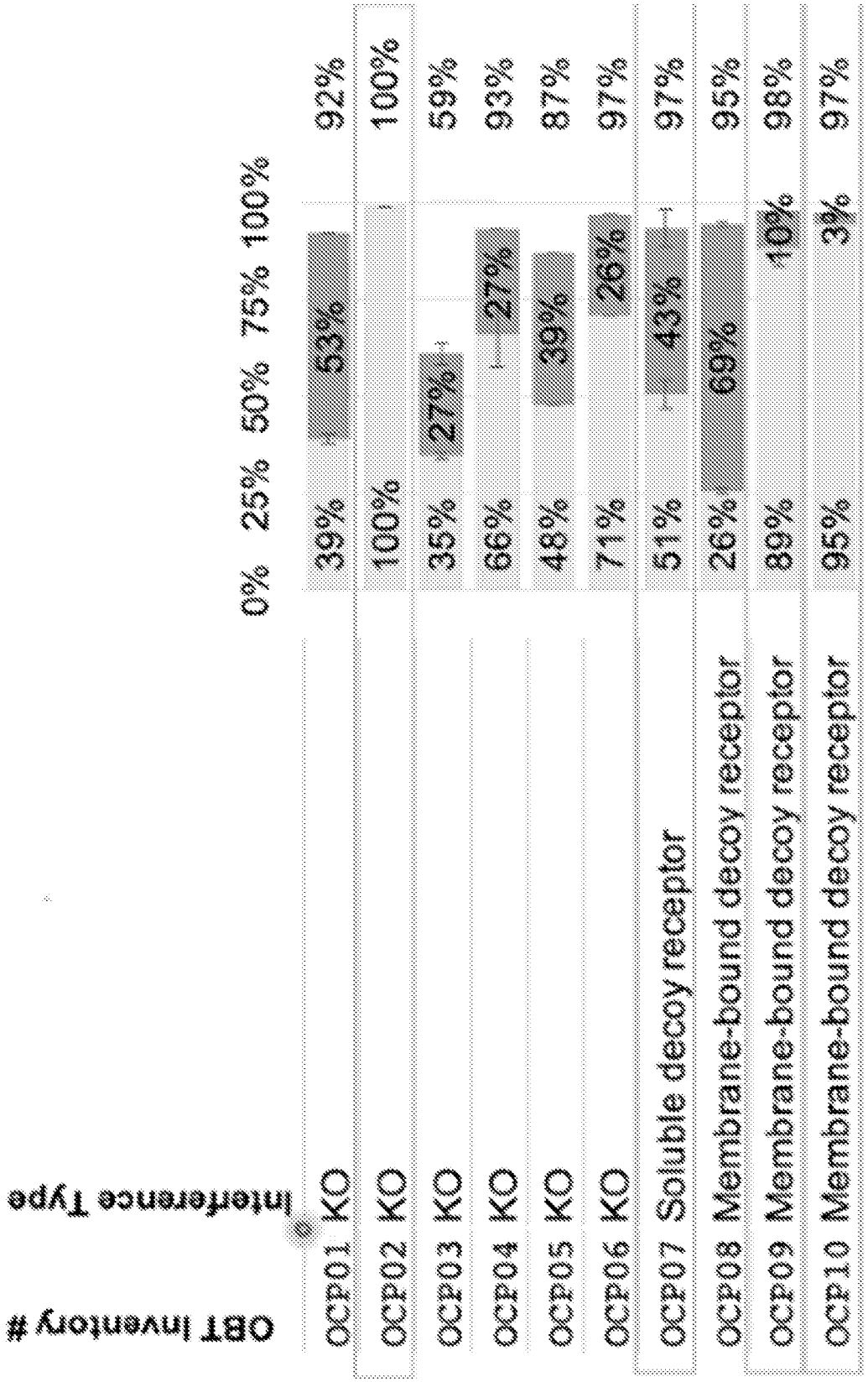

OBT inventory #
Interference Type
OCP01 KO
OCP02 KO
OCP03 KO
OCP04 KO
OCP05 KO
OCP06 KO
OCP07 Soluble decoy receptor
OCP08 Membrane-bound decoy receptor
OCP09 Membrane-bound decoy receptor
OCP10 Membrane-bound decoy receptor
0% 25% 50% 75% 100%
39% 53% 92%
100% 100%
35% 27% 59%
66% 27% 93%
48% 39% 87%
71% 26% 97%
51% 43% 97%
26% 69% 95%
89% 10% 98%
95% 3% 97%
Top edit
All other edits

FIG. 16A

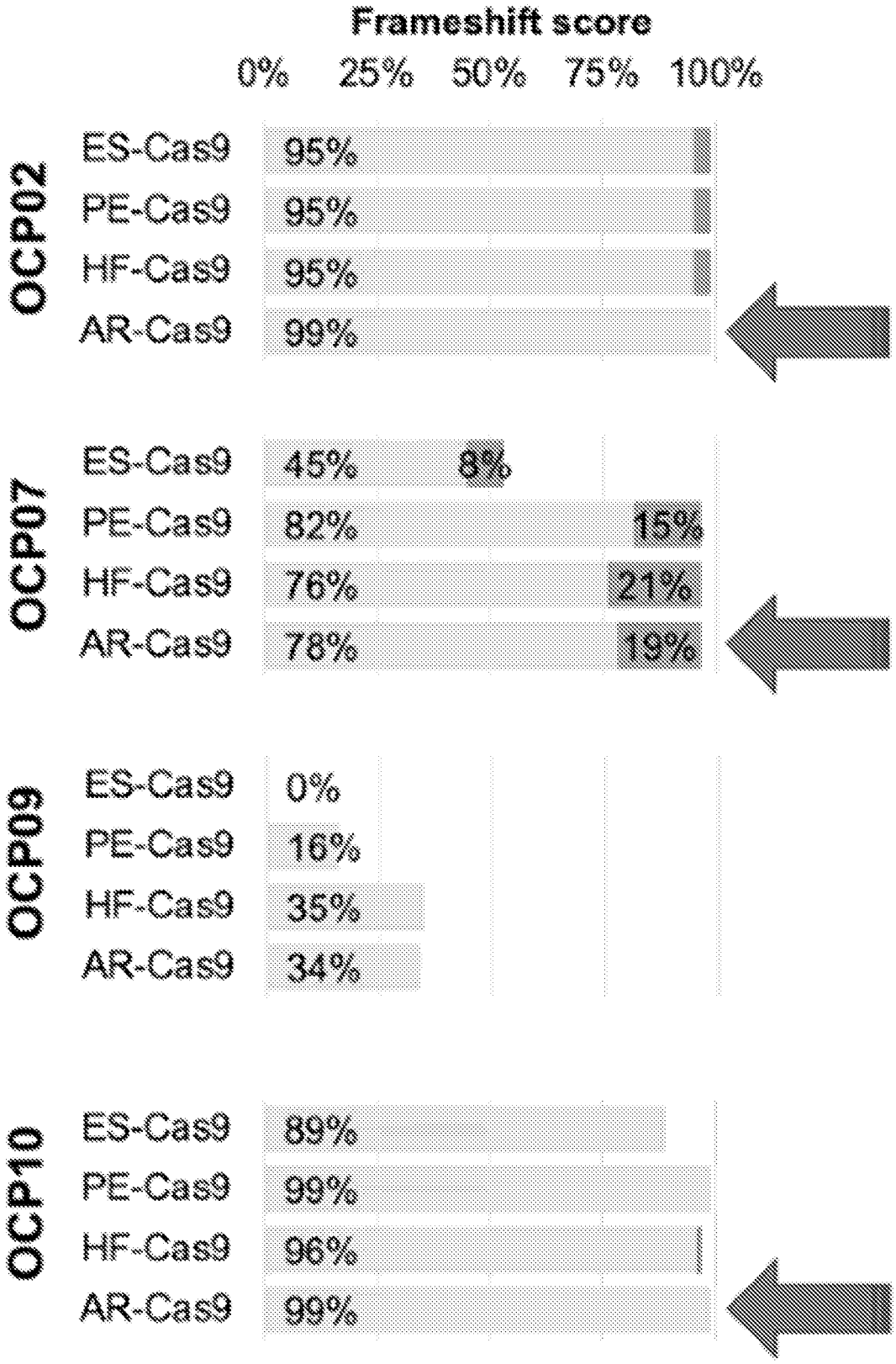

Frameshift score
0%
25%
50%
75%
100%
OCP02
ES-Cas9
PE-Cas9
HF-Cas9
AR-Cas9
95%
95%
95%
99%
OCP07
ES-Cas9
PE-Cas9
HF-Cas9
AR-Cas9
45%
8%
82%
15%
76%
21%
78%
19%
OCP09
ES-Cas9
PE-Cas9
HF-Cas9
AR-Cas9
0%
16%
35%
34%
OCP10
ES-Cas9
PE-Cas9
HF-Cas9
AR-Cas9
89%
99%
96%
99%

FIG. 16B

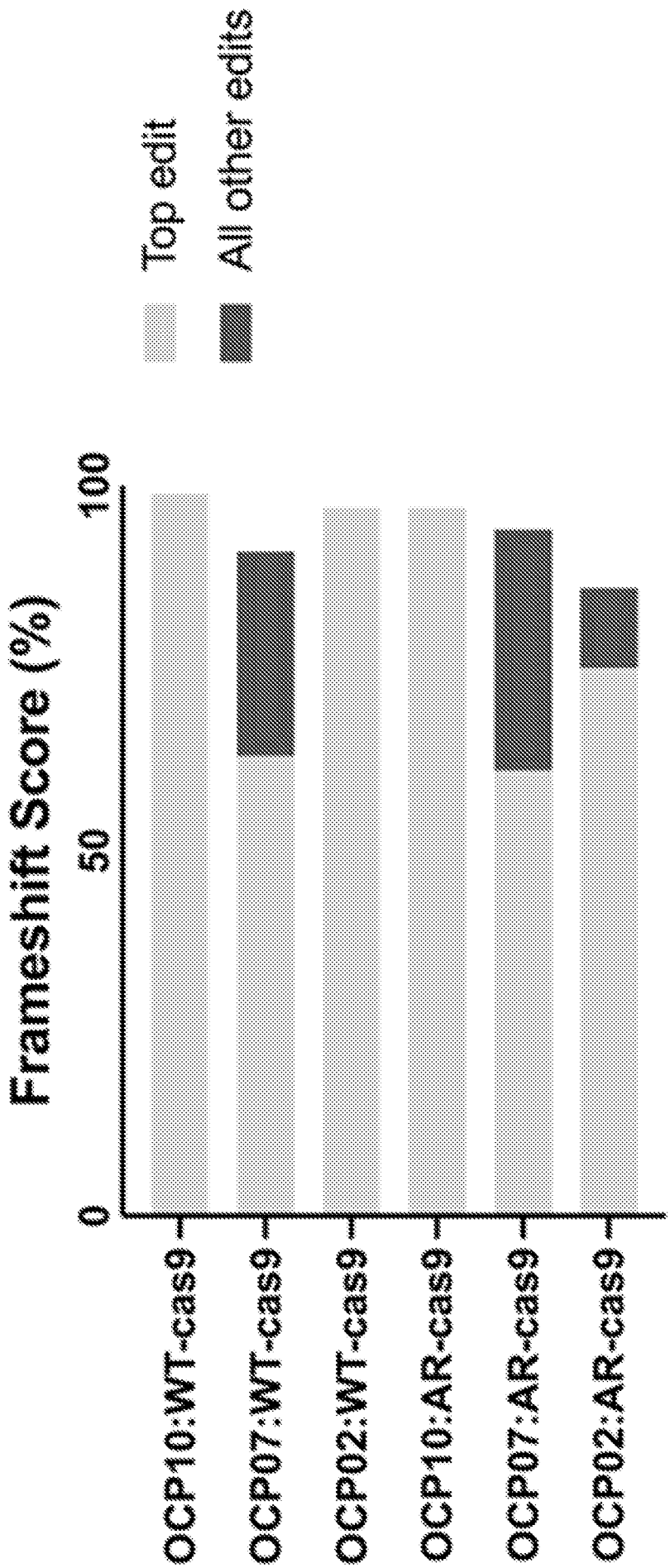

Top edit
All other edits
Frameshift Score (%)
0
50
100
OCP10:WT-cas9
OCP07:WT-cas9
OCP02:WT-cas9
OCP10:AR-cas9
OCP07:AR-cas9
OCP02:AR-cas9

FIG. 16C

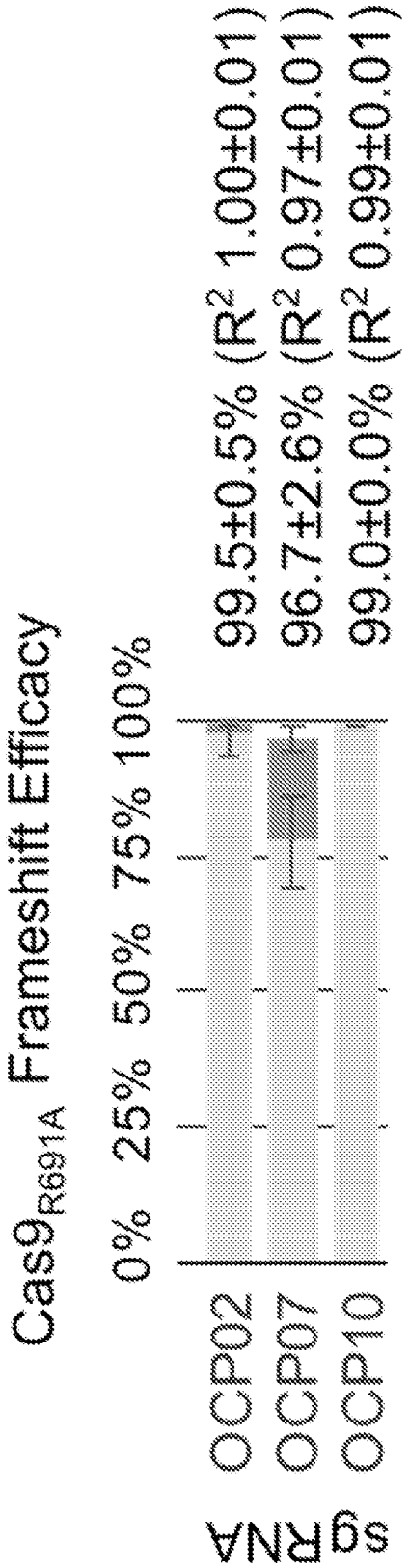

Cas9R691A Frameshift Efficacy
0% 25% 50% 75% 100%
sgRNA
OCP02
OCP07
OCP10
99.5±0.5% (R2 1.00±0.01)
96.7±2.6% (R2 0.97±0.01)
99.0±0.0% (R2 0.99±0.01)
Top frameshift edit
Other frameshift edits

FIG. 17A

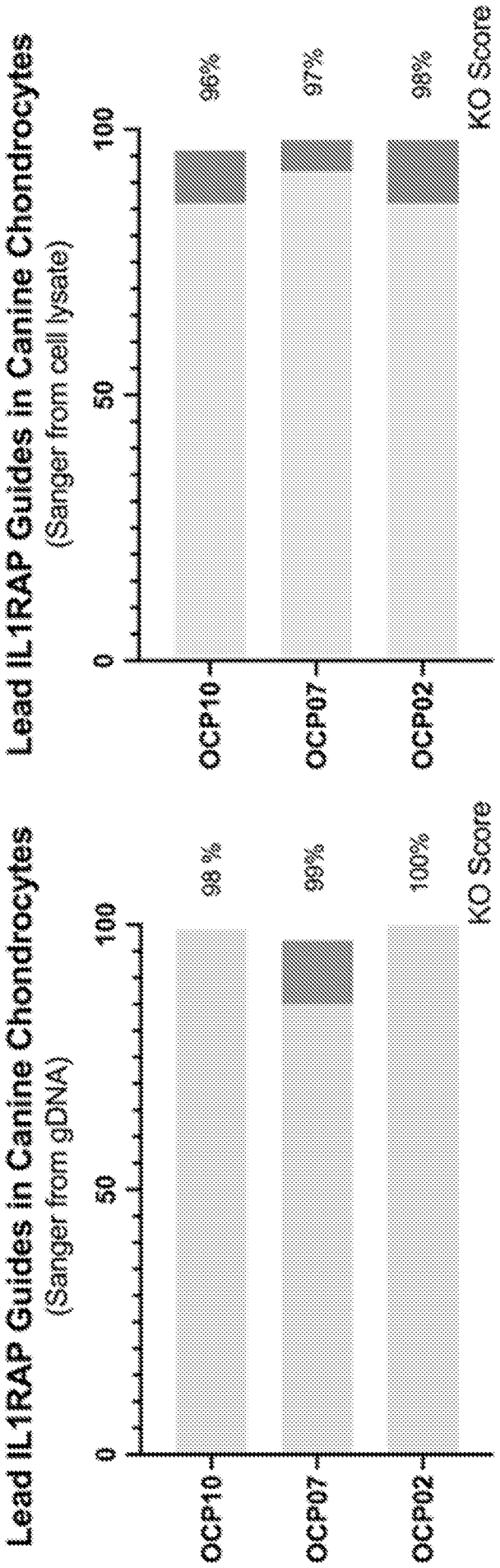

Lead IL1RAP Guides in Canine Chondrocytes
(Sanger from gDNA)
0
50
100
OCP10
OCP07
OCP02
98 %
99%
100%
KO Score
Lead IL1RAP Guides in Canine Chondrocytes
(Sanger from cell lysate)
0
50
100
OCP10
OCP07
OCP02
96%
97%
98%
KO Score

FIG. 17B

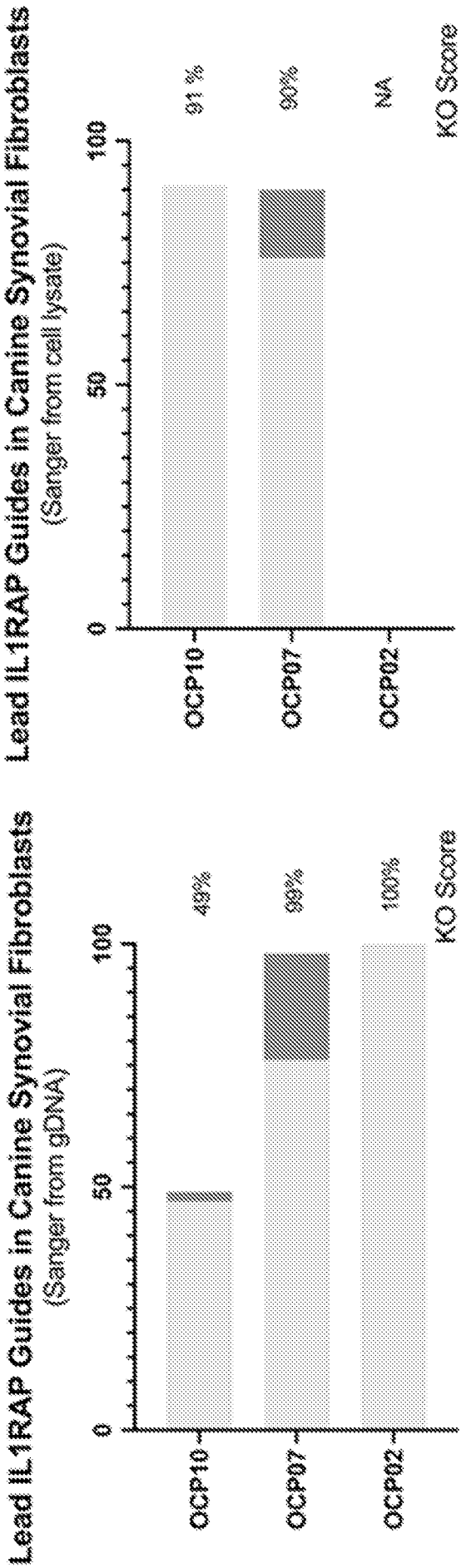

Lead IL1RAP Guides in Canine Synovial Fibroblasts
(Sanger from gDNA)
0
50
100
OCP10
OCP07
OCP02
49%
99%
100%
KO Score
Lead IL1RAP Guides in Canine Synovial Fibroblasts
(Sanger from cell lysate)
0
50
100
OCP10
OCP07
OCP02
91 %
90%
NA
KO Score

FIG. 17C

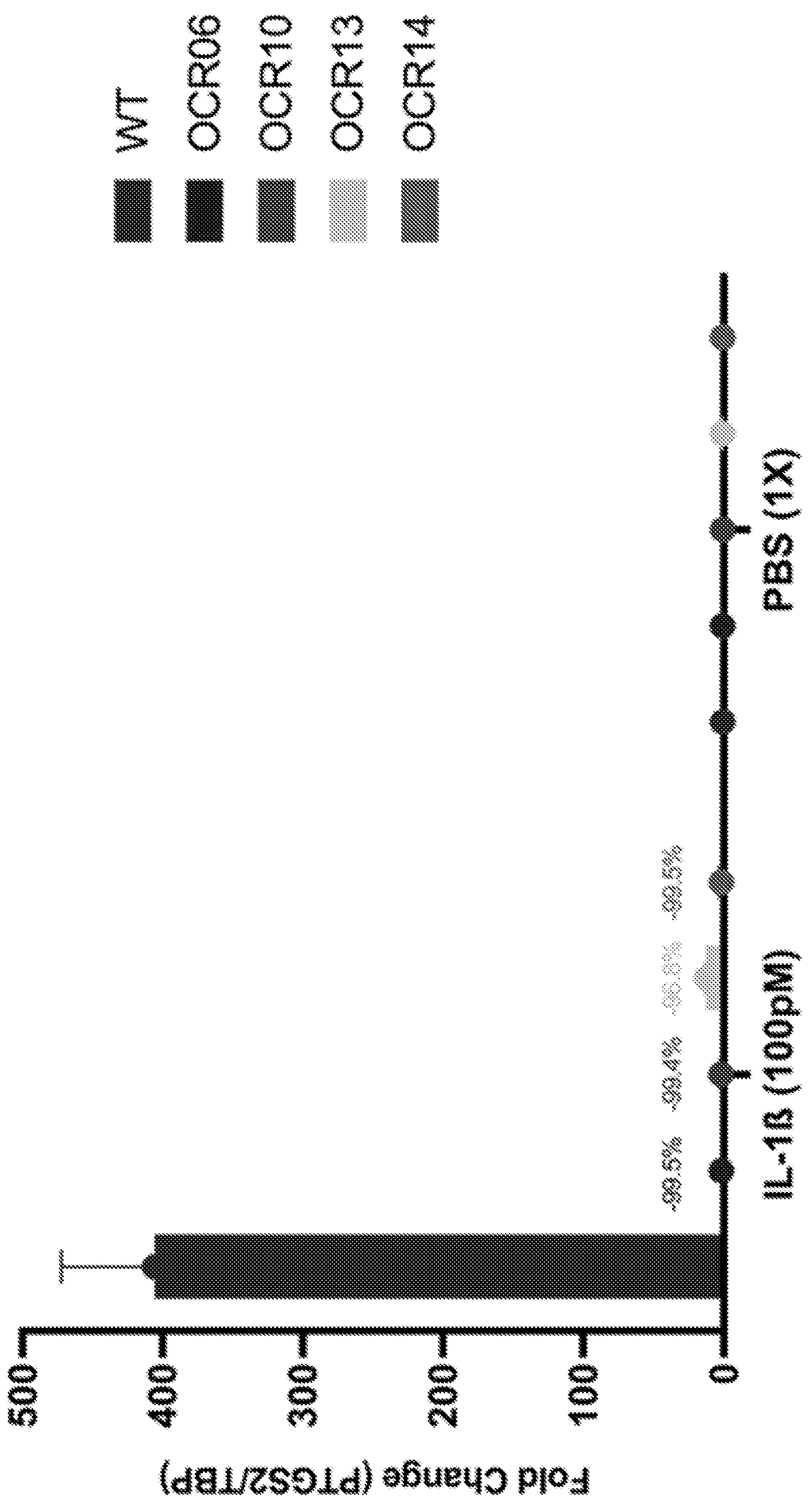

WT
OCR06
OCR10
OCR13
OCR14
Fold Change (PTGS2/TBP)
500
400
300
200
100
0
-99.6%
-99.4%
-99.6%
IL-1ß (100pM)
PBS (1X)

FIG. 18

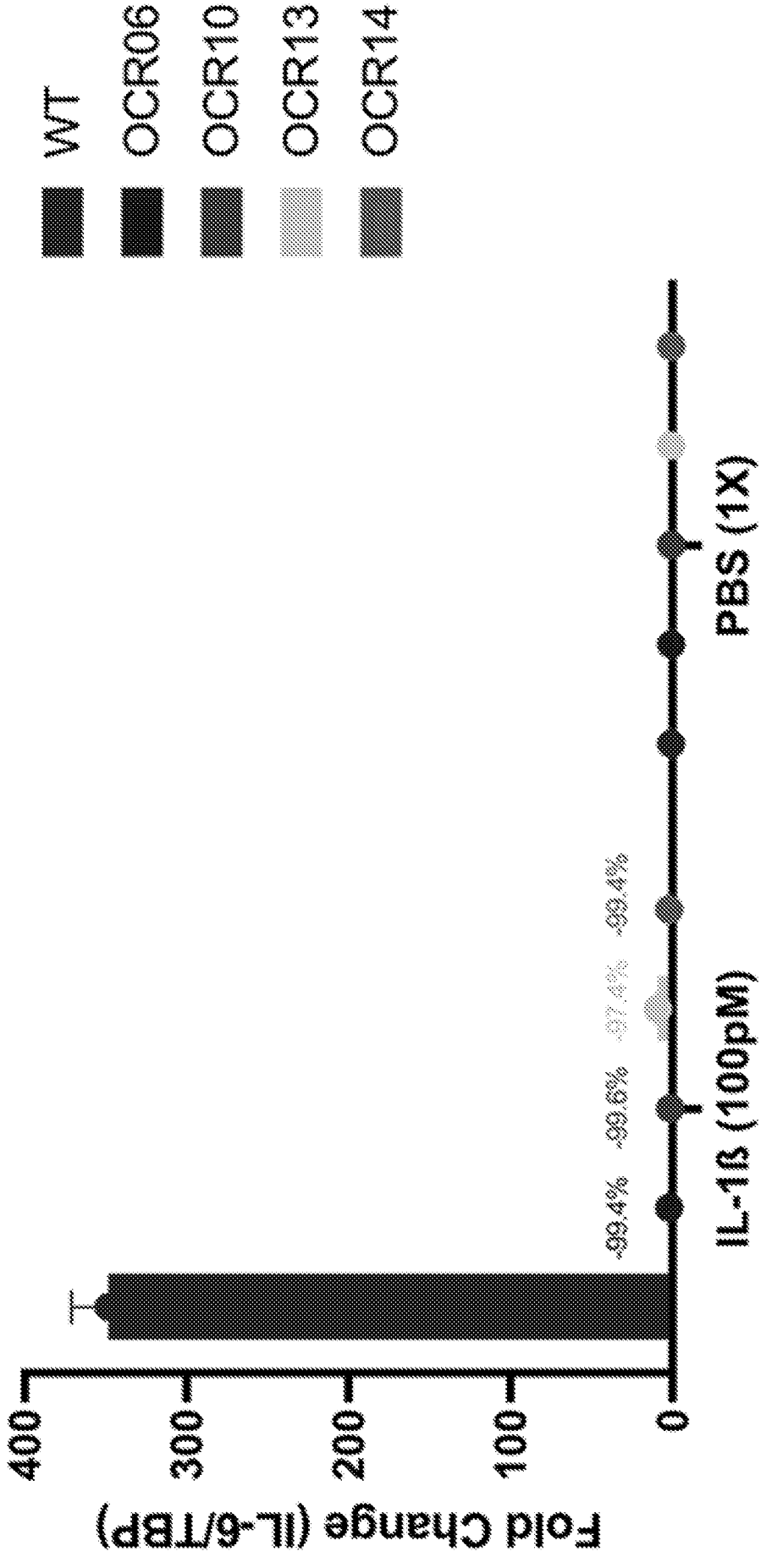

WT
OCR06
OCR10
OCR13
OCR14
Fold Change (IL-6/TBP)
400
300
200
100
0
-99.4%
-99.6%
-97.4%
-99.4%
IL-1β (100pM)
PBS (1X)

FIG. 19

Three IL1RAP lead sgRNAs
1. Cas9$_{RE91A}$ only – Control
2. OCP02::Cas9$_{RE91A}$ – KO
3. OCP07::Cas9$_{RE91A}$ – Soluble DR
4. OCP10::Cas9$_{RE91A}$ – Membrane-bound DR
Three inflammatory triggers
1. LPS (1 µg/ml)
2. IL1B (100 pM)
3. MSU crystals (200 µg/ml)
Three biological replicates (N=3)
LPS & MSU crystals
IL1B
IL1R1
IL1RAP
IL1RAP
IL1RAP
Global differential gene expression analysis (RNA-Seq)

FIG. 20

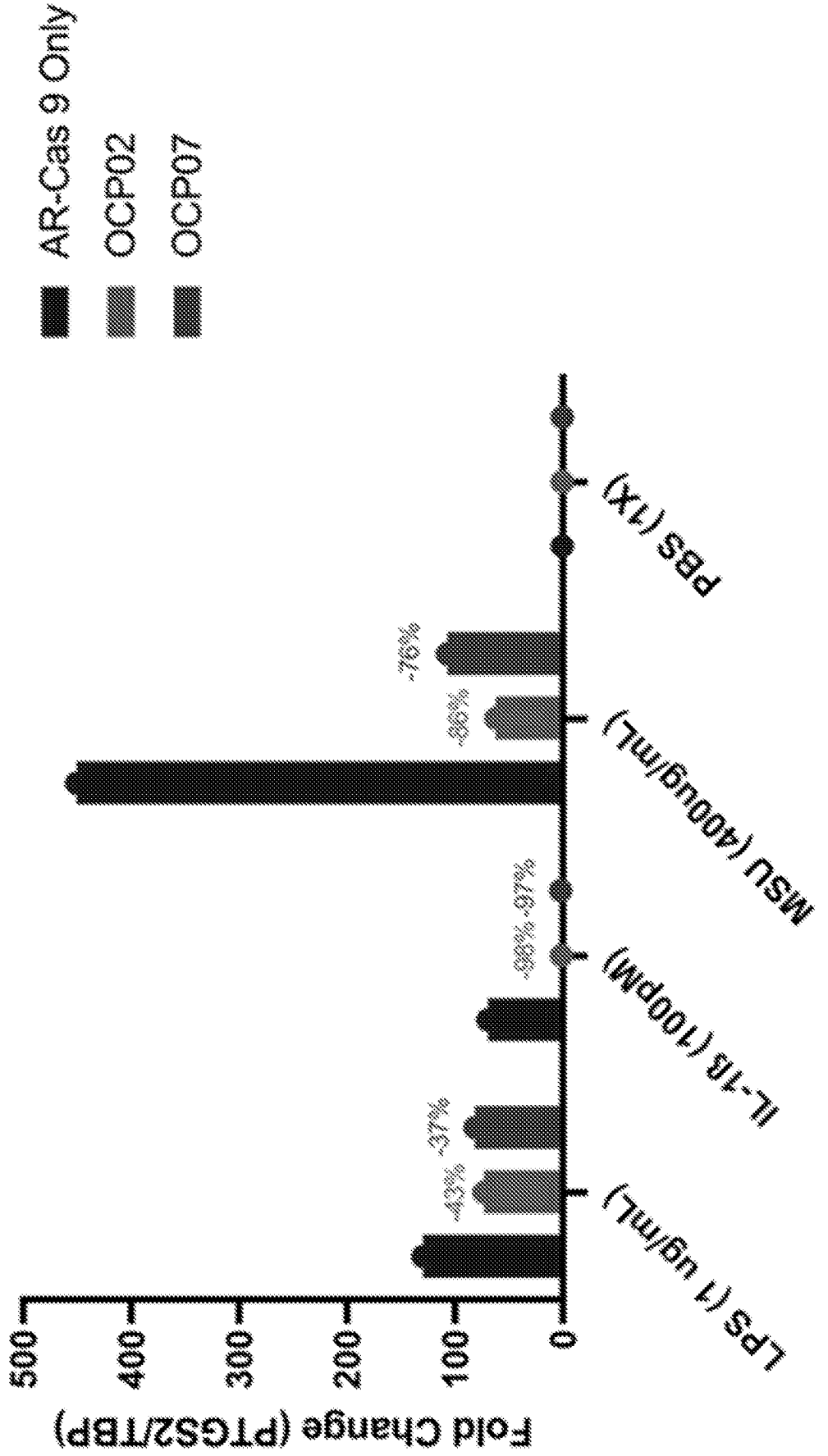

AR-Cas 9 Only
OCP02
OCP07
Fold Change (PTGS2/TBP)
500
400
300
200
100
0
LPS (1 ug/mL)
IL-1β (100pM)
MSU (400ug/mL)
PBS (1X)
-43%
-37%
-69%
-97%
-49%
-76%

FIG. 21A

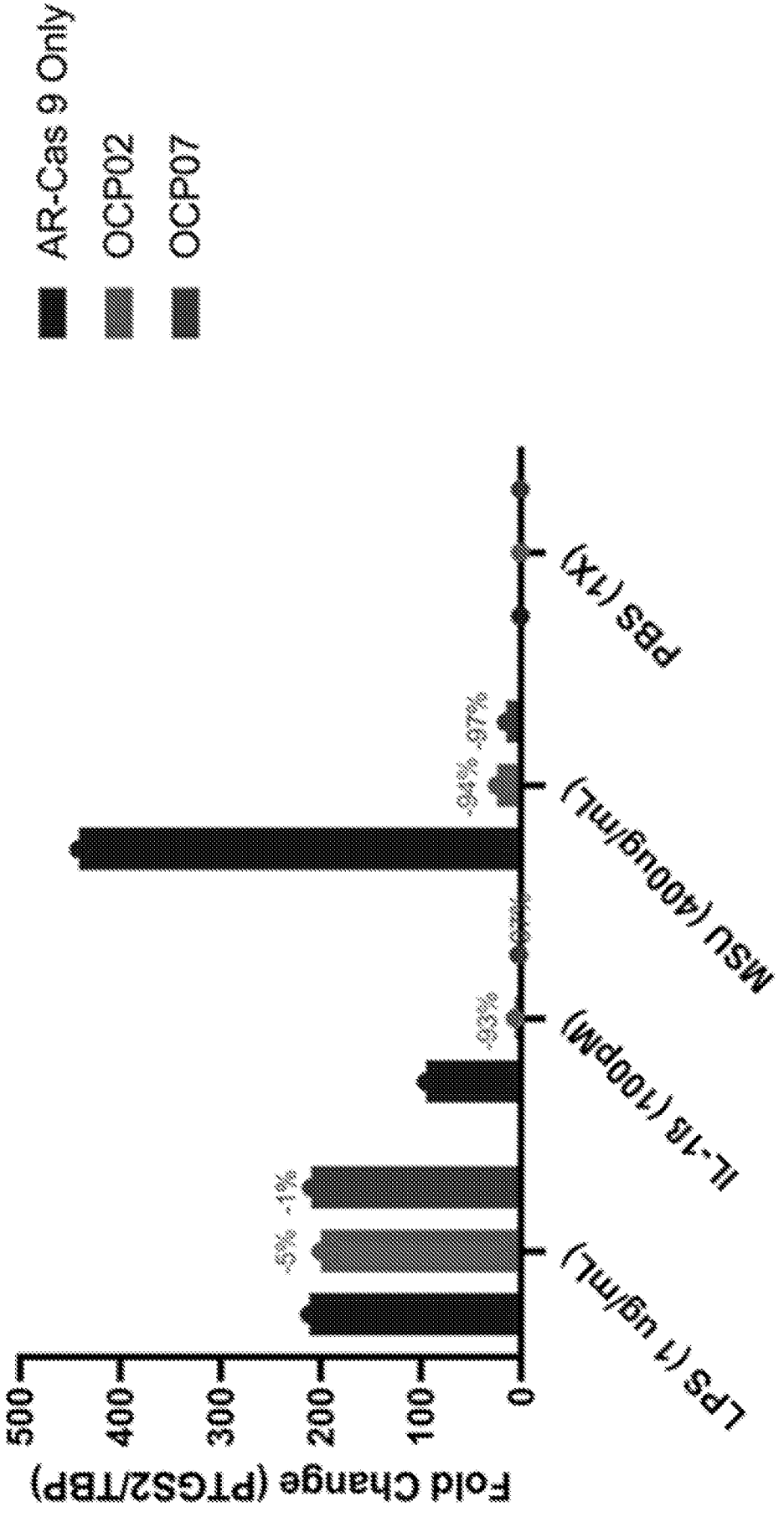

AR-Cas 9 Only
OCP02
OCP07
Fold change (PTGS2/TBP)
500
400
300
200
100
0
LPS (1 ug/mL)
IL-1B (100pM)
MSU (400ug/mL)
PBS (1X)
-6%
-1%
-55%
-94%
-97%

FIG. 21B

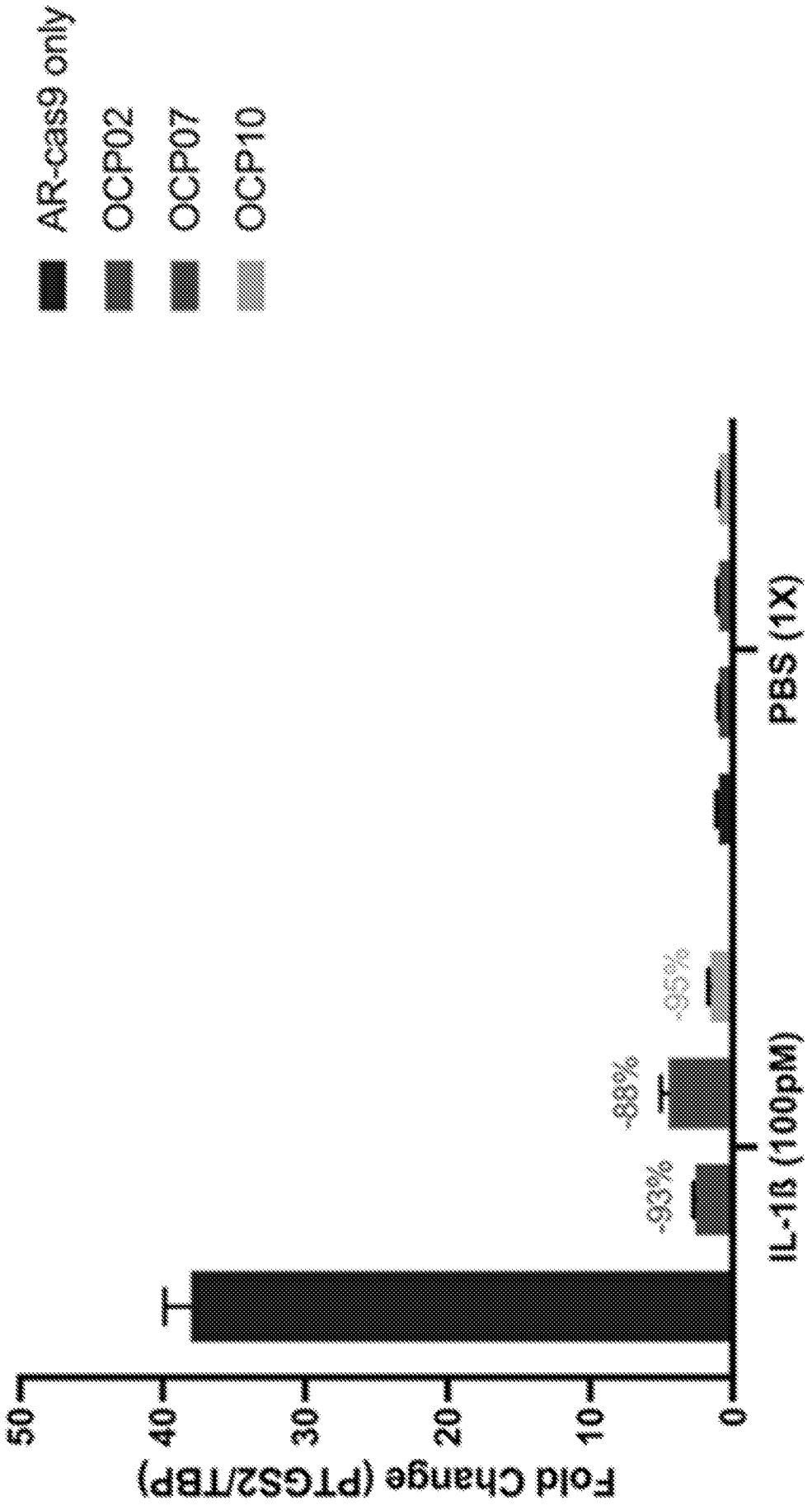

AR-cas9 only
OCP02
OCP07
OCP10
Fold Change (PTGS2/TBP)
0
10
20
30
40
50
-93%
-88%
-95%
IL-1β (100pM)
PBS (1X)

FIG. 22A

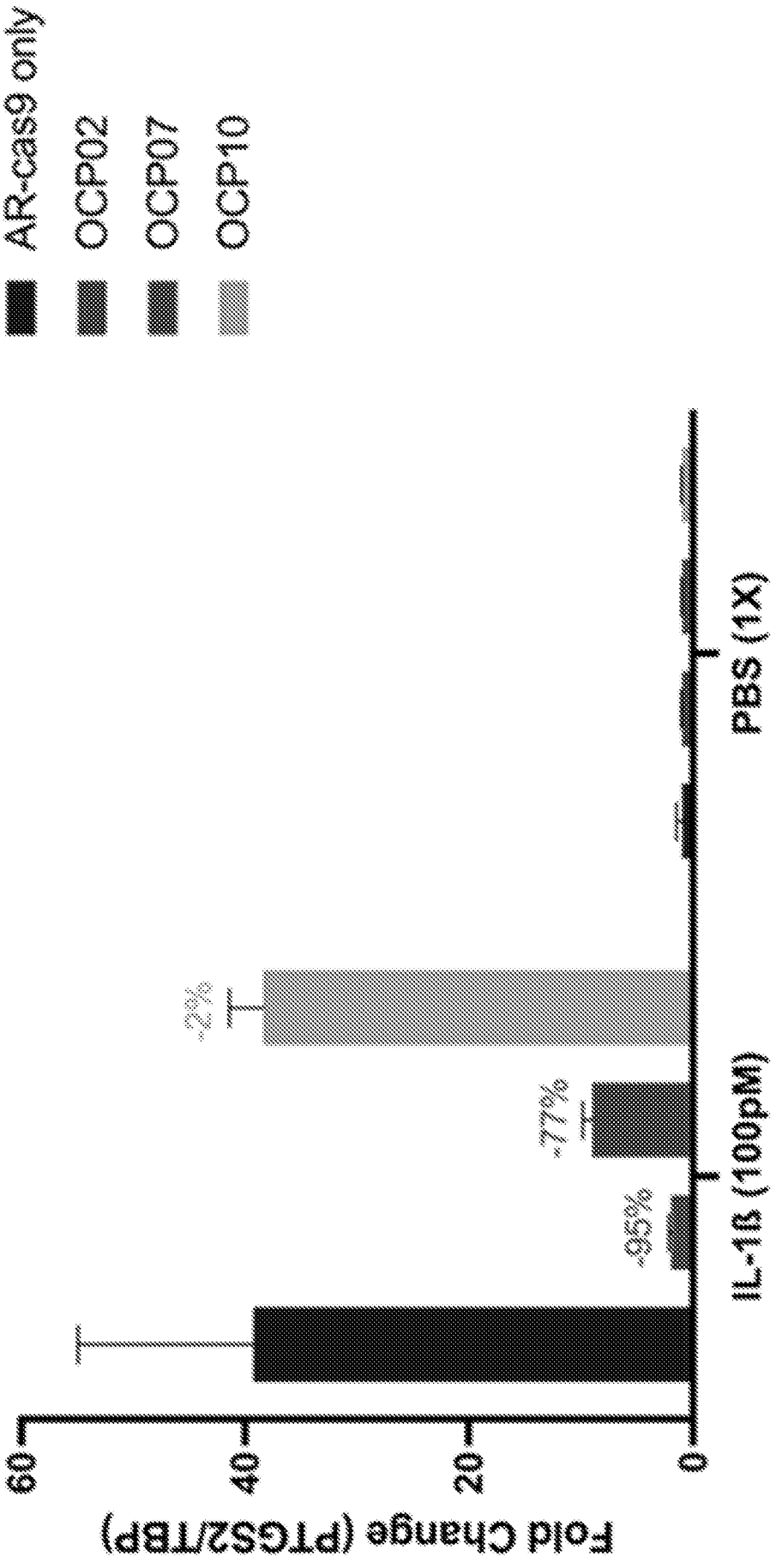

AR-cas9 only
OCP02
OCP07
OCP10
Fold Change (PTGS2/TBP)
60
40
20
0
IL-1ß (100pM)
PBS (1X)
-95%
-77%
-2%

FIG. 22B

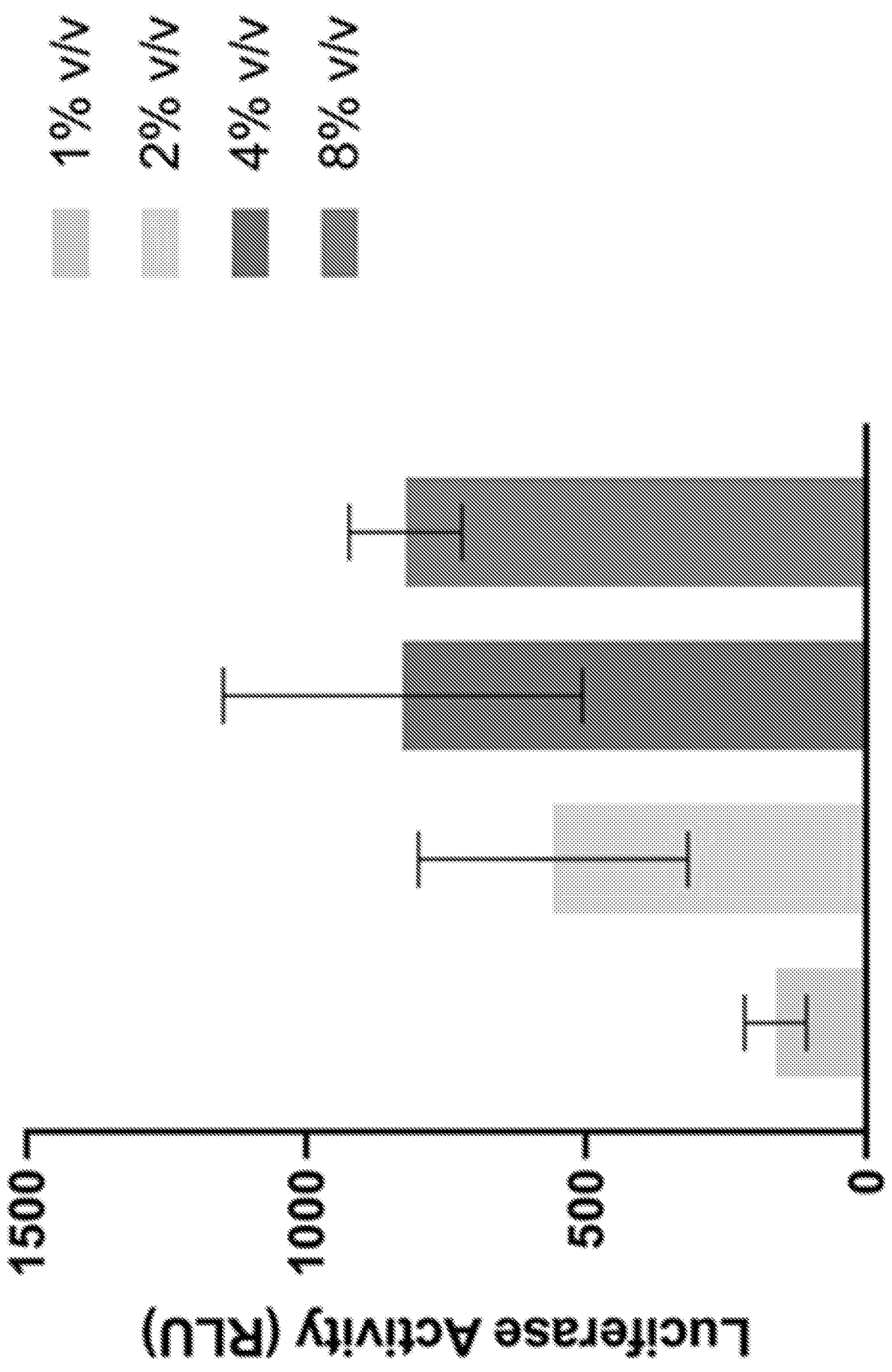


FIG. 23A

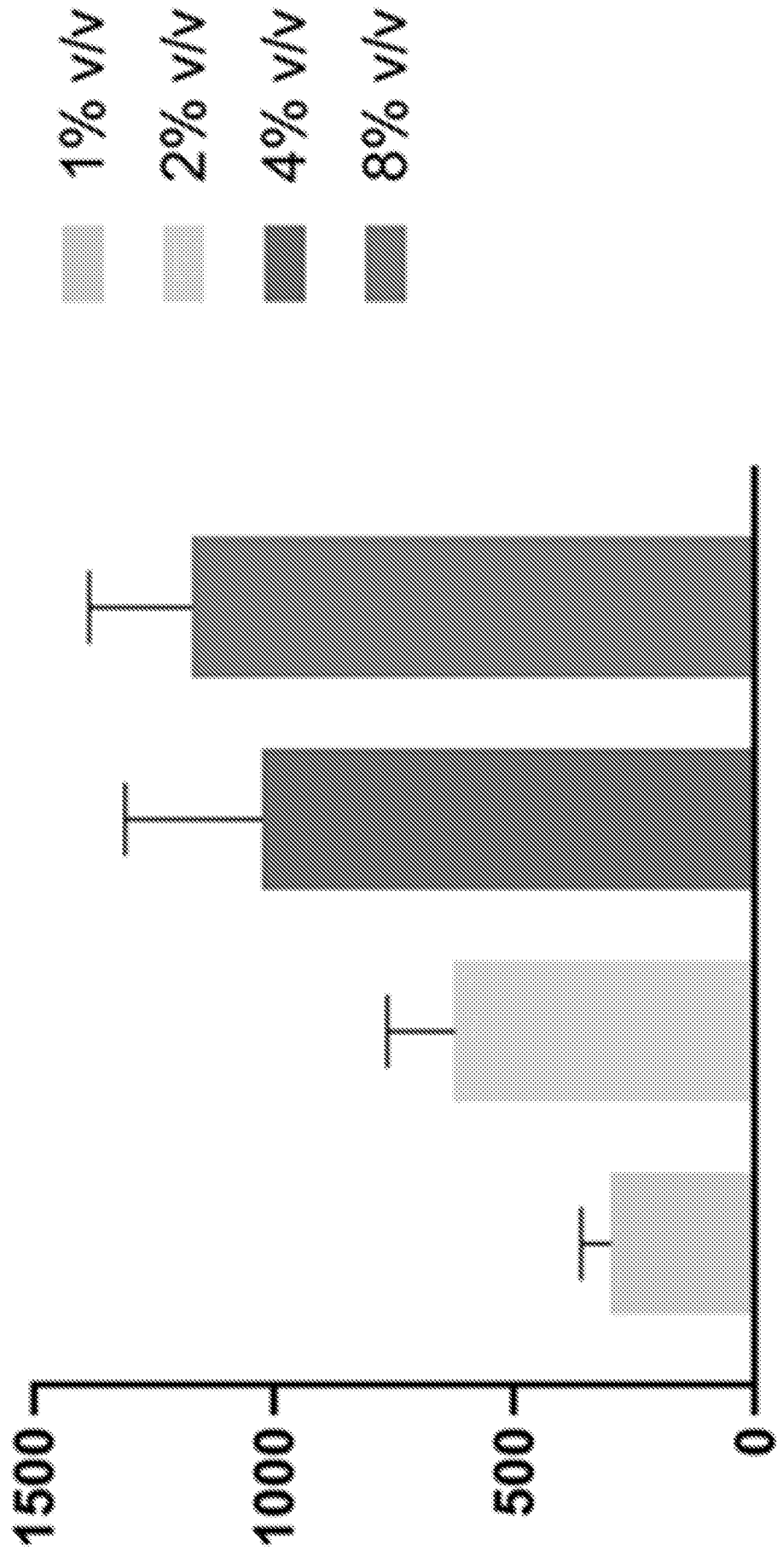


FIG. 23B

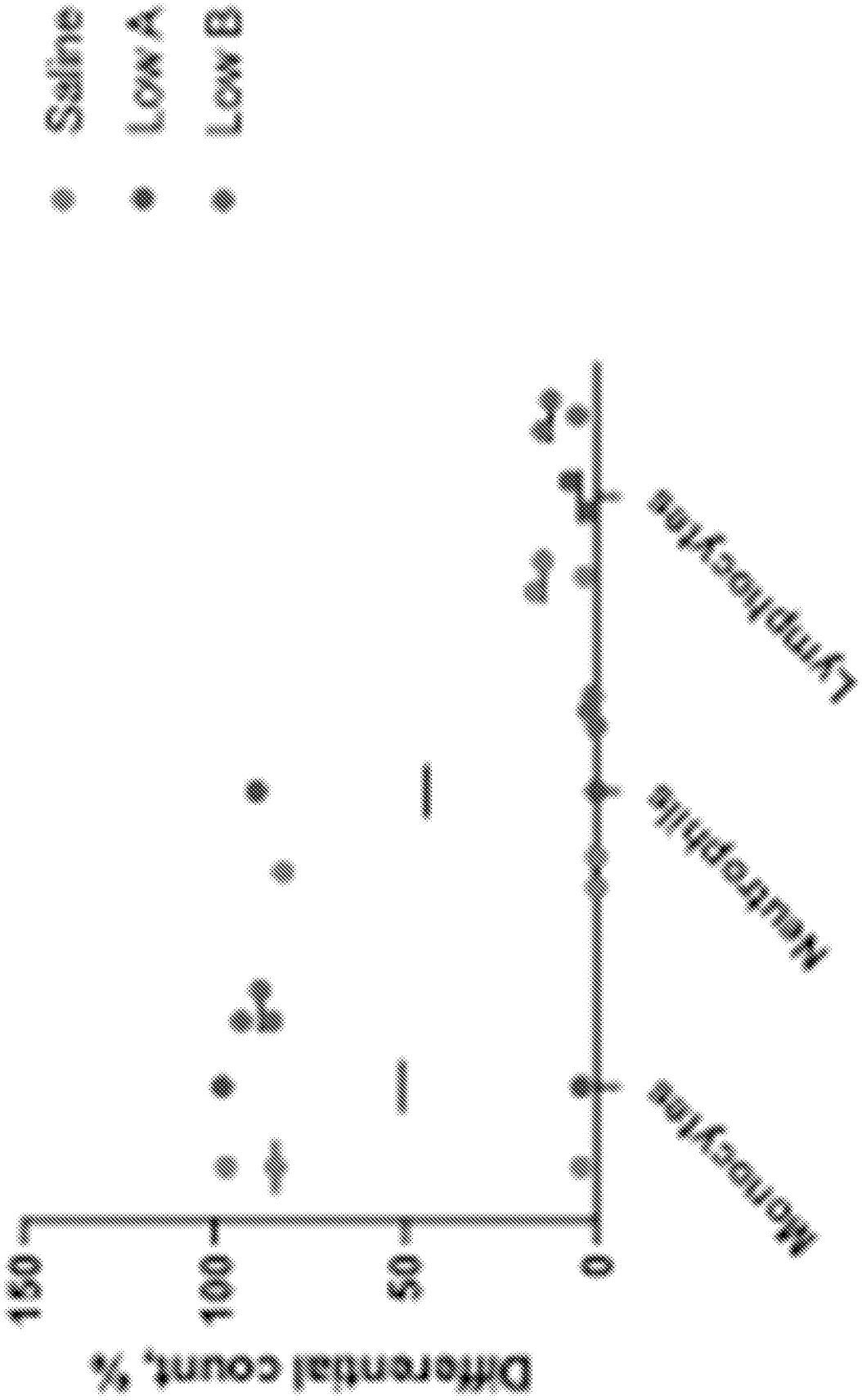

Saline
Low A
Low B
Differential count, %
150
100
50
0
Monocytes
Neutrophils
Lymphocytes

FIG. 24A

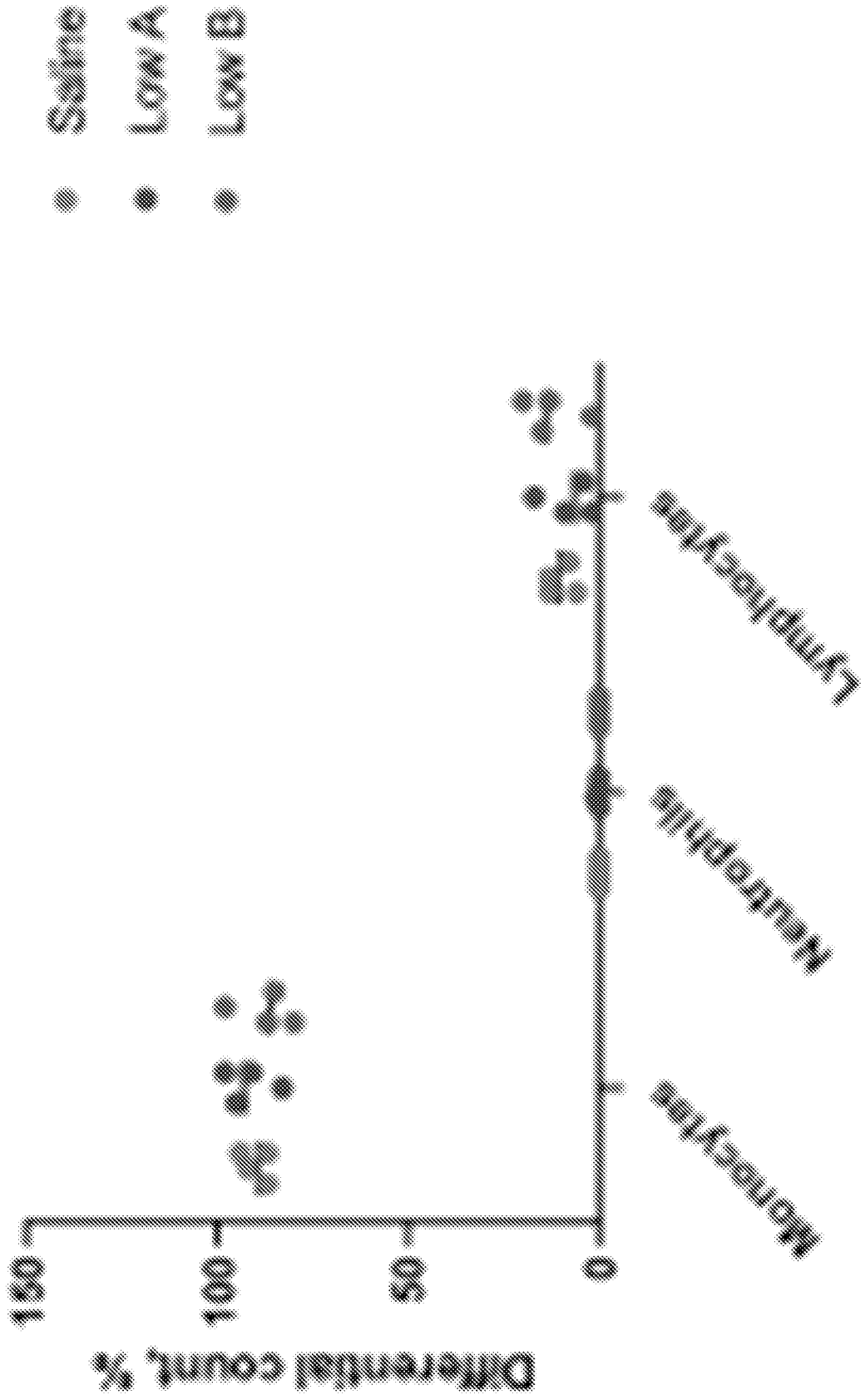

Saline
Low A
Low B
Differential count, %
150
100
50
0
Monocytes
Neutrophils
Lymphocytes

FIG. 24B

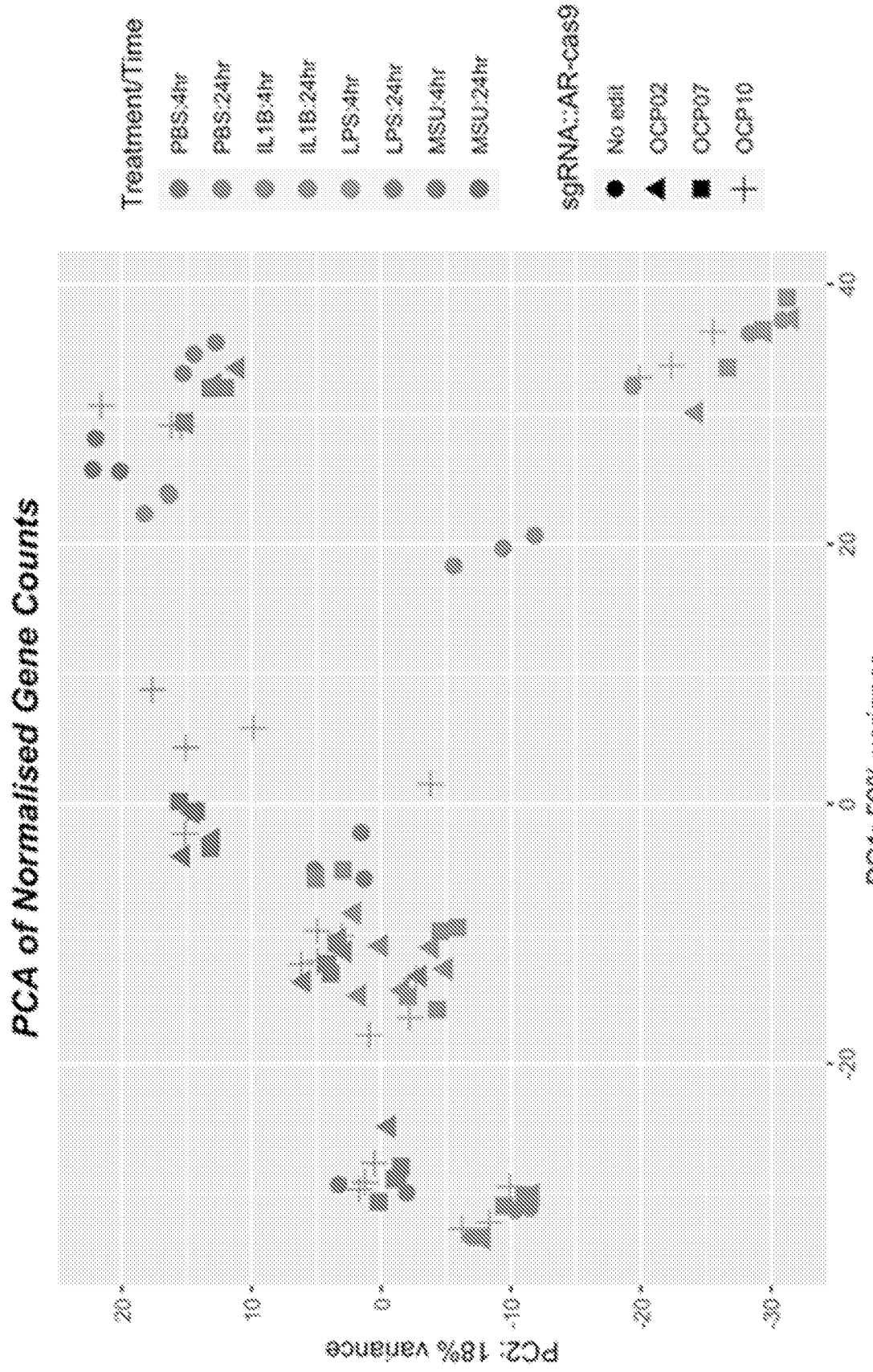

PCA of Normalised Gene Counts
Treatment/Time
PBS:4hr
PBS:24hr
IL1B:4hr
IL1B:24hr
LPS:4hr
LPS:24hr
MSU:4hr
MSU:24hr
sgRNA::AR-cas9
No edit
OCP02
OCP07
OCP10
PC2: 18% variance
PC1: 59% variance
20
10
0
-10
-20
-30
-20
0
20
40

FIG. 25A

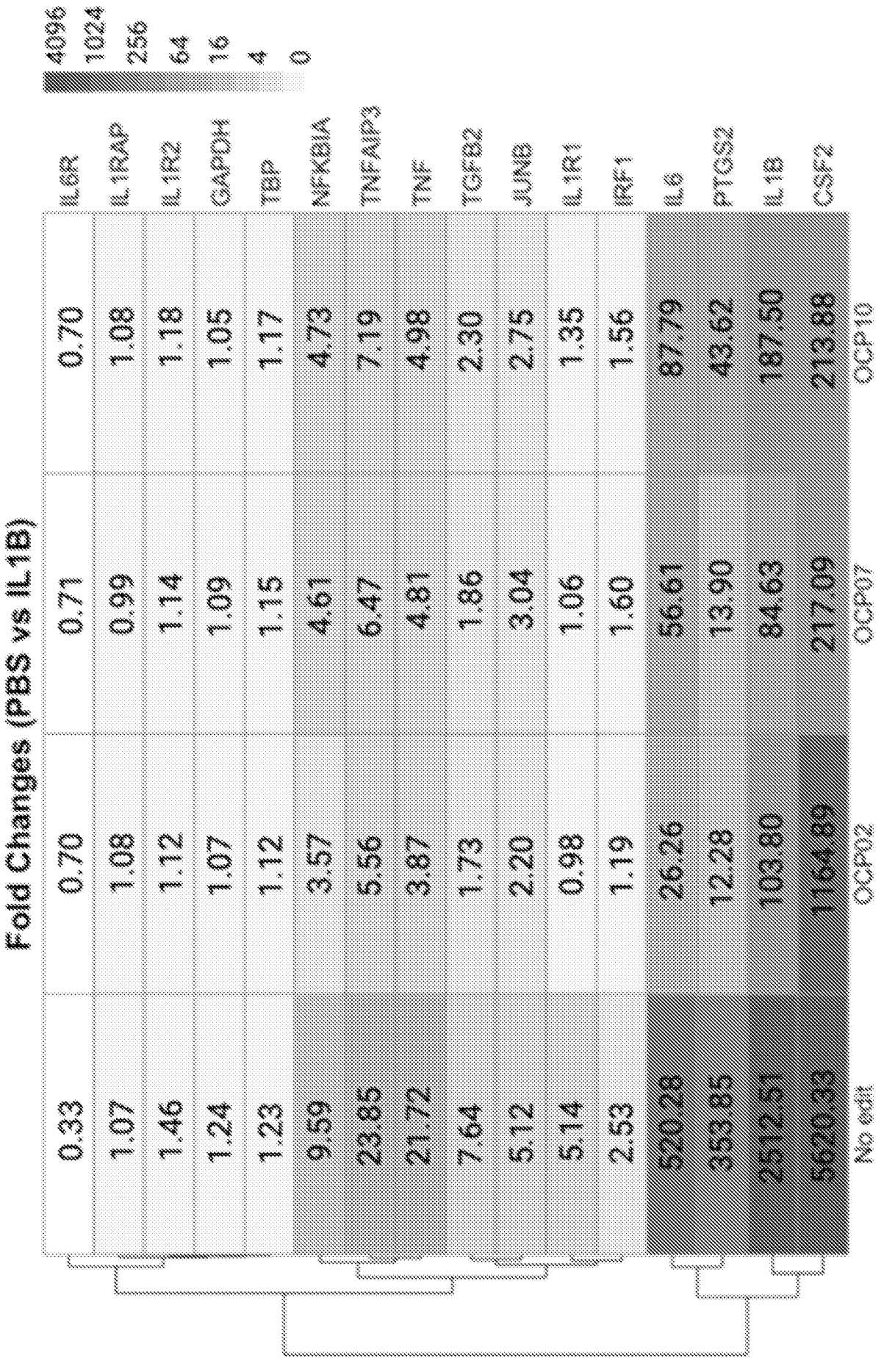

Fold Changes (PBS vs IL1B)
4096
1024
256
64
16
4
0
IL6R
IL1RAP
IL1R2
GAPDH
TBP
NFKBIA
TNFAIP3
TNF
TGFB2
JUNB
IL1R1
IRF1
IL6
PTGS2
IL1B
CSF2
0.33 0.70 0.71 0.70
1.07 1.08 0.99 1.08
1.46 1.12 1.14 1.18
1.24 1.07 1.09 1.05
1.23 1.12 1.15 1.17
9.59 3.57 4.61 4.73
23.85 5.56 6.47 7.19
21.72 3.87 4.81 4.98
7.64 1.73 1.86 2.30
5.12 2.20 3.04 2.75
5.14 0.98 1.06 1.35
2.53 1.19 1.60 1.56
520.28 26.26 56.61 87.79
353.85 12.28 13.90 43.62
2512.51 103.80 84.63 187.50
5620.33 1164.89 217.09 213.88
No edit
OCP02
OCP07
OCP10

FIG. 25B

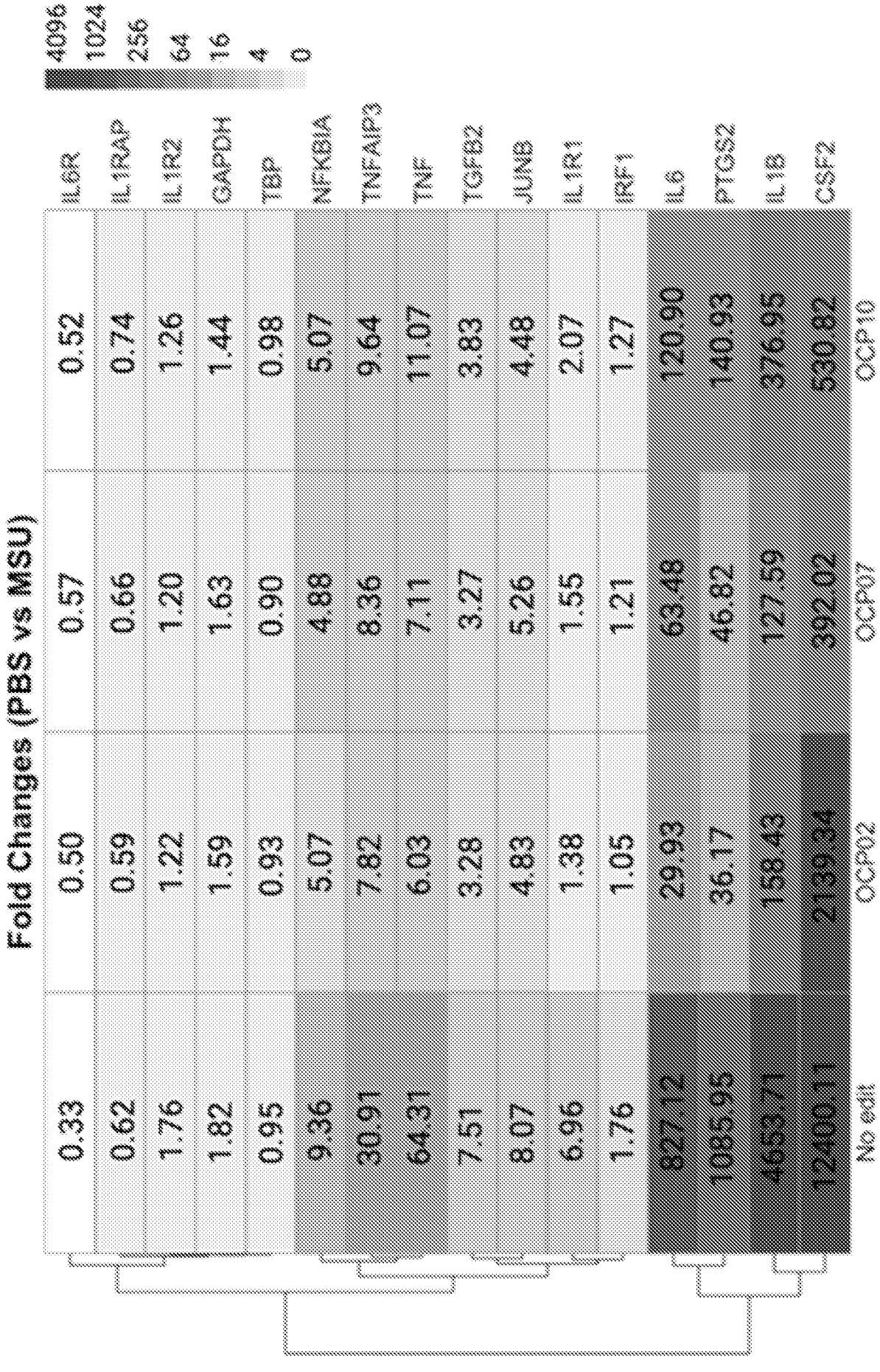

Fold Changes (PBS vs MSU)
4096
1024
256
64
16
4
0
IL6R
IL1RAP
IL1R2
GAPDH
TBP
NFKBIA
TNFAIP3
TNF
TGFB2
JUNB
IL1R1
IRF1
IL6
PTGS2
IL1B
CSF2
0.33 0.50 0.57 0.52
0.62 0.59 0.66 0.74
1.76 1.22 1.20 1.26
1.82 1.59 1.63 1.44
0.95 0.93 0.90 0.98
9.36 5.07 4.88 5.07
30.91 7.82 8.36 9.64
64.31 6.03 7.11 11.07
7.51 3.28 3.27 3.83
8.07 4.83 5.26 4.48
6.96 1.38 1.55 2.07
1.76 1.05 1.21 1.27
827.12 29.93 63.48 120.90
1085.95 36.17 46.82 140.93
465.71 158.43 127.59 376.95
1240.11 213.24 392.02 530.82
No edit
OCP02
OCP07
OCP10

FIG. 25C

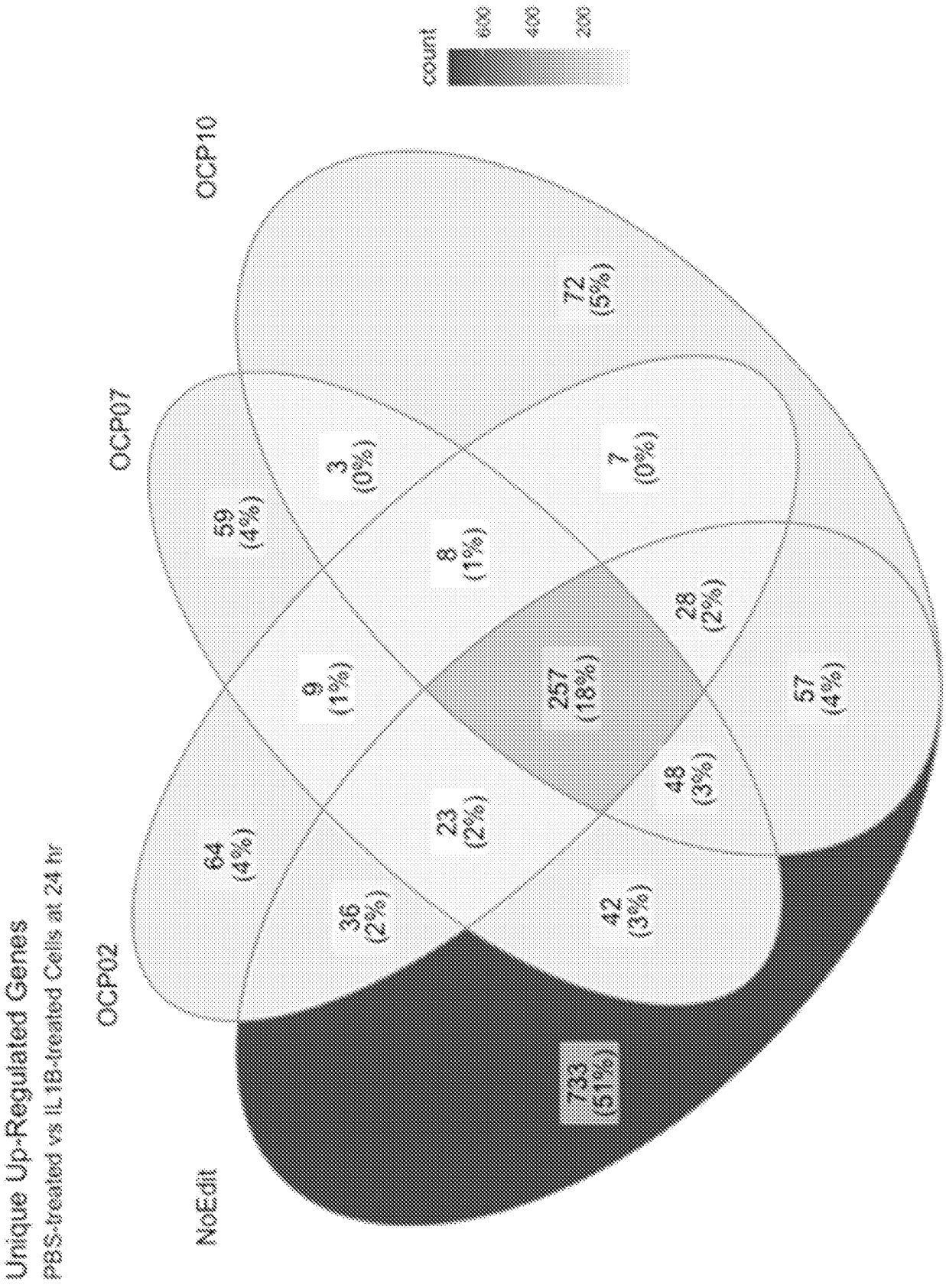

Unique Up-Regulated Genes
PBS-treated vs IL1B-treated Cells at 24 hr
NoEdit
OCP02
OCP07
OCP10
count
600
400
200
733 (51%)
64 (4%)
59 (4%)
72 (5%)
36 (2%)
9 (1%)
3 (0%)
23 (2%)
8 (1%)
7 (0%)
257 (18%)
28 (2%)
42 (3%)
48 (3%)
57 (4%)

FIG. 25D

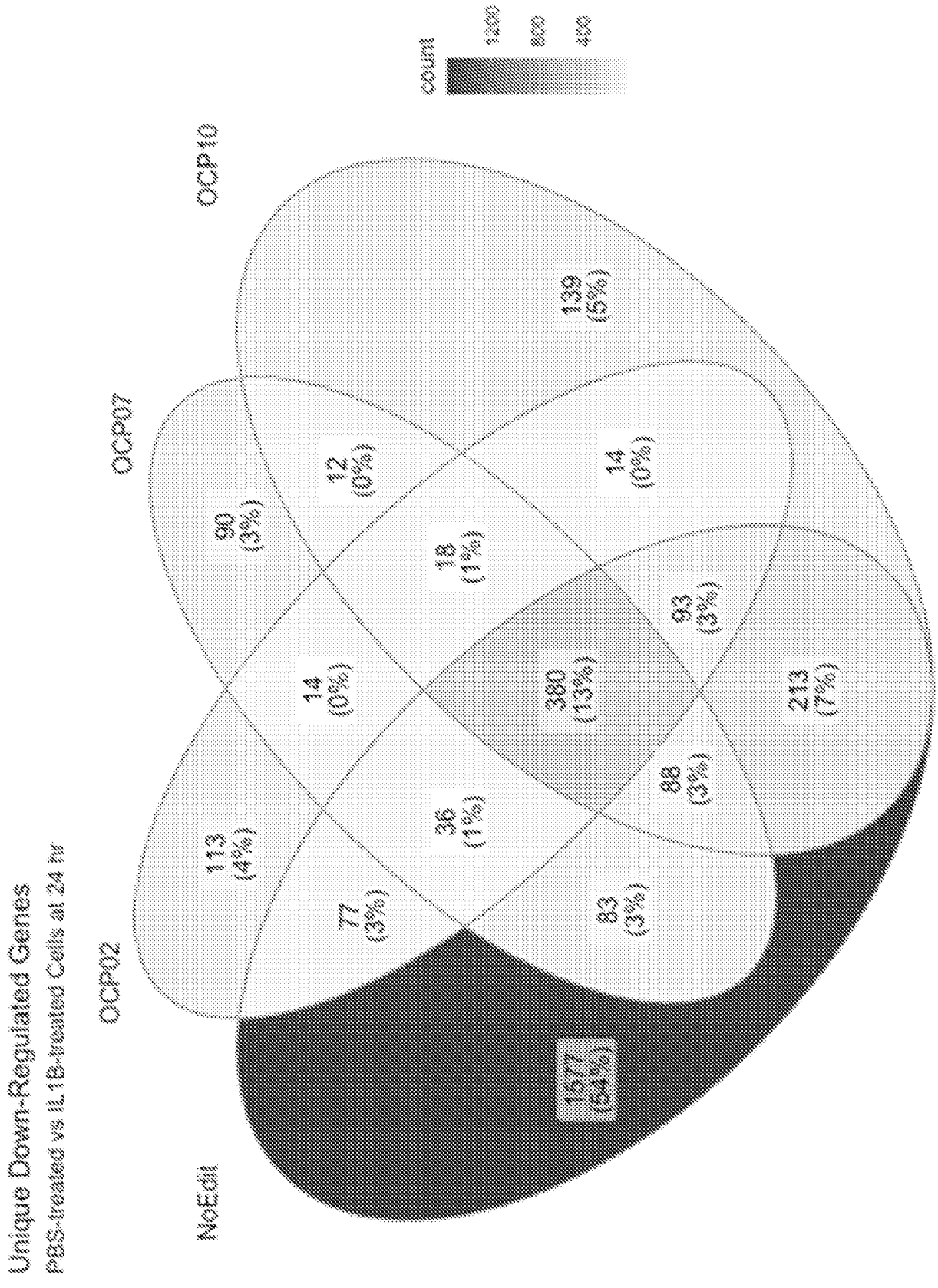

Unique Down-Regulated Genes
PBS-treated vs IL1B-treated Cells at 24 hr
NoEdit
OCP02
OCP07
OCP10
count
1200
800
400
1377
(54%)
113
(4%)
77
(3%)
36
(1%)
83
(3%)
90
(3%)
12
(0%)
14
(0%)
18
(1%)
380
(13%)
88
(3%)
14
(0%)
93
(3%)
213
(7%)
139
(5%)

FIG. 25E

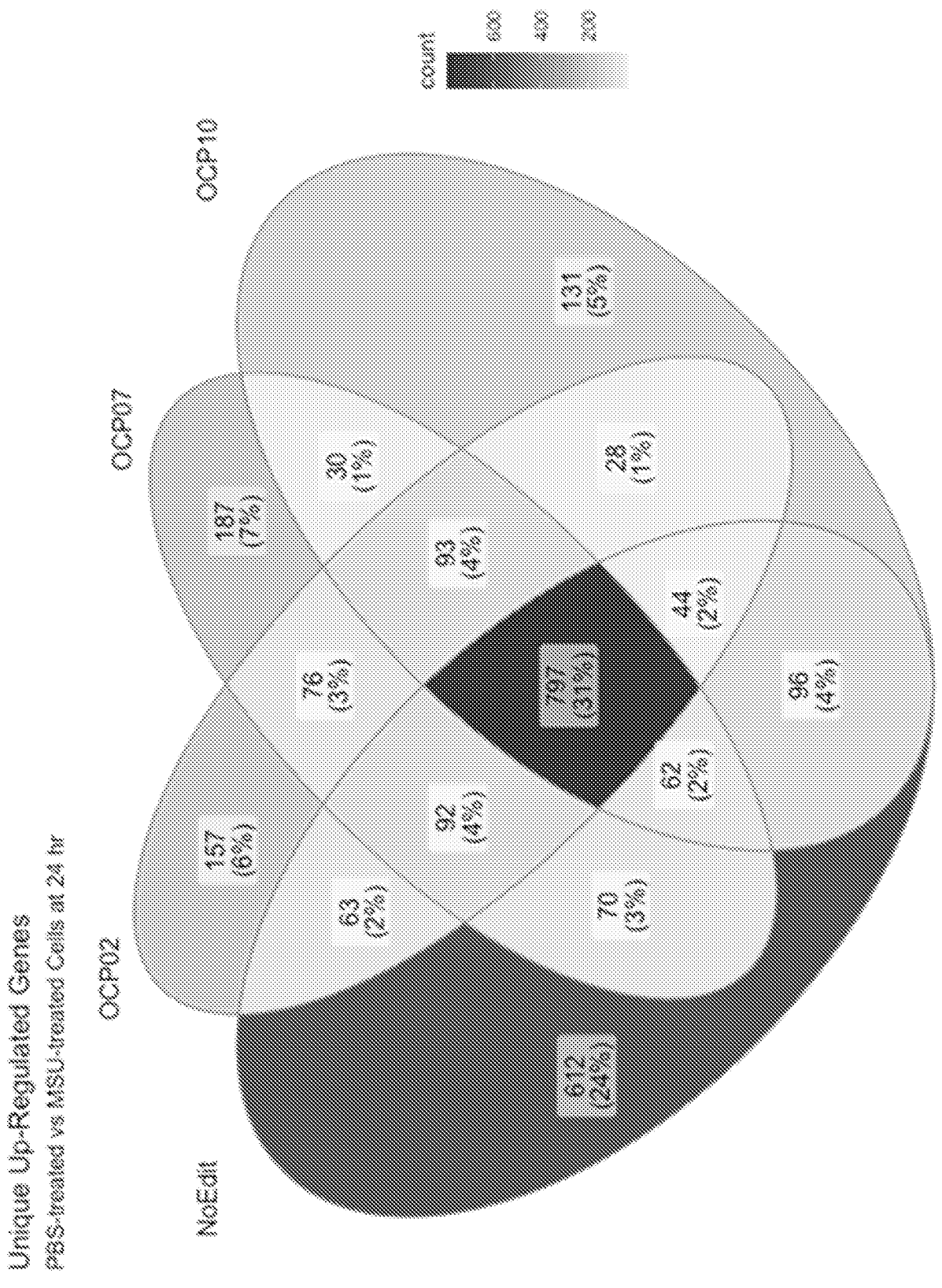

Unique Up-Regulated Genes
PBS-treated vs MSU-treated Cells at 24 hr
NoEdit
OCP02
OCP07
OCP10
count
600
400
200
612 (24%)
157 (6%)
187 (7%)
131 (5%)
63 (2%)
76 (3%)
30 (1%)
28 (1%)
92 (4%)
93 (4%)
797 (31%)
44 (2%)
70 (3%)
62 (2%)
96 (4%)

FIG. 25F

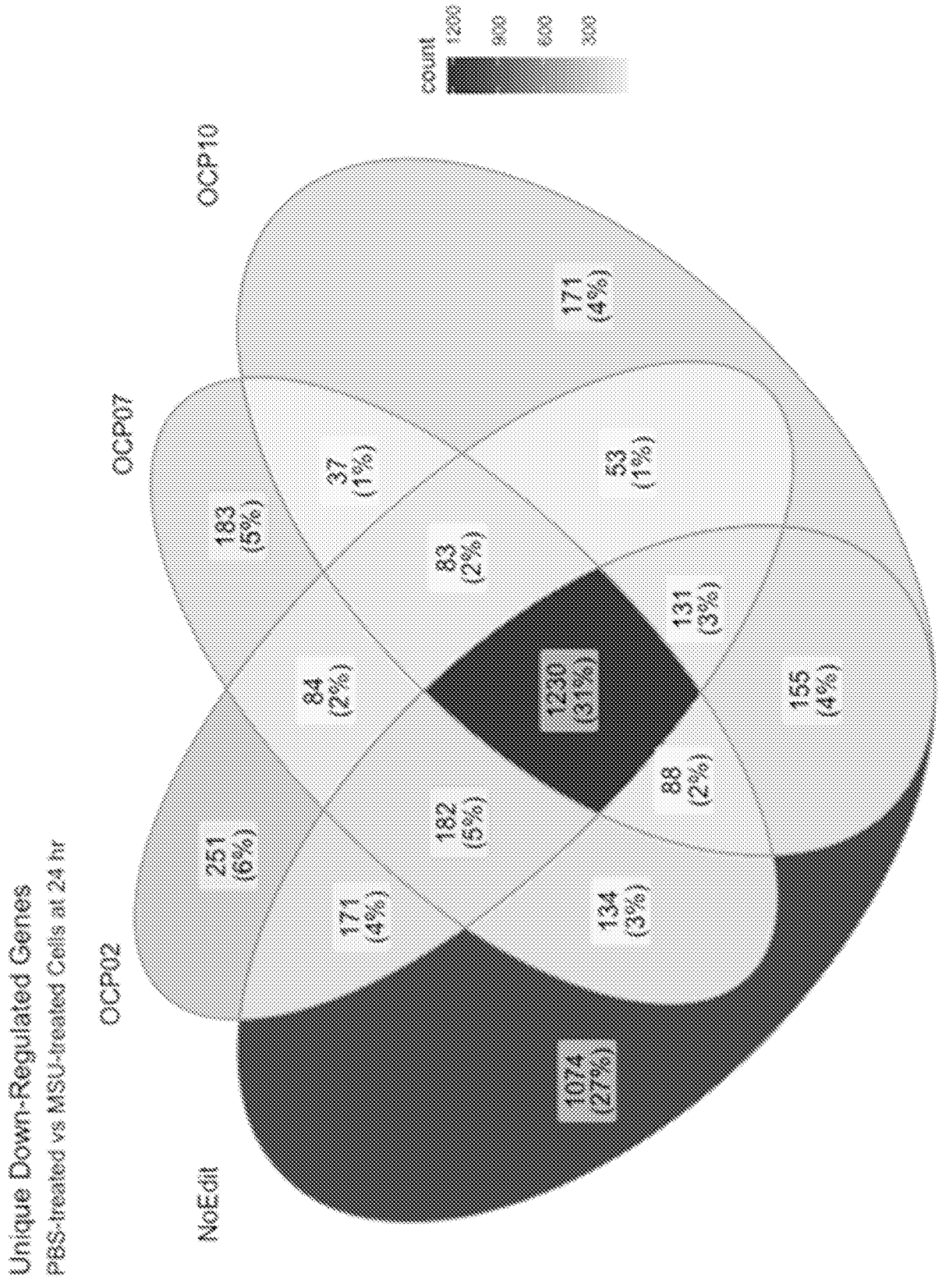

Unique Down-Regulated Genes
PBS-treated vs MSU-treated Cells at 24 hr
NoEdit
OCP02
OCP07
OCP10
Count
1200
900
600
300
1074 (27%)
251 (6%)
183 (5%)
171 (4%)
1230 (31%)
182 (6%)
84 (2%)
37 (1%)
83 (2%)
171 (4%)
134 (3%)
131 (3%)
53 (1%)
88 (2%)
155 (4%)

FIG. 25G

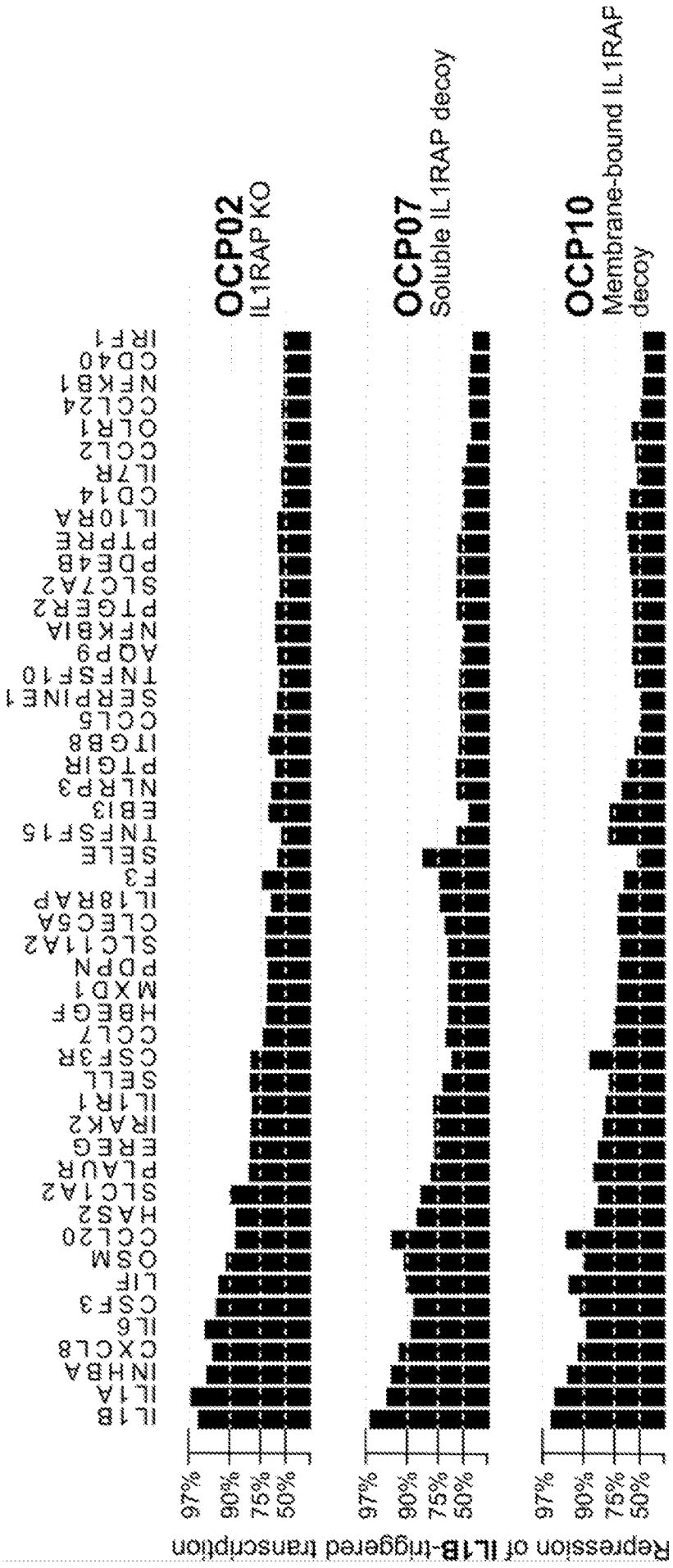

OCP02
IL1RAP KO
OCP07
Soluble IL1RAP decoy
OCP10
Membrane-bound IL1RAP decoy
97%
90%
75%
50%
Repression of IL1B-triggered transcription

FIG. 25H

SEQ ID NO:	Genomic cut coordinate	Exon	CDS cut position	CDS cut position %	Strand	Start coordinate	End coordinate	crRNA	GC content	PAM
680	102164864	4	152	8.9	+	102164848	102164867	CUUAACCCAAAUGAACACAA	35	AGG
681	102164910	4	198	11.6	-	102164908	102164927	GAGGCUUGUUCUGUAGAUAC	45	AGG
682	102166196	6	570	33.3	+	102166180	102166199	AUGUGGCUGAAAAGCAUAGA	40	GGG
683	102164971	4	259	15.1	+	102164955	102164974	UUGGUUUGUUCCUGCUAAGG	45	TGG
684	102164998	4	286	16.7	+	102164982	102165001	UUCAGGACAUUACUAUUGCG	40	TGG
685	102165219	5	401	23.5	+	102165203	102165222	AAGCAGAAACUACCCGUUGC	50	AGG
686	102166179	6	553	32.3	+	102166163	102166182	UAGGCUCAUCGUGAUGAAUG	45	TGG
687	102166195	6	569	33.3	+	102166179	102166198	AAUGUGGCUGAAAAGCAUAG	40	AGG
688	102166231	6	605	35.4	+	102166215	102166234	CAUGCAUCCUACACAUACUU	40	GGG
689	102166253	6	627	36.7	+	102166237	102166256	GCAAGCAAUAUCCUAUUACC	40	CGG
690	102166254	6	628	36.7	+	102166238	102166257	CAAGCAAUAUCCUAUUACCC	40	GGG
691	102168645	7	703	41.1	+	102168629	102168648	GAGCCCAGCUAAUGAGACAA	50	TGG
692	102171836	8	757	44.3	-	102171834	102171853	AGCAAUGUCACUCAACUGGC	50	CGG
693	102168658	7	716	41.9	+	102168642	102168661	GAGACAAUGGAAGUAGACUU	40	GGG
694	102164929	4	217	12.7	-	102164927	102164946	UUUGUGUUGAUGAAUCCUGG	40	AGG
695	102166227	6	601	35.1	-	102166225	102166244	UUGCUUGCCCAAGUAUGUGU	45	AGG
696	102171897	8	818	47.8	-	102171895	102171914	AAUAGUCUUCCCCUAGCACU	45	GGG
697	102165292	5	474	27.7	+	102165276	102165295	AUGAGUUACCUAAAUUACAG	30	TGG
698	102165299	5	481	28.1	+	102165283	102165302	ACCUAAAUUACAGUGGUAUA	30	AGG
699	102166160	6	534	31.2	+	102166144	102166163	ACUUUAGUGGAGUCAAAGAU	35	AGG
700	102171828	8	749	43.8	+	102171812	102171831	CAAUUGAUCUGUAAUGUCAC	35	CGG
701	102165228	5	410	24	+	102165212	102165231	CUACCCGUUGCAGGAGACGG	65	AGG
702	102166260	6	634	37.1	-	102166258	102166277	AGUAAUAAAUUCUAUUACCC	25	GGG
703	102171840	8	761	44.5	-	102171838	102171857	AGUAAGCAAUGUCACUCAAC	40	TGG
704	102171897	8	818	47.8	+	102171881	102171900	GAUGAAGAUGACCCAGUGCU	50	AGG
705	102164844	4	132	7.7	-	102164842	102164861	UCAUUUGGGUUAAGAGGACA	40	GGG
706	102164850	4	138	8.1	-	102164848	102164867	UUGUGUUCAUUUGGGUUAAG	35	AGG
707	102164981	4	269	15.7	+	102164965	102164984	CCUGCUAAGGUGGAGGAUUC	55	AGG
708	102165003	4	291	17	+	102164987	102165006	GACAUUACUAUUGCGUGGUA	40	AGG
709	102165220	5	402	23.5	-	102165218	102165237	AGUCCUCCGUCUCCUGCAAC	60	GGG
710	102165221	5	403	23.6	-	102165219	102165238	AAGUCCUCCGUCUCCUGCAA	55	CGG
711	102168623	7	681	39.8	-	102168621	102168640	UUAGCUGGGCUCACAAUCAC	50	AGG
712	102164970	4	258	15.1	-	102164968	102164987	CCUGAAUCCUCCACCUUAGC	55	AGG
713	102165175	5	357	20.9	-	102165173	102165192	UGUGCAUUAUAACAUAAGUU	25	AGG
714	102165248	5	430	25.1	+	102165232	102165251	AGGACUUGUGUGCCCUUAUA	45	TGG
715	102166230	6	604	35.3	+	102166214	102166233	UCAUGCAUCCUACACAUACU	40	TGG
716	102172784	9	937	54.8	-	102172782	102172801	AUGUGUAUUCUUGGCAAAAC	35	AGG
717	102157776	3	52	3	+	102157760	102157779	UCUACUGAUUUCUUCUCUGG	40	AGG
718	102164932	4	220	12.9	-	102164930	102164949	CUCUUUGUGUUGAUGAAUCC	40	TGG
719	102164974	4	262	15.3	+	102164958	102164977	GUUUGUUCCUGCUAAGGUGG	50	AGG
720	102166253	6	627	36.7	-	102166251	102166270	AAUUCUAUUACCCGGGUAAU	35	AGG
721	102168614	7	672	39.3	-	102168612	102168631	CUCACAAUCACAGGCCUUGU	50	GGG
722	102171853	8	774	45.3	+	102171837	102171856	AGUUGAGUGACAUUGCUUAC	40	TGG
723	102171898	8	819	47.9	+	102171882	102171901	AUGAAGAUGACCCAGUGCUA	45	GGG
724	102171899	8	820	48	+	102171883	102171902	UGAAGAUGACCCAGUGCUAG	50	GGG
725	102164877	4	165	9.6	+	102164861	102164880	AACACAAAGGCACUAUAACU	35	TGG
726	102164925	4	213	12.5	+	102164909	102164928	UAUCUACAGAACAAGCCUCC	45	AGG
727	102165200	5	382	22.3	-	102165198	102165217	GGGUAGUUUCUGCUUAAAUA	35	TGG
728	102166147	6	521	30.5	+	102166131	102166150	CUUGACAAUAUACACUUUAG	30	TGG
729	102166261	6	635	37.1	-	102166259	102166278	GAGUAAUAAAUUCUAUUACC	25	CGG

FIG. 26A

SEQ ID NO:	Genomic cut coordinate	Exon	CDS cut position	CDS cut position %	Strand	Start coordinate	End coordinate	crRNA	GC content	PAM
730	102168637	7	695	40.6	-	102168635	102168654	CUUCCAUUGUCUCAUUAGCU	40	GGG
731	102171809	8	730	42.7	-	102171807	102171826	AUUACAGAUCAAUUGUAUCU	25	GGG
732	102172724	9	877	51.3	-	102172722	102172741	UAUAUUAAGCACUGUGAUGA	30	GGG
733	102172777	9	930	54.4	-	102172775	102172794	UUCUUGGCAAAACAGGUAAA	35	TGG
734	102168657	7	715	41.8	+	102168641	102168660	UGAGACAAUGGAAGUAGACU	40	TGG
735	102168615	7	673	39.4	-	102168613	102168632	GCUCACAAUCACAGGCCUUG	55	TGG
736	102171913	8	834	48.8	+	102171897	102171916	UGCUAGGGGAAGACUAUUAC	45	AGG
737	102172708	9	861	50.4	+	102172692	102172711	AAAAUCCUGCAAACAAAAGA	30	AGG
738	102172739	9	892	52.2	+	102172723	102172742	CAUCACAGUGCUUAAUAUAU	30	CGG
739	102172793	9	946	55.3	-	102172791	102172810	AUCUAUACCAUGUGUAUUCU	30	TGG
740	102164968	4	256	15	+	102164952	102164971	ACUUUGGUUUGUUCCUGCUA	40	AGG
741	102165135	5	317	18.5	-	102165133	102165152	UUGCACUUAUUUUAAUUCUG	25	AGG
742	102171865	8	786	46	+	102171849	102171868	UUGCUUACUGGAAGUGGAAU	40	GGG
743	102171898	8	819	47.9	-	102171896	102171915	UAAUAGUCUUCCCCUAGCAC	45	TGG
744	102165225	5	407	23.8	+	102165209	102165228	AAACUACCCGUUGCAGGAGA	50	CGG
745	102166276	6	650	38	+	102166260	102166279	GUAAUAGAAUUUAUUACUCU	20	AGG
746	102168638	7	696	40.7	-	102168636	102168655	ACUUCCAUUGUCUCAUUAGC	40	TGG
747	102171864	8	785	45.9	+	102171848	102171867	AUUGCUUACUGGAAGUGGAA	40	TGG
748	102157780	3	56	3.3	+	102157764	102157783	CUGAUUUCUUCUCUGGAGGC	50	TGG
749	102164845	4	133	7.8	-	102164843	102164862	UUCAUUUGGGUUAAGAGGAC	40	AGG
750	102171810	8	731	42.7	-	102171808	102171827	CAUUACAGAUCAAUUGUAUC	30	TGG
751	102171859	8	780	45.6	+	102171843	102171862	GUGACAUUGCUUACUGGAAG	45	TGG
752	102172725	9	878	51.3	-	102172723	102172742	AUAUAUUAAGCACUGUGAUG	30	AGG
753	102166127	6	501	29.3	-	102166125	102166144	UGUAUAUUGUCAAGAAGUAG	30	AGG
754	102172702	9	855	50	-	102172700	102172719	GUACUCCUUCUUUUGUUUGC	40	AGG
755	102157773	3	49	2.9	+	102157757	102157776	AGCUCUACUGAUUUCUUCUC	40	TGG
756	102165155	5	337	19.7	+	102165139	102165158	UAAAAUAAGUGCAAAAUUUG	20	TGG
757	102165289	5	471	27.5	-	102165287	102165306	ACCUUAUACCACUGUAAUUU	30	AGG
758	102172797	9	950	55.6	+	102172781	102172800	UGUUUUGCCAAGAAUACACA	35	TGG
759	102175636	11	1294	75.7	+	102175620	102175639	UGGAAGGGAUGACUACGUUG	50	GGG
760	102175640	11	1298	75.9	+	102175624	102175643	AGGGAUGACUACGUUGGGGA	55	AGG
761	102176437	12	1368	81.2	+	102176421	102176440	ACAUCAGGCUUCAGCUGGCU	55	GGG
762	102176472	12	1423	83.2	-	102176470	102176489	CUGAACAAGAGCAUUAUACA	35	TGG
763	102176593	12	1544	90.3	-	102176591	102176610	GUGUAAAGUCCCCCUGACCAG	55	CGG
764	102176594	12	1545	90.4	+	102176578	102176597	AUGGGGCUAUCCGCUGGUCA	60	GGG
765	102176595	12	1546	90.4	+	102176579	102176598	UGGGGCUAUCCGCUGGUCAG	65	GGG
766	102176607	12	1558	91.1	+	102176591	102176610	CUGGUCAGGGGACUUUACAC	55	AGG
767	102176608	12	1559	91.2	+	102176592	102176611	UGGUCAGGGGACUUUACACA	50	GGG
768	102175595	11	1253	73.3	+	102175579	102175598	GAGGUCUUGGAAAAACAGUG	45	TGG
769	102175498	11	1156	67.6	-	102175496	102175515	AUACAGUAUAUAUGCGUCAU	30	AGG
770	102175525	11	1183	69.2	+	102175509	102175528	ACUGUAUCCAAAGACUGUUG	40	GGG
771	102175634	11	1292	75.6	+	102175618	102175637	UAUGGAAGGGAUGACUACGU	45	TGG
772	102176621	12	1572	91.9	-	102176619	102176638	AACCUUGUCUUUGCAGACUG	45	TGG
773	102174694	10	1099	64.3	+	102174678	102174697	UGACAUUGUGCUUUGGUACA	40	GGG
774	102175635	11	1293	75.6	+	102175619	102175638	AUGGAAGGGAUGACUACGUU	45	GGG
775	102176588	12	1539	90	+	102176572	102176591	AGAAACAUGGGGCUAUCCGC	55	TGG
776	102176440	12	1391	81.3	+	102176424	102176443	UCAGGCUUCAGCUGGCUGGG	65	TGG
777	102174709	10	1114	65.1	-	102174707	102174726	UAUUGGGAGAAAAUCAUAGC	35	AGG
778	102175524	11	1182	69.1	+	102175508	102175527	UACUGUAUCCAAAGACUGUU	35	GGG
779	102175529	11	1187	69.4	+	102175513	102175532	UAUCCAAAGACUGUUGGGGA	45	AGG

FIG. 26B

SEQ ID NO:	Genomic cut coordinate	Exon	CDS cut position	CDS cut position %	Strand	Start coordinate	End coordinate	crRNA	GC content	PAM
780	102175546	11	1204	70.4	-	102175544	102175563	CACAAAAAUAUCACAGUCAG	35	AGG
781	102176436	12	1387	81.1	+	102176420	102176439	AACAUCAGGCUUCAGCUGGC	55	TGG
782	102176488	12	1439	84.2	+	102176472	102176491	UAUAAUGCUCUUGUUCAGGA	35	TGG
783	102176577	12	1528	89.4	+	102176561	102176580	AUUCAUUAAGCAGAAACAUG	30	GGG
784	102176593	12	1544	90.3	+	102176577	102176596	CAUGGGGCUAUCCGCUGGUC	65	AGG
785	102176630	12	1581	92.5	+	102176614	102176633	GACCACAGUCUGCAAAGACA	50	AGG
786	102176648	12	1599	93.5	+	102176632	102176651	CAAGGUUCUGGAAGAAUGUC	45	AGG
787	102175620	11	1278	74.7	+	102175604	102175623	AUAAGCUGUUCAUUUAUGGA	30	AGG
788	102174687	10	1092	63.9	+	102174671	102174690	UCAAGAUUGACAUUGUGCUU	35	TGG
789	102175523	11	1181	69.1	+	102175507	102175526	AUACUGUAUCCAAAGACUGU	35	TGG
790	102175616	11	1274	74.5	+	102175600	102175619	GGAUAUAAGCUGUUCAUUUA	30	TGG
791	102176636	12	1587	92.8	+	102176620	102176639	AGUCUGCAAAGACAAGGUUC	45	TGG
792	102174693	10	1098	64.2	+	102174677	102174696	UUGACAUUGUGCUUUGGUAC	40	AGG
793	102175521	11	1179	68.9	-	102175519	102175538	GACCCUUCCCCAACAGUCUU	55	TGG
794	102175576	11	1234	72.2	+	102175560	102175579	UGUGUUUAAAGUCUUGCCUG	40	AGG
795	102175621	11	1279	74.8	+	102175605	102175624	UAAGCUGUUCAUUUAUGGAA	30	GGG
796	102176432	12	1383	80.9	+	102176416	102176435	GAGAAACAUCAGGCUUCAGC	50	TGG
797	102176552	12	1503	87.9	-	102176550	102176569	UUAAUGAAUUUAAUCGAUUC	20	TGG
798	102176576	12	1527	89.3	+	102176560	102176579	AAUUCAUUAAGCAGAAACAU	25	GGG
799	102175530	11	1188	69.5	+	102175514	102175533	AUCCAAAGACUGUUGGGGAA	45	GGG
800	102176422	12	1373	80.3	+	102176406	102176425	AUUUUAGUCAGAGAAACAUC	30	AGG
801	102176484	12	1435	83.9	+	102176468	102176487	CAUGUAUAAUGCUCUUGUUC	35	AGG
802	102175581	11	1239	72.5	-	102175579	102175598	CACUGUUUUUCCAAGACCUC	45	AGG
803	102175582	11	1240	72.5	+	102175566	102175585	UAAAGUCUUGCCUGAGGUCU	45	TGG
804	102176533	12	1484	86.8	-	102176531	102176550	CUGGCAUUUUCUCAUAGUCU	40	TGG
805	102176575	12	1526	89.2	+	102176559	102176578	AAAUUCAUUAAGCAGAAACA	25	TGG
806	102174725	10	1130	66.1	+	102174709	102174728	UAUGAUUUUCUCCCAAUAAA	25	AGG
807	102176512	12	1463	85.6	-	102176510	102176529	GGAUUUUCUCCAGCUCAAGC	50	AGG
808	102176514	12	1465	85.7	+	102176498	102176517	UAAAGUUGUCCUGCUUGAGC	45	TGG
809	102172833	9	986	57.7	+	102172817	102172836	UAUAUCCAGUUAAUAUAUCC	25	AGG
810	102174608	10	1013	59.2	+	102174592	102174611	AAUUUCCAGAAGCACAUGAU	35	TGG
811	102174602	10	1007	58.9	-	102174600	102174619	AUAUACCAAUCAUGUGCUUC	35	TGG
812	102176753	12	1704	99.6	-	102176751	102176770	ACUUCUCCAUGCUACCCGAG	55	AGG
813	102176672	12	1623	94.9	+	102176656	102176675	ACCACAUGCCAGUCCAGCGA	60	CGG
814	102176750	12	1701	99.5	+	102176734	102176753	GAGAGGCUCACGUGCCUCUC	65	GGG
815	102176733	12	1684	98.5	+	102176717	102176736	UAAGGAGAAACUGCAAAGAG	40	AGG
816	102176669	12	1620	94.7	-	102176667	102176686	GAAGGUGACCGUCGCUGGAC	65	TGG
817	102176701	12	1652	96.6	-	102176699	102176718	UAGUGGCUGGUGACAGUAAC	50	TGG
818	102176715	12	1666	97.4	+	102176699	102176718	GUUACUGUCACCAGCCACUA	50	AGG
819	102176662	12	1613	94.3	-	102176660	102176679	ACCGUCGCUGGACUGGCAUG	65	TGG
820	102176674	12	1625	95	-	102176672	102176691	UAGAUGAAGGUGACCGUCGC	55	TGG
821	102176718	12	1669	97.6	-	102176716	102176735	UCUUUGCAGUUUCUCCUUAG	40	TGG
822	102176749	12	1700	99.4	+	102176733	102176752	AGAGAGGCUCACGUGCCUCU	60	CGG
823	102176687	12	1638	95.8	-	102176685	102176704	AGUAACUGGUGUUUAGAUGA	35	AGG
824	102176714	12	1665	97.4	-	102176712	102176731	UGCAGUUUCUCCUUAGUGGC	50	TGG

FIG. 26C

SEQ ID NO:	MIT	CFD	Elevation	CFD	Offtarget #	Azimuth	DeepSpCas9	CrisprScan	CFD	Lindel	inDelphi	Frameshift	Precision	Graf Motifs	Bioscore	CFD / OFF	CFD / ON	CFD/OFF/ON	Interference predictions
680	61	73	78	68	236	70	68	50	63	81	92	82	64	OK	56	65	80	74	Knockout
681	85	92	59	79	110	47	51	68	55	80	85	82	56	OK	54	67	80	72	Knockout
682	65	79	59	68	280	53	55	54	54	96	92	88	63	OK	59	61	78	70	Knockout
683	75	86	60	74	167	49	54	63	55	81	88	84	53	OK	59	64	79	71	Knockout
684	91	92	52	78	87	64	75	30	56	87	90	89	60	OK	73	67	83	74	Knockout
685	93	97	47	79	71	41	53	36	43	84	87	85	56	TT	50	61	82	69	Knockout
686	77	75	54	69	155	70	66	65	67	85	85	85	59	OK	56	68	77	74	Knockout
687	69	73	58	67	258	65	56	34	52	84	92	88	57	OK	65	59	77	69	Knockout
688	74	90	57	74	142	54	56	56	55	80	85	82	57	TT	72	64	78	70	Knockout
689	87	92	61	80	77	50	57	36	48	84	90	87	60	OK	60	64	83	71	Knockout
690	83	93	58	78	90	62	68	32	54	80	91	85	59	OK	61	68	82	72	Knockout
691	81	90	56	76	113	64	62	59	62	83	91	87	60	OK	59	69	82	75	Knockout
692	80	87	60	76	131	59	42	30	44	82	91	86	63	OK	61	60	81	69	Knockout
693	63	83	58	68	278	63	68	58	63	78	88	83	58	TT	64	65	76	71	Knockout
694	72	81	60	71	200	66	47	37	50	84	84	84	44	OK	62	60	78	68	Knockout
695	77	86	60	74	120	66	59	53	59	71	73	72	54	OK	66	67	73	68	Knockout
696	86	92	53	77	108	60	66	56	60	84	71	67	49	OK		69	72	68	Knockout
697	69	83	60	71	162	65	48	32	48	76	88	83	58	OK	61	60	77	67	Knockout
698	74	88	66	76	130	39	32	34	35	93	91	91	64	OK	73	55	84	67	Knockout
699	71	87	59	72	147	57	45	46	49	78	82	80	54	OK	63	61	76	67	Knockout
700	73	84	60	72	140	62	41	37	47	77	85	81	56	GK	67	60	77	67	Knockout
701	85	92	39	72	87	63	61	59	61	65	67	66	57	OK		66	69	66	Knockout
702	70	83	62	72	234	59	60	17	45	76	87	82	58	OK	67	59	77	66	Knockout
703	83	92	60	78	83	49	35	21	35	80	89	85	53	OK	62	57	81	66	Knockout
704	67	85	53	68	192	53	60	39	51	79	79	79	63	OK	61	59	74	66	Knockout
705	70	83	53	69	202	61	52	48	54	70	75	73	51	OK	55	61	71	65	Knockout
706	67	81	60	69	219	47	16	60	41	80	88	84	62	OK	45	55	77	65	Knockout
707	73	87	47	69	152	39	18	51	36	85	96	90	61	TT	59	53	79	65	Knockout
708	96	94	55	82	48	44	26	50	40	76	88	72	48	OK	69	61	77	65	Knockout
709	77	92	47	72	104	46	51	47	48	72	79	76	49	OK		60	74	65	Knockout
710	75	85	53	71	121	58	49	55	54	73	68	70	52	OK		62	71	65	Knockout
711	69	89	53	70	177	53	55	52	53	70	74	72	58	OK	60	62	71	65	Knockout
712	81	89	48	73	131	50	18	35	34	80	90	85	60	GK	62	53	79	64	Knockout
713	67	86	62	72	212	46	37	22	35	80	88	84	56	OK	59	53	78	64	Knockout
714	74	87	61	74	148	26	7	62	32	83	90	86	58	GK	70	53	80	64	Knockout
715	76	90	57	74	148	49	36	15	33	81	86	84	65	OK	71	54	79	64	Knockout
716	64	85	61	70	213	37	18	60	38	79	86	83	59	OK	46	54	76	64	Knockout
717	46	67	63	59	470	55	60	48	54	74	75	74	44	OK	54	57	67	63	Knockout
718	76	88	60	75	159	35	20	21	25	96	93	89	56	OK	59	50	82	63	Knockout
719	77	84	53	71	137	46	46	62	52	76	84	80	51	OK	66	62	80	63	Knockout
720	89	91	54	78	73	35	13	32	27	81	90	85	52	OK	67	52	82	63	Knockout
721	69	87	59	72	161	39	26	46	37	75	87	81	63	TT	46	54	76	63	Knockout
722	78	90	60	76	121	39	11	25	25	86	93	88	63	TT	65	51	83	63	Knockout
723	76	85	59	73	163	57	52	47	52	69	80	84	41	OK	55	63	69	63	Knockout
724	78	88	52	73	138	64	46	51	54	80	84	82	44	GK	55	63	87	63	Knockout
725	74	88	60	74	193	47	36	29	37	71	77	74	56	OK	65	56	74	62	Knockout
726	68	84	53	68	179	56	49	29	45	77	68	73	49	GK	60	57	79	62	Knockout
727	79	89	66	78	112	29	20	17	22	82	90	86	56	OK	52	50	82	62	Knockout
728	68	82	60	70	236	37	11	40	29	81	90	86	59	OK	53	50	78	62	Knockout
729	49	81	47	69	212	55	40	42	46	76	85	80	59	OK	67	52	79	62	Knockout

FIG. 26D

SEQ ID NO:	MIT	CFD	Elevation	CFD	Offtarget #	Azimuth	DeepSpCas9	CrisprScan	CFD	Lindel	inDelphi	Frameshift	Precision	Graf Motifs	Bioscore	CFD	OOF	CFD	Interference predictions
730	78	87	60	75	159	44	17	28	30	77	86	82	65	OK	44	52	76	62	Knockout
731	69	83	61	71	193	50	26	20	32	81	85	83	55	OK	69	52	77	62	Knockout
732	61	77	60	66	260	60	53	37	50	68	69	69	62	OK	61	58	67	62	Knockout
733	56	72	63	64	328	34	21	49	35	86	90	88	62	OK	58	49	76	62	Knockout
734	69	79	60	69	239	43	38	14	32	82	79	80	42	OK	64	51	75	61	Knockout
735	59	81	61	67	274	51	41	16	36	78	76	77	48	TT	36	51	72	60	Knockout
736	82	92	59	78	107	35	17	49	34	87	78	68	62	TT		56	73	69	Knockout
737	42	62	65	56	594	52	42	28	41	60	86	83	54	OK	47	46	70	60	Knockout
738	64	76	66	68	230	36	11	29	25	80	83	87	58	OK	59	47	77	60	Knockout
739	75	88	62	75	158	34	12	21	22	79	87	83	60	TT	49	49	79	60	Knockout
740	68	75	61	68	226	50	44	39	44	67	82	84	46	OK	60	56	66	59	Knockout
741	49	60	70	60	444	58	4	41	34	80	85	83	56	OK	60	47	71	59	Knockout
742	56	76	51	61	247	47	32	48	42	71	76	74	51	OK	60	52	67	59	Knockout
743	85	93	53	77	63	36	57	18	38	63	60	61	41	OK		57	69	59	Knockout
744	72	84	41	66	98	60	39	69	56	58	47	53	47	OK	45	61	69	58	Knockout
745	57	79	65	67	314	49	18	18	28	81	79	80	43	TT	45	48	74	58	Knockout
746	76	85	60	74	128	28	13	12	18	80	88	84	61	OK	44	46	79	58	Knockout
747	61	72	48	60	251	59	38	37	45	70	67	69	48	OK	69	52	64	58	Knockout
748	50	68	66	61	360	46	26	31	34	67	84	76	66	OK	48	48	68	57	Knockout
749	77	86	53	72	127	42	12	54	36	57	68	63	48	OK	45	54	67	57	Knockout
750	78	92	61	77	116	31	5	11	12	79	84	81	62	OK	69	44	79	57	Knockout
751	70	81	61	71	169	44	29	42	38	69	53	61	50	OK	61	55	66	57	Knockout
752	61	76	57	65	276	58	46	23	42	69	61	65	47	OK	61	54	65	57	Knockout
753	57	79	61	66	235	52	30	30	37	61	67	64	54	OK	67	51	65	56	Knockout
754	67	76	66	69	176	23	7	8	13	80	92	86	59	TT	37	41	78	56	Knockout
755	58	81	65	68	238	37	13	22	24	66	81	74	62	TT	51	46	71	55	Knockout
756	79	88	60	75	112	47	1	19	22	82	91	86	61	TT	40	39	71	55	Knockout
757	49	70	67	59	321	30	17	16	21	69	79	74	58	TT	54	40	66	51	Knockout
758	66	83	66	71	265	56	41	18	42	85	86	86	56	OK	48	57	79	66	Knockout or soluble decoy receptor
759	89	91	49	76	100	62	71	78	70	71	78	75	48	OK	63	73	75	74	Membrane-bound decoy receptor
760	80	86	48	71	127	56	61	58	59	79	78	79	50	OK	55	65	75	70	Membrane-bound decoy receptor
761	73	86	53	71	171	49	44	60	51	86	86	91	67	OK	60	61	81	71	Membrane-bound decoy receptor
762	77	90	64	77	141	61	42	22	42	91	85	93	65	OK	68	59	85	71	Membrane-bound decoy receptor
763	76	93	53	74	95	69	74	66	70	82	74	78	42	OK	69	79	76	74	Membrane-bound decoy receptor
764	84	96	39	76	82	54	54	60	56	79	81	80	49	OK	65	66	78	71	Membrane-bound decoy receptor
765	82	93	48	74	80	59	65	69	64	85	85	85	59	OK	65	69	80	73	Membrane-bound decoy receptor
766	85	93	51	76	93	61	48	52	54	79	86	87	65	OK	53	65	82	72	Membrane-bound decoy receptor
767	79	93	58	77	131	73	55	63	64	89	95	93	61	OK	52	70	84	77	Membrane-bound decoy receptor
768	55	70	53	59	303	76	63	52	64	87	89	88	56	OK	64	62	74	70	Membrane-bound decoy receptor
769	89	90	54	76	116	60	33	45	46	83	82	82	68	OK	59	62	80	69	Membrane-bound decoy receptor
770	72	85	61	73	154	67	64	56	62	73	74	73	50	OK	62	67	73	69	Membrane-bound decoy receptor
771	91	91	53	78	75	57	50	50	52	69	84	76	59	OK	67	65	77	69	Membrane-bound decoy receptor
772	69	83	52	68	207	56	52	51	53	83	88	85	57	OK	47	60	77	69	Membrane-bound decoy receptor
773	71	85	59	72	177	62	42	40	48	83	84	84	63	OK	69	60	76	68	Membrane-bound decoy receptor
774	92	96	51	80	80	39	41	76	52	68	78	73	52	TT	63	66	76	68	Membrane-bound decoy receptor
775	94	94	42	77	82	54	59	23	45	83	81	82	48	OK	64	61	79	68	Membrane-bound decoy receptor
776	53	66	40	53	300	62	61	44	56	90	93	91	62	OK	56	54	72	67	Membrane-bound decoy receptor
777	76	90	64	77	186	48	26	27	33	81	88	85	65	OK	60	55	81	65	Membrane-bound decoy receptor
778	74	85	61	73	142	37	24	28	30	91	90	90	64	TT	62	52	82	65	Membrane-bound decoy receptor
779	66	83	60	70	186	57	37	42	45	80	81	80	51	OK	49	56	75	65	Membrane-bound decoy receptor

FIG. 26E

SEQ ID NO:	MIT	CFD	Elevation	OOF	Offtarget #	Azimuth	DeepSpCas9	CrisprScan	ON	Lindel	inDelphi	Frameshift	Precision	Graf Motifs	Bioscore	ON / OFF	ON / ON	OFF / OFF	Interference predictions
780	59	76	70	68	322	59	19	44	41	75	89	82	66	OK	57	54	75	64	Membrane-bound decoy receptor
781	70	84	59	71	154	39	37	18	31	85	96	90	78	OK	61	51	80	64	Membrane-bound decoy receptor
782	71	82	60	71	149	52	53	28	44	80	74	77	54	OK	58	58	74	64	Membrane-bound decoy receptor
783	51	72	59	61	359	66	46	35	49	82	83	83	49	OK	66	55	72	64	Membrane-bound decoy receptor
784	92	94	38	75	48	34	29	59	41	79	77	78	43	OK	68	58	76	64	Membrane-bound decoy receptor
785	60	79	61	67	242	67	63	22	51	76	71	73	50	OK	62	59	70	64	Membrane-bound decoy receptor
786	50	69	56	58	403	45	51	51	49	80	87	83	62	OK	67	54	71	64	Membrane-bound decoy receptor
787	60	79	56	65	248	56	34	23	38	84	88	86	63	OK	63	51	75	63	Membrane-bound decoy receptor
788	67	86	60	71	164	44	36	31	37	77	80	79	47	TT	73	54	75	62	Membrane-bound decoy receptor
789	66	84	61	70	166	50	50	31	33	80	86	83	45	OK	59	52	77	62	Membrane-bound decoy receptor
790	71	88	64	74	164	22	12	29	21	85	93	89	61	TT	70	48	82	62	Membrane-bound decoy receptor
791	71	85	49	68	208	49	54	34	46	71	75	73	49	TT	60	57	71	62	Membrane-bound decoy receptor
792	76	89	59	75	145	45	9	39	31	78	77	78	48	OK	69	53	76	61	Membrane-bound decoy receptor
793	73	88	53	71	145	36	22	15	24	84	91	88	60	TT	63	48	79	61	Membrane-bound decoy receptor
794	66	79	60	68	241	62	41	48	50	75	54	65	58	OK	57	59	66	61	Membrane-bound decoy receptor
795	60	72	60	64	252	56	37	44	46	78	72	75	47	OK	63	55	69	61	Membrane-bound decoy receptor
796	62	82	59	68	216	52	40	22	38	79	75	77	56	OK	60	53	72	61	Membrane-bound decoy receptor
797	82	93	61	79	204	30	0	13	14	82	90	86	56	TT	56	46	82	60	Membrane-bound decoy receptor
798	50	74	62	62	366	52	44	32	43	68	85	76	59	OK	66	52	69	60	Membrane-bound decoy receptor
799	58	74	61	64	224	60	28	49	46	73	63	68	52	OK	51	55	66	59	Membrane-bound decoy receptor
800	55	72	59	62	301	52	29	24	35	81	80	81	52	OK	58	49	71	59	Membrane-bound decoy receptor
801	80	89	59	76	127	36	26	44	36	56	66	61	49	TT	63	56	69	56	Membrane-bound decoy receptor
802	70	86	64	73	200	47	29	45	40	67	46	57	57	OK	67	57	65	57	Membrane-bound decoy receptor
803	66	81	51	66	193	37	19	72	43	57	67	62	52	OK	62	54	64	57	Membrane-bound decoy receptor
804	62	85	65	71	270	43	22	29	31	64	69	67	52	OK	55	51	69	56	Membrane-bound decoy receptor
805	37	60	63	53	643	53	38	16	36	78	82	80	55	OK	54	45	67	56	Membrane-bound decoy receptor
806	50	71	65	62	363	32	17	29	26	76	81	78	62	OK	63	44	70	55	Membrane-bound decoy receptor
807	69	84	56	70	164	49	39	13	34	56	66	61	61	OK	65	52	65	55	Membrane-bound decoy receptor
808	78	89	53	73	109	44	25	27	32	64	47	56	54	OK	55	53	64	54	Membrane-bound decoy receptor
809	67	82	55	68	199	47	47	17	37	87	94	90	57	OK	53	53	79	65	Soluble decoy receptor
810	69	86	60	72	248	50	39	34	41	74	74	74	61	OK	53	56	73	62	Soluble decoy receptor
811	78	92	60	77	123	34	14	18	22	69	66	67	45	TT	39	49	72	55	Soluble decoy receptor
812	92	92	52	79	67	73	64	61	66	77	83	80	51	OK	47	72	79	75	Wildtype-like
813	83	92	45	73	86	59	72	46	59	84	80	82	48	OK	48	66	78	72	Wildtype-like
814	81	93	48	74	120	42	34	83	53	85	88	87	64	TT	49	64	80	71	Wildtype-like
815	52	66	65	61	432	61	76	55	64	85	84	84	53	OK	49	62	73	70	Wildtype-like
816	94	95	36	75	46	46	40	52	46	83	87	85	52	OK	57	60	80	69	Wildtype-like
817	82	89	48	73	127	41	39	70	50	80	89	85	64	OK	48	61	79	69	Wildtype-like
818	73	88	49	70	129	50	50	49	50	78	86	83	60	OK	42	60	76	68	Wildtype-like
819	43	93	33	57	48	62	64	55	60	82	87	85	53	OK	61	59	71	67	Wildtype-like
820	98	98	41	79	25	53	32	40	42	75	79	77	60	OK	46	60	78	66	Wildtype-like
821	62	75	64	67	292	31	28	59	39	96	93	89	62	OK	38	53	78	65	Wildtype-like
822	79	88	46	71	165	51	37	47	45	77	74	76	44	TT	45	58	73	64	Wildtype-like
823	73	82	59	71	182	57	50	29	45	68	79	74	57	OK	53	58	73	63	Wildtype-like
824	70	86	57	71	199	41	27	22	30	83	91	87	63	OK	34	51	79	63	Wildtype-like

FIG. 26F

SEQ ID NO:	Genomic cut coordinate	Exon	Strand	Start coordinate	End coordinate	crRNA	GC content	PAM
825	40844041	4	-	40844038	40844057	CAGUAAGACACCUAUAUCUA	35	TGG
826	40844027	4	-	40844024	40844043	UAUCUAUGGAAGUAGACUCU	35	AGG
827	40843981	4	+	40843965	40843984	CCCGAAUCCUCCACCUUAGC	60	AGG
828	40843981	4	-	40843978	40843997	GUGGUUUGUUCCUGCUAAGG	50	TGG
829	40843949	4	-	40843946	40843965	GACAUUACUAUUGUGUCGUA	35	AGG
830	40843776	5	+	40843760	40843779	UCUGUGUUGUAACACAAGUU	35	AGG
831	40842574	6	-	40842571	40842590	CAUCAUAGCGAAUGUGACUA	40	CGG
832	40842564	6	-	40842561	40842580	AAUGUGACUACGGCGCAUAA	45	TGG
833	40842563	6	-	40842560	40842579	AUGUGACUACGGCGCAUAAU	45	GGG
834	40842519	6	+	40842503	40842522	GGUAAUACGAUAUUGCUUUC	35	CGG
835	40842506	6	-	40842503	40842522	GAAAGCAAUAUCGUAUUACC	35	CGG
836	40842505	6	-	40842502	40842521	AAAGCAAUAUCGUAUUACCC	35	GGG
837	40844000	4	-	40843997	40844016	AUCAGCACAAAGAUAAACUG	35	TGG
838	40844173	4	-	40844170	40844189	UCCUUUUAAAGAUACAUGUG	30	AGG
839	40844041	4	+	40844025	40844044	GAGUCUACUUCCAUAGAUAU	35	AGG
840	40843971	4	-	40843968	40843987	CCUGCUAAGGUGGAGGAUUC	55	GGG
841	40844111	4	+	40844095	40844114	UUGGGUUUAAAAAACAUGCA	30	CGG
842	40843978	4	-	40843975	40843994	GUUUGUUCCUGCUAAGGUGG	50	AGG
843	40843727	5	-	40843724	40843743	AAACUACUUGUUGCGGCAGA	45	TGG
844	40843653	5	-	40843650	40843669	UCCCAAAAUACAGUGGCAUA	40	AGG
845	40842528	6	-	40842525	40842544	GGAGCAUUUUAUACAUACUC	35	CGG
846	40847110	3	-	40847107	40847126	AGAAUAUGAAAGAGUUACUC	30	AGG
847	40843984	4	-	40843981	40844000	ACUGUGGUUUGUUCCUGCUA	45	AGG
848	40843660	5	-	40843657	40843676	AUGAGCUUCCCAAAAUACAG	40	TGG
849	40843704	5	-	40843701	40843720	ACAACUUGUGUGUCCUUAUA	35	TGG
850	40842549	6	-	40842546	40842565	CAUAAUGGGAAAUAUACUUG	30	TGG
851	40844088	4	-	40844085	40844104	UUAAACCCAAAUGAAGAGAA	30	AGG
852	40844075	4	-	40844072	40844091	AAGAGAAAGGCACUAUAAUU	30	TGG
853	40843972	4	-	40843969	40843988	UCCUGCUAAGGUGGAGGAUU	50	CGG
854	40847066	3	-	40847063	40847082	CUCAUUUCUUCUCUGGAAGC	45	CGG
855	40844092	4	+	40844076	40844095	AUAGUGCCUUUCUCUUCAUU	35	TGG
856	40843734	5	-	40843731	40843750	UAAACAGAAACUACUUGUUG	30	CGG
857	40844093	4	+	40844077	40844096	UAGUGCCUUUCUCUUCAUUU	35	GGG
858	40842631	6	+	40842615	40842634	UUUAUAUUGUCAAGAAGCAG	30	AGG
859	40844149	4	+	40844133	40844152	GCAGAUGAAACUAAAAUUAC	30	TGG
860	40847073	3	-	40847070	40847089	AGCUAUACUCAUUUCUUCUC	35	TGG
861	40843662	5	+	40843646	40843665	ACCUUAUGCCACUGUAUUUU	35	GGG
862	40842612	6	-	40842609	40842628	CUUGACAAUAUAAACUUUAU	20	TGG
863	40843816	5	+	40843800	40843819	UAGCAGUUAUUUUAAUUUUG	20	AGG
864	40843661	5	+	40843645	40843664	UACCUUAUGCCACUGUAUUU	35	TGG

FIG. 27A

SEQ ID NO:	Genomic cut coordinate	Exon	Strand	Start coordinate	End coordinate	crRNA	GC content	PAM
865	40842498	6	+	40842482	40842501	AGUAGUAAGUUCUAUAACCC	35	GGG
866	40842497	6	+	40842481	40842500	UAGUAGUAAGUUCUAUAACC	30	CGG
867	40840164	7	-	40840161	40840180	GAGUCCAGCUAAUGAGACAG	50	TGG
868	40835118	8	+	40835102	40835121	GUUGCACAGCAAUUGUAGCU	45	TGG
869	40835100	8	-	40835097	40835116	CAAUUGCUGUGCAACGUCAG	50	TGG
870	40834157	9	+	40834141	40834160	AUCUGUAUUCUUCGCUACAC	40	AGG
871	40840198	7	-	40840195	40840214	CAGAAGAACACAAACCUGUG	45	AGG
872	40840194	7	+	40840178	40840197	CUCACAAUUAUAGGCCUCAC	45	AGG
873	40835063	8	-	40835060	40835079	UUGUCUACUGGACGUGGAAU	45	GGG
874	40834164	9	+	40834148	40834167	UUCUUCGCUACACAGGUAAA	40	GGG
875	40834145	9	-	40834142	40834161	UGUGUAGCGAAGAAUACAGA	40	TGG
876	40835044	8	-	40835041	40835060	UGGGUCAUCAAUUGAUAUAG	35	AGG
877	40840151	7	-	40840148	40840167	GAGACAGUGGAAGCAAGUUU	45	GGG
878	40835069	8	-	40835066	40835085	GUGACUUUGUCUACUGGACG	50	TGG
879	40835064	8	-	40835061	40835080	UUUGUCUACUGGACGUGGAA	45	TGG
880	40835032	8	-	40835029	40835048	UGAUAUAGAGGACUCAGUGC	45	TGG
881	40840170	7	+	40840154	40840173	GCUUCCACUGUCUCAUUAGC	50	TGG
882	40835087	8	+	40835071	40835090	AGUAGACAAAGUCACUAAAG	35	TGG
883	40834163	9	+	40834147	40834166	AUUCUUCGCUACACAGGUAA	40	AGG
884	40840152	7	-	40840149	40840168	UGAGACAGUGGAAGCAAGUU	45	TGG
885	40835029	8	-	40835026	40835045	UAUAGAGGACUCAGUGCUGG	50	AGG
886	40842483	6	-	40842480	40842499	GUUAUAGAACUUACUACUAU	25	AGG
887	40840185	7	+	40840169	40840188	UUAGCUGGACUCACAAUUAU	35	AGG
888	40835075	8	-	40835072	40835091	ACUUUAGUGACUUUGUCUAC	35	TGG
889	40834208	9	+	40834192	40834211	CACUUCUAAAAUAUUAAGCA	25	TGG
890	40835026	8	-	40835023	40835042	AGAGGACUCAGUGCUGGAGG	60	AGG
891	40834197	9	-	40834194	40834213	CAUGCUUAAUAUUUUAGAAG	25	TGG
892	40834239	9	+	40834223	40834242	GUACUCUUUCUUUUUUUUGA	25	AGG
3336	40831351	10	-	40831348	40831367	UGACAUUGUGCUUUGGUACA	40	GGG
3337	40830330	11	-	40830327	40830346	ACUAUACCCAAAGACCCUUG	45	GGG
3338	40830326	11	+	40830310	40830329	AGAGGUGGACCCUUCCCCAA	60	GGG
3339	40830325	11	+	40830309	40830328	UAGAGGUGGACCCUUCCCCA	60	AGG
3340	40830220	11	-	40830217	40830236	AUGGAAGGGAUGCCUAUGUU	45	GGG
3341	40830219	11	-	40830216	40830235	UGGAAGGGAUGCCUAUGUUG	50	GGG
3342	40830218	11	+	40830202	40830221	ACACAUACCUUCCCCAACAU	45	AGG
3343	40830215	11	-	40830212	40830231	AGGGAUGCCUAUGUUGGGGA	55	AGG
3344	40829220	12	+	40829204	40829223	GCUCUUCAGAAGAAUUCCCC	50	AGG
3345	40829076	12	-	40829073	40829092	AGAAACAUGGGGCCAUCCGC	60	TGG
3346	40829074	12	+	40829058	40829077	AAAGUCCCCUGACCAGCGGA	60	TGG
3347	40829070	12	+	40829054	40829073	UGCUAAAGUCCCCUGACCAG	55	CGG

FIG. 27B

SEQ ID NO:	Genomic cut coordinate	Exon	Strand	Start coordinate	End coordinate	crRNA	GC content	PAM
3348	40829070	12	-	40829067	40829086	AUGGGGCCAUCCGCUGGUCA	65	GGG
3349	40829069	12	-	40829066	40829085	UGGGGCCAUCCGCUGGUCAG	70	GGG
3350	40830260	11	-	40830257	40830276	GAGGUCUUGGAAGAACAGUG	50	TGG
3351	40829226	12	-	40829223	40829242	CAUCAGGAUUGGGCUGCCUG	60	GGG
3352	40830326	11	-	40830323	40830342	UACCCAAAGACCCUUGGGGA	55	AGG
3353	40829286	12	-	40829283	40829302	AGGUAGCUAAUGAAAACAUA	30	AGG
3354	40830331	11	-	40830328	40830347	UACUAUACCCAAAGACCCUU	40	GGG
3355	40830332	11	-	40830329	40830348	AUACUAUACCCAAAGACCCU	40	TGG
3356	40829071	12	-	40829068	40829087	CAUGGGGCCAUCCGCUGGUC	70	AGG
3357	40830235	11	-	40830232	40830251	AUAAGCUGUUCAUUUAUGGA	30	AGG
3358	40831358	10	-	40831355	40831374	UCAAGGUUGACAUUGUGCUU	40	TGG
3359	40830221	11	-	40830218	40830237	UAUGGAAGGGAUGCCUAUGU	45	TGG
3360	40830356	11	+	40830340	40830359	GUAUAGUAUGUAUGCAUCAU	30	AGG
3361	40831352	10	-	40831349	40831368	UUGACAUUGUGCUUUGGUAC	40	AGG
3362	40829087	12	-	40829084	40829103	AUUCAUUAAGCAGAAACAUG	30	GGG
3363	40829151	12	+	40829135	40829154	GGAUUUUCUCCAGUUCAAGC	45	AGG
3364	40830334	11	+	40830318	40830337	ACCCUUCCCCCAAGGGUCUUU	55	GGG
3365	40831320	10	-	40831317	40831336	UAUGAGUUUCUCCCCCAAAAA	35	AGG
3366	40829237	12	-	40829234	40829253	GGUCCCAGAAACAUCAGGAU	50	TGG
3367	40830239	11	-	40830236	40830255	GGAUAUAAGCUGUUCAUUUA	30	TGG
3368	40830279	11	-	40830276	40830295	UGUGUUUAAAGUCUUGCCUG	40	AGG
3369	40830273	11	-	40830270	40830289	UAAAGUCUUGCCUGAGGUCU	45	TGG
3370	40830234	11	-	40830231	40830250	UAAGCUGUUCAUUUAUGGAA	30	GGG
3371	40829236	12	-	40829233	40829252	GUCCCAGAAACAUCAGGAUU	45	GGG
3372	40830325	11	-	40830322	40830341	ACCCAAAGACCCUUGGGGAA	55	GGG
3373	40829180	12	-	40829177	40829196	AAUGUACAAUGCUUUUGUUC	30	AGG
3374	40830333	11	+	40830317	40830336	GACCCUUCCCCAAGGGUCUU	60	TGG
3375	40829176	12	-	40829173	40829192	UACAAUGCUUUUGUUCAGGA	35	TGG
3376	40829244	12	+	40829228	40829247	AGCCCAAUCCUGAUGUUUCU	45	GGG
3377	40829088	12	-	40829085	40829104	AAUUCAUUAAGCAGAAACAU	25	GGG
3378	40829243	12	+	40829227	40829246	CAGCCCAAUCCUGAUGUUUC	50	TGG
3379	40830273	11	+	40830257	40830276	CACUGUUCUUCCAAGACCUC	50	AGG
3380	40830311	11	+	40830295	40830314	AAAAAUAUCUGAGUUAGAGG	30	TGG
3381	40831319	10	+	40831303	40831322	ACAACAUUGUACCUUUUUUG	30	GGG
3382	40829130	12	+	40829114	40829133	CUGGCAUUUUCUCAUAGUCU	40	TGG
3383	40829150	12	-	40829147	40829166	UAAAGUUGUCCUGCUUGAAC	40	TGG
3384	40829227	12	-	40829224	40829243	ACAUCAGGAUUGGGCUGCCU	55	GGG
3385	40829089	12	-	40829086	40829105	AAAUUCAUUAAGCAGAAACA	25	TGG
3386	40830308	11	+	40830292	40830311	CACAAAAAUAUCUGAGUUAG	30	AGG
3387	40829258	12	-	40829255	40829274	CAGAAGACUGAUCAUCAUUU	35	TGG

FIG. 27C

SEQ ID NO:	Genomic cut coordinate	Exon	Strand	Start coordinate	End coordinate	crRNA	GC content	PAM
3388	40829242	12	-	40829239	40829258	AUUUUGGUCCCAGAAACAUC	40	AGG
3389	40830374	11	-	40830371	40830390	UUUUCACCUCUAGCUUCAGA	40	TGG
3390	40831317	10	+	40831301	40831320	AUACAACAUUGUACCUUUUU	25	TGG
3391	40829306	12	-	40829303	40829322	GUCUUUUUCAGACAUUGUUG	35	AGG
3392	40831318	10	+	40831302	40831321	UACAACAUUGUACCUUUUUU	25	GGG
3393	40829228	12	-	40829225	40829244	AACAUCAGGAUUGGGCUGCC	55	TGG
3394	40829104	12	+	40829088	40829107	UUUCUGCUUAAUGAAUUUAA	20	TGG
3395	40831375	10	-	40831372	40831391	UUUCAUCUACAAAAUCUUCA	25	AGG
3396	40829111	12	+	40829095	40829114	UUAAUGAAUUUAAUGGUUUC	20	TGG
3397	40829056	12	-	40829053	40829072	UGGUCAGGGGACUUUAGCAA	50	GGG
3398	40829057	12	-	40829054	40829073	CUGGUCAGGGGACUUUAGCA	55	AGG
3399	40829016	12	-	40829013	40829032	CAAGGUUCUGGAAGAACGUC	50	AGG
3400	40829028	12	-	40829025	40829044	AAUCUGCAAAGACAAGGUUC	40	TGG
3401	40829034	12	-	40829031	40829050	GAUUGCAAUCUGCAAAGACA	40	AGG
3402	40834109	9	-	40834106	40834125	UAUAUCCAAUUAAUACAUCC	25	AGG
3403	40831437	10	-	40831434	40831453	GAUUUCAAGAAGCACAUGAU	35	TGG
3404	40831450	10	+	40831434	40831453	AUCAUGUGCUUCUUGAAAUC	35	AGG
3405	40834114	9	+	40834098	40834117	UUUUACCUGGAUGUAUUAAU	25	TGG
3406	40829003	12	-	40829000	40829019	GAACGUCAGGUACCACAUGC	55	CGG
3407	40828995	12	-	40828992	40829011	GGUACCACAUGCCGGUCCAG	65	CGG
3408	40828945	12	+	40828929	40828948	CGUCUUCGAGUCUGGCCUGG	65	TGG
3409	40829001	12	+	40828985	40829004	GCUGCCGCUGGACCGGCAUG	75	TGG
3410	40828942	12	+	40828926	40828945	CAGCGUCUUCGAGUCUGGCC	65	TGG
3411	40828994	12	+	40828978	40828997	GAAGGUGGCUGCCGCUGGAC	70	CGG
3412	40828969	12	+	40828953	40828972	CAAGGACAGAGACUGGUGUU	50	TGG
3413	40828937	12	+	40828921	40828940	CUCUGCAGCGUCUUCGAGUC	60	TGG
3414	40828979	12	+	40828963	40828982	GACUGGUGUUUGGAUGAAGG	50	TGG
3415	40828976	12	+	40828960	40828979	AGAGACUGGUGUUUGGAUGA	45	AGG
3416	40828958	12	-	40828955	40828974	CAAACACCAGUCUCUGUCCU	50	TGG
3417	40828962	12	+	40828946	40828965	UGGUGGCCAAGGACAGAGAC	60	TGG
3418	40828951	12	+	40828935	40828954	CGAGUCUGGCCUGGUGGCCA	70	AGG
3419	40828950	12	-	40828947	40828966	AGUCUCUGUCCUUGGCCACC	60	AGG
3420	40828989	12	+	40828973	40828992	UGGAUGAAGGUGGCUGCCGC	65	TGG

FIG. 27D

SEQ ID NO:	MIT	CFD	GTT	OffTarget #	Azimuth	DeepSpCas9	CrisprScan	Chi	Lindel	inDelphi	Frameshift	Precision	Graf motifs	On - Off	GRT - KO	INTEGRATED	Interference predictions
825	87	94	91	81	46	49	33	43	78	75	77	66	OK	67	84	70	Knockout
826	74	85	80	124	55	51	33	46	84	87	86	48	TT	63	83	71	Knockout
827	85	93	89	78	47	15	36	33	80	90	85	60	OK	61	87	69	Knockout
828	80	92	86	106	51	62	66	60	82	88	85	53	OK	73	86	77	Knockout
829	91	94	93	51	54	22	58	45	81	79	80	55	OK	69	86	72	Knockout
830	81	93	87	146	44	47	46	46	80	84	82	55	OK	66	84	71	Knockout
831	84	92	88	62	56	40	38	45	76	80	78	57	OK	66	83	70	Knockout
832	97	99	98	15	45	26	37	36	82	85	84	57	OK	67	91	73	Knockout
833	96	98	98	22	24	17	67	36	70	82	76	65	OK	67	87	70	Knockout
834	80	93	87	74	35	13	34	27	87	93	90	61	TT	57	88	68	Knockout
835	91	93	92	62	50	41	36	42	78	83	80	59	OK	67	86	72	Knockout
836	89	94	92	63	67	68	32	56	69	81	75	59	OK	74	83	74	Knockout
837	57	76	67	274	67	70	36	56	81	90	86	60	OK	62	76	70	Knockout
838	59	71	65	347	64	55	37	52	87	86	86	63	OK	58	76	68	Knockout
839	85	94	90	90	47	39	49	45	64	72	68	61	OK	67	79	68	Knockout
840	78	89	84	141	39	24	57	40	75	86	80	59	TT	62	82	68	Knockout
841	49	78	64	380	63	43	44	50	88	88	88	62	OK	57	76	67	Knockout
842	77	84	81	130	53	48	67	56	76	52	64	51	OK	68	72	67	Knockout
843	72	94	83	67	52	19	59	43	76	74	75	50	OK	63	79	67	Knockout
844	66	84	75	201	53	35	32	40	86	84	85	51	OK	57	80	67	Knockout
845	72	88	80	136	47	42	42	44	71	85	78	57	OK	62	79	67	Knockout
846	65	76	71	312	48	56	22	42	80	91	85	59	OK	56	78	66	Knockout
847	73	83	78	194	53	53	47	51	67	63	65	46	OK	64	71	65	Knockout
848	41	77	59	204	64	58	30	51	79	91	85	59	OK	55	72	65	Knockout
849	77	87	82	142	25	9	43	26	79	86	82	58	OK	54	82	63	Knockout
850	62	80	71	235	64	46	29	46	72	72	72	42	TT	59	72	63	Knockout
851	48	61	55	457	47	44	49	47	80	83	82	60	OK	51	68	61	Knockout
852	63	79	71	320	32	17	52	34	75	81	78	54	OK	52	74	61	Knockout
853	79	88	84	131	26	21	50	32	68	69	68	46	OK	58	76	61	Knockout
854	50	74	62	308	49	15	30	31	81	86	83	54	OK	47	73	59	Knockout
855	62	76	69	267	27	6	30	21	80	85	83	48	TT	45	76	58	Knockout
856	68	80	74	213	58	55	39	51	53	47	50	58	OK	62	62	58	Knockout
857	38	56	47	622	29	14	49	31	84	89	87	57	TT	39	67	55	Knockout
858	60	74	67	289	56	29	32	39	62	58	60	51	OK	53	63	55	Knockout
859	60	79	70	259	38	11	15	21	62	80	71	63	TT	45	70	54	Knockout
860	54	78	66	259	35	9	11	18	72	86	79	63	TT	42	72	54	Knockout
861	51	70	61	234	17	5	27	16	78	88	83	60	TT	38	72	53	Knockout
862	61	76	69	279	10	1	12	8	77	89	83	60	TT	38	76	53	Knockout
863	39	51	45	557	36	2	37	25	84	90	87	62	TT	35	66	52	Knockout
864	55	71	63	244	14	5	12	10	78	89	83	55	TT	37	73	52	Knockout

FIG. 27E

SEQ ID NO:	MIT	CFD	DIT	OffTarget #	Azimuth	DeepSpCas9	CrisprScan	ott	Lindel	InDelphi	Frameshift	Precision	Graf motifs	ON OFF	OFF ES	OVERALL	Inventeera predictions
865	84	94	89	103	61	70	47	59	69	81	75	59	OK	74	82	74	Knockout or soluble decoy recepto
866	81	86	84	128	53	69	48	57	75	77	76	53	OK	70	80	72	Knockout or soluble decoy recepto
867	73	86	80	145	68	68	69	68	80	88	84	59	OK	74	82	77	Knockout or soluble decoy recepto
868	89	96	92	65	49	38	34	40	82	82	82	54	OK	66	87	71	Knockout or soluble decoy recepto
869	92	97	95	56	65	41	60	55	77	84	81	59	OK	75	88	77	Knockout or soluble decoy recepto
870	93	94	94	73	58	25	49	44	80	89	85	58	OK	69	89	74	Knockout or soluble decoy recepto
871	66	78	72	274	69	56	41	55	87	78	83	62	OK	64	77	70	Knockout or soluble decoy recepto
872	87	92	90	67	50	21	52	41	72	78	75	62	OK	65	82	69	Knockout or soluble decoy recepto
873	86	94	90	75	43	32	56	44	71	77	74	54	OK	67	82	69	Knockout or soluble decoy recepto
874	87	90	89	69	45	35	45	42	79	75	77	63	OK	65	83	69	Knockout or soluble decoy recepto
875	71	87	79	142	64	48	31	48	76	84	80	52	OK	63	79	69	Knockout or soluble decoy recepto
876	88	89	89	76	46	38	29	38	71	86	78	57	OK	63	83	68	Knockout or soluble decoy recepto
877	56	79	68	306	41	51	61	51	81	83	82	50	TT	59	75	67	Knockout or soluble decoy recepto
878	87	94	91	58	54	36	35	42	77	62	70	50	OK	66	80	67	Knockout or soluble decoy recepto
879	88	90	89	98	52	22	38	37	74	72	73	47	OK	63	81	66	Knockout or soluble decoy recepto
880	82	90	86	125	52	61	19	44	64	72	68	52	OK	65	77	66	Knockout or soluble decoy recepto
881	82	90	86	105	47	17	16	27	80	85	83	61	OK	56	84	65	Knockout or soluble decoy recepto
882	68	80	74	218	58	59	41	53	67	72	70	58	OK	63	72	65	Knockout or soluble decoy recepto
883	87	93	90	60	48	10	44	34	77	62	69	53	OK	62	80	64	Knockout or soluble decoy recepto
884	62	79	71	287	28	35	40	34	81	85	83	55	OK	52	77	63	Knockout or soluble decoy recepto
885	61	82	72	168	61	56	62	60	65	52	58	49	OK	66	65	63	Knockout or soluble decoy recepto
886	80	90	85	116	46	27	23	32	61	61	61	46	OK	58	73	59	Knockout or soluble decoy recepto
887	82	93	88	85	25	15	35	25	56	74	65	64	TT	56	76	59	Knockout or soluble decoy recepto
888	73	86	80	130	45	13	9	22	74	77	76	44	OK	51	78	59	Knockout or soluble decoy recepto
889	47	77	62	270	51	28	17	32	87	80	83	56	OK	47	73	59	Knockout or soluble decoy recepto
890	45	58	52	441	59	51	74	61	64	50	57	48	OK	56	54	56	Knockout or soluble decoy recepto
891	54	76	65	285	47	7	25	26	75	66	71	45	OK	46	68	54	Knockout or soluble decoy recepto
892	10	14	12	2255	19	1	15	5	79	88	83	59	OK	8	48	33	Knockout or soluble decoy recepto
3336	77	90	84	140	60	45	39	48	83	83	83	62	OK	66	83	72	Membrane-bound decoy receptor
3337	83	91	87	87	72	66	53	63	79	83	81	46	TT	75	84	77	Membrane-bound decoy receptor
3338	73	81	77	212	67	51	91	70	74	78	76	45	OK	73	77	74	Membrane-bound decoy receptor
3339	67	86	77	137	60	65	52	59	85	79	82	55	OK	68	79	73	Membrane-bound decoy receptor
3340	78	88	83	167	41	44	70	52	75	85	80	64	TT	67	82	72	Membrane-bound decoy receptor
3341	83	83	83	177	62	67	79	69	63	75	69	50	OK	76	76	74	Membrane-bound decoy receptor
3342	80	92	86	117	60	67	47	56	58	82	71	60	OK	72	78	72	Membrane-bound decoy receptor
3343	68	82	75	189	59	57	64	60	79	80	80	50	OK	67	77	71	Membrane-bound decoy receptor
3344	61	85	73	150	57	66	44	56	81	85	83	44	OK	64	78	71	Membrane-bound decoy receptor
3345	89	92	91	82	50	51	24	42	82	78	80	43	OK	66	85	71	Membrane-bound decoy receptor
3346	83	92	88	92	57	56	49	54	84	84	84	51	OK	71	86	75	Membrane-bound decoy receptor
3347	78	91	85	106	66	69	64	66	80	73	77	42	OK	75	81	76	Membrane-bound decoy receptor

FIG. 27F

SEQ ID NO:	MIT	CFD	elit	OffTarget #	Azimuth	DeepSpCas9	CrisprScan	cfd	Lindel	inDelphi	Frameshift	Precision	Graf motifs	on_off	off_off	on Bowtie	Interference predictions
3348	90	93	92	67	50	53	60	54	73	80	77	48	OK	73	84	74	Membrane-bound decoy receptor
3349	79	90	85	125	56	65	73	65	82	85	83	59	OK	75	84	77	Membrane-bound decoy receptor
3350	36	71	54	281	78	71	65	71	89	90	89	55	OK	62	71	71	Membrane-bound decoy receptor
3351	61	82	72	221	64	49	60	58	86	73	80	56	OK	65	76	70	Membrane-bound decoy receptor
3352	72	84	78	157	57	41	35	44	80	81	81	53	OK	61	79	68	Membrane-bound decoy receptor
3353	62	81	72	219	51	42	45	46	85	87	86	50	OK	59	79	68	Membrane-bound decoy receptor
3354	83	92	88	94	41	38	24	34	83	81	82	47	TT	61	85	68	Membrane-bound decoy receptor
3355	82	90	86	95	53	55	10	39	77	80	79	47	OK	63	82	68	Membrane-bound decoy receptor
3356	89	93	91	86	31	22	59	37	76	76	76	42	OK	64	84	68	Membrane-bound decoy receptor
3357	67	85	76	183	56	34	23	38	86	87	87	63	OK	57	81	67	Membrane-bound decoy receptor
3358	71	86	79	168	47	48	33	43	76	81	79	45	TT	61	79	67	Membrane-bound decoy receptor
3359	80	91	86	120	35	32	45	37	67	84	75	57	OK	61	80	66	Membrane-bound decoy receptor
3360	76	89	83	119	52	45	48	48	53	74	63	70	OK	65	73	65	Membrane-bound decoy receptor
3361	82	91	87	106	45	11	38	31	76	76	76	47	OK	59	81	65	Membrane-bound decoy receptor
3362	53	75	64	320	66	44	35	48	81	84	82	48	OK	56	73	65	Membrane-bound decoy receptor
3363	84	93	89	98	54	39	11	35	64	76	70	61	OK	62	79	64	Membrane-bound decoy receptor
3364	76	84	80	150	28	13	34	25	84	88	86	57	TT	52	83	64	Membrane-bound decoy receptor
3365	64	82	73	205	40	32	35	36	81	85	83	61	OK	54	78	64	Membrane-bound decoy receptor
3366	73	90	82	161	44	39	30	38	74	71	72	46	OK	60	77	64	Membrane-bound decoy receptor
3367	70	87	79	161	22	12	29	21	87	93	90	61	TT	50	84	63	Membrane-bound decoy receptor
3368	66	84	75	227	62	41	48	50	73	54	63	58	OK	63	69	63	Membrane-bound decoy receptor
3369	76	87	82	131	40	24	74	46	56	67	61	51	OK	64	71	63	Membrane-bound decoy receptor
3370	65	76	71	219	56	37	44	46	75	69	72	47	OK	58	71	63	Membrane-bound decoy receptor
3371	68	87	78	179	39	45	50	45	67	65	66	46	OK	61	72	63	Membrane-bound decoy receptor
3372	63	75	69	217	59	41	47	49	73	63	68	53	OK	59	69	62	Membrane-bound decoy receptor
3373	69	86	78	168	34	18	43	32	77	76	77	50	TT	55	77	62	Membrane-bound decoy receptor
3374	73	87	80	153	22	13	12	16	81	94	87	67	TT	48	84	61	Membrane-bound decoy receptor
3375	66	79	73	194	40	29	30	33	81	75	78	54	OK	53	75	61	Membrane-bound decoy receptor
3376	70	84	77	150	39	11	26	25	76	82	79	60	TT	51	78	60	Membrane-bound decoy receptor
3377	50	72	61	357	52	44	32	43	67	85	76	59	OK	52	68	60	Membrane-bound decoy receptor
3378	75	90	83	122	23	9	28	20	76	81	78	57	TT	51	80	60	Membrane-bound decoy receptor
3379	67	85	76	198	52	42	53	49	65	85	55	56	OK	62	65	60	Membrane-bound decoy receptor
3380	63	70	67	329	64	34	26	41	73	73	73	51	OK	54	70	60	Membrane-bound decoy receptor
3381	61	78	70	233	50	22	20	31	71	89	80	64	TT	50	75	60	Membrane-bound decoy receptor
3382	70	86	78	234	41	22	33	32	65	70	67	52	OK	55	73	59	Membrane-bound decoy receptor
3383	78	90	84	83	37	21	35	31	66	58	62	50	OK	57	73	59	Membrane-bound decoy receptor
3384	42	68	55	504	47	34	51	44	79	73	76	56	GGC	50	65	58	Membrane-bound decoy receptor
3385	46	67	56	459	52	37	16	35	81	82	82	54	OK	46	70	58	Membrane-bound decoy receptor
3386	62	73	68	273	46	9	36	27	73	80	77	61	OK	47	72	57	Membrane-bound decoy receptor
3387	49	84	67	187	32	25	22	26	71	84	77	56	TT	46	72	57	Membrane-bound decoy receptor

FIG. 27G

SEQ ID NO:	MIT	CFD	SST	OffTarget #	Azimuth	DeepSpCas9	CrisprScan	Cfd	Lindel	inDelphi	Frameshift	Precision	Graf motifs	out_of_frame	out_of_5	out_of_3n+1	Indel/transcript predictions
3388	53	75	64	296	50	22	30	34	72	72	72	51	OK	49	68	57	Membrane-bound decoy receptor
3389	72	77	75	202	46	10	19	25	67	74	71	49	OK	50	73	57	Membrane-bound decoy receptor
3390	65	80	73	217	14	0	23	12	80	88	84	62	TT	42	78	56	Membrane-bound decoy receptor
3391	55	72	64	244	56	42	29	42	63	49	56	55	OK	53	60	54	Membrane-bound decoy receptor
3392	62	73	68	262	27	8	28	20	67	80	74	64	TT	44	71	54	Membrane-bound decoy receptor
3393	48	55	52	451	39	31	26	32	79	74	76	68	GGC	42	64	53	Membrane-bound decoy receptor
3394	52	58	55	455	18	1	31	17	74	83	78	63	OK	36	67	50	Membrane-bound decoy receptor
3395	47	67	57	421	38	7	14	20	62	76	69	69	TT	38	63	49	Membrane-bound decoy receptor
3396	12	45	29	1187	17	0	3	6	85	93	89	58	TT	19	59	42	Membrane-bound decoy receptor
3397	81	93	87	118	65	51	78	65	82	83	82	67	OK	76	85	78	Membrane-bound decoy receptor or Wildtype-like
3398	82	90	86	112	57	36	40	45	82	86	84	54	OK	65	85	72	Membrane-bound decoy receptor or Wildtype-like
3399	74	89	82	146	47	46	58	50	68	73	70	48	OK	66	75	67	Membrane-bound decoy receptor or Wildtype-like
3400	67	84	76	209	54	50	34	46	74	76	75	49	TT	61	75	65	Membrane-bound decoy receptor or Wildtype-like
3401	36	64	50	423	65	56	18	46	70	72	71	50	OK	48	60	56	Membrane-bound decoy receptor or Wildtype-like
3402	76	88	82	147	64	52	16	41	89	90	89	57	OK	61	86	71	Soluble decoy receptor
3403	71	88	80	209	48	34	43	42	74	80	77	66	OK	61	78	66	Soluble decoy receptor
3404	60	75	63	579	44	25	40	36	84	89	87	54	OK	49	75	62	Soluble decoy receptor
3405	67	79	73	223	21	3	47	24	85	89	87	60	OK	48	80	61	Soluble decoy receptor
3406	90	96	93	44	66	57	37	53	85	88	87	57	OK	73	90	78	Wildtype-like
3407	85	96	91	51	66	65	71	67	75	76	76	46	OK	79	83	78	Wildtype-like
3408	79	89	84	80	63	43	49	52	88	96	92	65	OK	68	88	76	Wildtype-like
3409	87	90	89	147	55	51	57	54	78	82	80	60	OK	71	84	74	Wildtype-like
3410	86	93	90	69	45	28	60	44	80	88	84	49	GGC	67	87	73	Wildtype-like
3411	78	85	82	189	45	48	82	58	76	79	77	47	OK	70	79	72	Wildtype-like
3412	60	79	70	310	53	59	61	58	83	89	86	62	TT	64	78	71	Wildtype-like
3413	88	96	92	76	39	12	39	30	84	91	88	56	OK	61	80	70	Wildtype-like
3414	60	77	69	222	69	60	54	61	78	86	82	53	OK	65	75	70	Wildtype-like
3415	63	76	70	247	57	61	39	52	77	88	82	57	OK	61	76	68	Wildtype-like
3416	53	76	65	323	53	43	33	43	79	88	83	58	TT	54	74	64	Wildtype-like
3417	43	74	59	452	54	47	58	53	61	77	69	61	OK	56	64	60	Wildtype-like
3418	55	75	65	222	45	44	45	45	70	71	70	46	OK	55	68	60	Wildtype-like
3419	54	71	63	348	46	44	15	35	75	82	78	62	OK	49	70	59	Wildtype-like
3420	71	85	78	207	48	39	42	43	60	37	49	59	OK	61	63	57	Wildtype-like

FIG. 27H

SEQ ID NO:	Exon	Strand	Start coordinate	End coordinate	crRNA	Off	Off	Frameshift	Frameshift	Interference predictions
893	5	-	7,697,098	7,697,117	AUGAGUUACCCGAAAUACAG	86	61	86	78	Knockout
894	7	+	7,693,664	7,693,683	UUAACUGGACUCACGAUCAG	96	59	80	78	Knockout
895	3	-	7,701,535	7,701,554	AAACCUGGUGUGCUCUUGCA	86	57	85	76	Knockout
896	4	+	7,697,467	7,697,486	GAGUCUCGUUCCAUAGACAC	89	67	71	76	Knockout
897	4	-	7,697,388	7,697,407	GACAUUACUAUUGUGCAGUA	91	47	88	75	Knockout
898	7	-	7,693,656	7,693,675	GAGUCCAGUUAAUGAGACGA	89	59	79	75	Knockout
899	8	-	7,689,765	7,689,784	ACAUUGCUUUGCAGGAUCGC	93	40	93	75	Knockout
900	6	+	7,696,224	7,696,243	UAUUGUCGAGAAGUAGAGGU	89	56	77	74	Knockout
901	6	+	7,696,086	7,696,105	GAGUAAUAAGUCCUAUAACC	90	54	78	74	Knockout
902	4	-	7,697,559	7,697,578	CUGCAUAUGAAAUUGACGUU	90	52	77	73	Knockout
903	5	-	7,697,174	7,697,193	UUUACACAGAAACUACCCCU	85	53	82	73	Knockout
904	6	-	7,696,130	7,696,149	CAUAUAUCCUACACACACUU	85	52	84	73	Knockout
905	6	+	7,696,087	7,696,106	AGUAAUAAGUCCUAUAACCC	88	53	78	73	Knockout
906	7	-	7,693,643	7,693,662	GAGACGAUGGAAGUGGACUU	76	62	80	73	Knockout
907	8	-	7,689,712	7,689,731	UUACUGACUUUGUGUACUGG	84	50	84	73	Knockout
908	3	+	7,701,534	7,701,553	UUGCAAGAGCACACCAGGUU	89	44	83	72	Knockout
909	3	+	7,701,529	7,701,548	CAGCCUUGCAAGAGCACACC	83	46	88	72	Knockout
910	4	-	7,697,466	7,697,485	UGUCUAUGGAACGAGACUCU	89	43	84	72	Knockout
911	5	+	7,697,201	7,697,220	UGUGCAUUGUAACACAAGUC	89	46	82	72	Knockout
912	5	-	7,697,091	7,697,110	ACCCGAAAUACAGUGGUAUA	88	38	91	72	Knockout
913	6	-	7,696,108	7,696,127	GAAAACAAUAUCCUAUUACC	84	43	85	70	Knockout
914	7	+	7,693,673	7,693,692	CUCACGAUCAGAGGCUUCGU	90	47	72	70	Knockout
915	6	-	7,696,166	7,696,185	AAUGUGACAGAAGCGCAUAA	88	41	78	69	Knockout
916	6	-	7,696,107	7,696,126	AAAACAAUAUCCUAUUACCC	79	51	78	69	Knockout
917	6	+	7,696,094	7,696,113	AGUCCUAUAACCCGGGUAAU	97	28	82	69	Knockout
918	6	-	7,696,165	7,696,184	AUGUGACAGAAGCGCAUAAA	79	49	77	68	Knockout
919	7	+	7,693,672	7,693,691	ACUCACGAUCAGAGGCUUCG	89	40	74	68	Knockout
920	8	+	7,689,657	7,689,676	UAUACUCUUCCACCAGCACU	79	54	71	68	Knockout
921	4	-	7,697,480	7,697,499	CAGCGAGACACCUGUGUCUA	84	38	79	67	Knockout
922	4	-	7,697,417	7,697,436	GUUUGUUCCUGCUAAAAUAG	75	41	86	67	Knockout

FIG. 28A

SEQ ID NO:	Exon	Strand	Start coordinate	End coordinate	crRNA	OOF	On	Frameshift	OOF+On	Interference predictions
923	10	-	7,686,632	7,686,651	GAUUUCCAGAAGCACGUGAU	87	49	86	74	Soluble decoy receptor
924	9	-	7,688,746	7,688,765	UAUGUCCAAUUAAGACAACC	91	50	78	73	Soluble decoy receptor
925	10	+	7,686,633	7,686,652	UCACGUGCUUCUGGAAAUCA	75	47	84	69	Soluble decoy receptor
926	9	-	7,688,871	7,688,890	AAAACCCUUCCCUCAAAAGA	70	51	83	68	Soluble decoy receptor
927	9	-	7,688,834	7,688,853	AGUGCUUAAUAUUUCGGCAG	93	43	61	66	Soluble decoy receptor
928	9	+	7,688,788	7,688,807	UUCUUGGCUAAACAGGUAAA	74	30	91	65	Soluble decoy receptor
929	9	+	7,688,781	7,688,800	AUAUGAAUUCUUGGCUAAAC	88	29	79	65	Soluble decoy receptor
930	9	-	7,688,782	7,688,801	UGUUUAGCCAAGAAUUCAUA	79	25	84	63	Soluble decoy receptor
931	10	+	7,686,632	7,686,651	AUCACGUGCUUCUGGAAAUC	80	29	81	63	Soluble decoy receptor
932	10	+	7,686,597	7,686,616	AUGUAAUUGCUACUGUUAAC	82	26	81	63	Soluble decoy receptor
933	9	+	7,688,864	7,688,883	UAUGCCUUCUUUUGAGGGAA	84	38	83	62	Soluble decoy receptor
934	9	+	7,688,863	7,688,882	GUAUGCCUUCUUUUGAGGGA	70	33	83	62	Soluble decoy receptor
935	9	+	7,688,859	7,688,878	AAGUGUAUGCCUUCUUUUGA	70	32	85	62	Soluble decoy receptor
936	9	+	7,688,858	7,688,877	UAAGUGUAUGCCUUCUUUUG	84	34	89	62	Soluble decoy receptor
937	9	+	7,688,795	7,688,814	CUAAACAGGUAAAUGGAUAU	71	28	86	62	Soluble decoy receptor
938	9	+	7,688,738	7,688,757	GUUUACCUGGUUGUCUUAAU	79	26	80	62	Soluble decoy receptor
939	9	+	7,688,772	7,688,791	ACUUCUACCAUAUGAAUUCU	65	24	86	58	Soluble decoy receptor
940	10	+	7,686,624	7,686,643	AUAUGCCAAUCACGUGCUUC	78	23	67	56	Soluble decoy receptor
941	9	-	7,688,840	7,688,859	UAUCACAGUGCUUAAUAUUU	65	24	75	54	Soluble decoy receptor

FIG. 28B

SEQ ID NO:	Exon	Strand	Start coordinate	End coordinate	crRNA	OOF	On	Frameshift	OOF+On	Interference predictions
942	10	-	7,686,546	7,686,565	UGACCUGGUGCUUUGGUACA	88	55	84	75	Membrane-bound decoy receptor
943	11	-	7,685,612	7,685,631	GAGGUCUUGGAAAAACAGUG	69	64	88	73	Membrane-bound decoy receptor
944	10	+	7,686,540	7,686,559	AAUCCCUGUACCAAAGCACC	85	52	81	72	Membrane-bound decoy receptor
945	11	+	7,685,665	7,685,684	AGAGGUGGACCCUUCCCCAA	71	70	76	72	Membrane-bound decoy receptor
946	10	-	7,686,553	7,686,572	UCAAGGUUGACCUGGUGCUU	83	42	81	69	Membrane-bound decoy receptor
947	10	-	7,686,547	7,686,566	UUGACCUGGUGCUUUGGUAC	90	39	76	68	Membrane-bound decoy receptor
948	10	+	7,686,501	7,686,520	ACAAAAUUGUACCUUUUGGG	70	46	86	68	Membrane-bound decoy receptor
949	11	+	7,685,664	7,685,683	UAGAGGUGGACCCUUCCCCA	64	59	82	68	Membrane-bound decoy receptor
950	11	-	7,685,572	7,685,591	AUGGAAGAGAUGACUAUGUU	78	47	80	68	Membrane-bound decoy receptor
951	11	-	7,685,571	7,685,590	UGGAAGAGAUGACUAUGUUG	74	61	65	67	Membrane-bound decoy receptor
952	11	-	7,685,591	7,685,610	GGCUACAAGCUGUUCAUUJA	84	18	92	65	Membrane-bound decoy receptor
953	11	-	7,685,567	7,685,586	AGAGAUGACUAUGUUGGGGA	63	56	77	65	Membrane-bound decoy receptor
954	10	-	7,686,561	7,686,580	UAAGCUCUUCAAGGUUGACC	85	41	66	64	Membrane-bound decoy receptor
955	11	+	7,685,695	7,685,714	AUACAGUAUGUAUGCAUCAU	84	48	60	64	Membrane-bound decoy receptor
956	11	-	7,685,573	7,685,592	UAUGGAAGAGAUGACUAUGU	78	43	71	64	Membrane-bound decoy receptor
957	10	+	7,686,500	7,686,519	UACAAAAUUGUACCUUUUGG	64	44	81	63	Membrane-bound decoy receptor
958	11	-	7,685,631	7,685,650	UGUGUUUAAAGUCUUGCCUG	71	50	64	62	Membrane-bound decoy receptor
959	11	+	7,685,650	7,685,669	AAAAAUAUCUGAGUUAGAGG	70	41	73	61	Membrane-bound decoy receptor
960	11	-	7,685,626	7,685,644	UAAAGUCUUGCCUGAGGUCU	76	43	61	60	Membrane-bound decoy receptor
961	11	+	7,685,647	7,685,666	CACAAAAAUAUCUGAGUUAG	72	27	77	59	Membrane-bound decoy receptor
962	11	+	7,685,612	7,685,631	CACUGUUUUUCCAAGACCUC	75	42	56	58	Membrane-bound decoy receptor
963	10	-	7,686,570	7,686,589	UUUCAUCUAUAAGCUCUUCA	68	28	74	57	Membrane-bound decoy receptor
964	10	+	7,686,499	7,686,518	AUACAAAAUUGUACCUUUUG	62	29	81	57	Membrane-bound decoy receptor
965	10	+	7,686,498	7,686,517	AAUACAAAAUUGUACCUUUU	62	21	84	56	Membrane-bound decoy receptor
966	10	+	7,686,497	7,686,516	GAAUACAAAAUUGUACCUUU	69	18	75	54	Membrane-bound decoy receptor
967	11	-	7,685,726	7,685,745	AUUUUCCCUUUAGCUUCAGA	62	25	71	53	Membrane-bound decoy receptor

FIG. 28C

SEQ ID NO:	Exon	Strand	Start coordinate	End coordinate	crRNA	Off-target		Frameshift		Interference predictions
968	7	-	60,443,782	60,443,801	GAGUCCAACUAAUGAGACAA	86	60	86	77	Knockout
969	6	-	60,445,847	60,445,866	AAAGCAGUAUCGUAUUACCC	93	59	76	76	Knockout
970	6	-	60,445,905	60,445,924	AUGUGACUGCAGCACAUAAG	78	62	86	75	Knockout
971	4	-	60,447,318	60,447,337	GACAUUACUAUUGUGCAGUA	88	46	89	74	Knockout
972	6	-	60,445,848	60,445,867	GAAAGCAGUAUCGUAUUACC	93	48	81	74	Knockout
973	6	+	60,445,827	60,445,846	AGUGAGAAGUUCUAUAACCC	87	59	76	74	Knockout
974	6	+	60,445,826	60,445,845	GAGUGAGAAGUUCUAUAACC	85	56	79	74	Knockout
975	8	-	60,438,392	60,438,411	UGAUGAAGACGACCCAGUGU	89	52	80	74	Knockout
976	4	-	60,447,353	60,447,372	ACUUUGGUUUGUUCCCGCUA	93	49	76	73	Knockout
977	4	+	60,447,336	60,447,355	UCCCGAAUCCUCUACCUUAG	93	39	88	73	Knockout
978	8	-	60,438,460	60,438,479	CAGUUGAUCUGCAAUGUCAG	86	56	77	73	Knockout
979	4	-	60,447,396	60,447,415	UAUCUAUGGAAGUAGACUCC	85	48	83	72	Knockout
980	7	-	60,443,762	60,443,781	UGGAAGCAAGUCUGGGUAAG	70	54	92	72	Knockout
981	8	+	60,438,465	60,438,484	AUUGCAGAUCAACUGUAGCC	88	39	88	72	Knockout
982	4	-	60,447,457	60,447,476	CUUAACCCGAAUGAAAAGAA	76	52	85	71	Knockout
983	4	-	60,447,410	60,447,429	CAGCAAGACACCUAUAUCUA	92	43	78	71	Knockout
984	5	-	60,447,026	60,447,045	AUGAGUUACCCAAAAUACAG	71	56	86	71	Knockout
985	6	-	60,445,906	60,445,925	AAUGUGACUGCAGCACAUAA	80	46	88	71	Knockout
986	6	-	60,445,870	60,445,889	CAAGCAUCCUAUACAUACUU	85	47	82	71	Knockout
987	8	-	60,438,389	60,438,408	UGAAGACGACCCAGUGUUGG	85	57	71	71	Knockout
988	8	+	60,438,377	60,438,396	AAUAAUCCUCCACCAACACU	83	50	79	71	Knockout
989	4	-	60,447,347	60,447,366	GUUUGUUCCCGCUAAGGUAG	92	47	72	70	Knockout
990	4	-	60,447,340	60,447,359	CCCGCUAAGGUAGAGGAUUC	90	40	81	70	Knockout
991	4	+	60,447,337	60,447,356	CCCGAAUCCUCUACCUUAGC	91	37	83	70	Knockout
992	5	+	60,447,084	60,447,103	AGUUGUCCAUCUCUUGCAAU	85	44	80	70	Knockout
993	7	-	60,443,769	60,443,788	GAGACAAUGGAAGCAAGUCU	74	54	82	70	Knockout
994	5	+	60,447,129	60,447,148	UCUGCAUUGUAACACAAGUU	83	42	82	69	Knockout
995	5	-	60,447,093	60,447,112	AAACUACCCAUUGCAAGAGA	82	44	82	69	Knockout
996	8	-	60,438,486	60,438,505	UACAUUGCUUUGCAGGAUCC	82	36	90	69	Knockout
997	4	+	60,447,397	60,447,416	GAGUCUACUUCCAUAGAUAU	90	46	69	68	Knockout

FIG. 29A

SEQ ID NO:	Exon	Strand	Start coordinate	End coordinate	crRNA	OOF	GH	Frameshift	CFSAM1	Interference predictions
998	9	-	60,437,463	60,437,482	UAUAUCCAAUUGAUACAUCC	84	47	87	73	Soluble decoy receptor
999	9	+	60,437,498	60,437,517	AUCUGUAUUCUUGGCUACAC	82	45	82	70	Soluble decoy receptor
1000	9	+	60,437,505	60,437,524	UUCUUGGCUACACAGGUAAA	79	33	90	67	Soluble decoy receptor
1001	9	-	60,437,499	60,437,518	UGUGUAGCCAAGAAUACAGA	74	47	78	66	Soluble decoy receptor
1002	9	+	60,437,455	60,437,474	GUUUACCUGGAUGUAUCAAU	81	36	82	66	Soluble decoy receptor
1003	10	-	60,434,976	60,434,995	GAUUUCAAGAAGCACACAAU	71	35	84	63	Soluble decoy receptor
1004	10	+	60,434,977	60,434,996	UUGUGUGCUUCUUGAAAUCA	61	35	86	61	Soluble decoy receptor
1005	9	+	60,437,489	60,437,508	AUUUAUACCAUCUGUAUUCU	68	19	85	57	Soluble decoy receptor
1006	10	+	60,434,976	60,434,995	AUUGUGUGCUUCUUGAAAUC	57	30	85	57	Soluble decoy receptor
1007	9	-	60,437,551	60,437,570	AGUACUUAAUAUUUCAGAAG	63	34	68	55	Soluble decoy receptor
1008	9	+	60,437,580	60,437,599	GUGUUCUUUCUUUUGGUUGA	52	16	87	52	Soluble decoy receptor
1009	9	+	60,437,573	60,437,592	GAUGAUUGUGUUCUUUCUUU	46	26	69	47	Soluble decoy receptor

FIG. 29B

SEQ ID NO:	Exon	Strand	Start coordinate	End coordinate	crRNA	OOF	GH	Frameshift	CFSAM1	Interference predictions
1010	11	-	60,433,927	60,433,946	UGGAAGGGACGCCUAUGUUG	90	67	71	76	Membrane-bound decoy receptor
1011	11	+	60,434,021	60,434,040	CGAGGUGGACCCUUCCCCAA	82	65	77	75	Membrane-bound decoy receptor
1012	11	-	60,433,928	60,433,947	AUGGAAGGGACGCCUAUGUU	94	49	82	75	Membrane-bound decoy receptor
1013	11	-	60,433,923	60,433,942	AGGGACGCCUAUGUUGGGGA	85	61	80	75	Membrane-bound decoy receptor
1014	11	-	60,434,038	60,434,057	ACUAUAUCCAAAGACCCUUG	78	60	81	73	Membrane-bound decoy receptor
1015	11	-	60,433,968	60,433,987	GAGGUCUUGGAAAAACAGUG	68	64	88	73	Membrane-bound decoy receptor
1016	11	+	60,433,913	60,433,932	ACACAUACCUUCCCCAACAU	85	59	72	72	Membrane-bound decoy receptor
1017	11	+	60,434,020	60,434,039	UCGAGGUGGACCCUUCCCCA	76	56	82	71	Membrane-bound decoy receptor
1018	10	-	60,434,890	60,434,909	UGACAUUGUGCUUUGGUACA	78	48	83	70	Membrane-bound decoy receptor
1019	11	-	60,433,929	60,433,948	UAUGGAAGGGACGCCUAUGU	94	34	81	70	Membrane-bound decoy receptor
1020	10	-	60,434,897	60,434,916	UCAAGGUUGACAUUGUGCUU	81	43	78	67	Membrane-bound decoy receptor
1021	10	+	60,434,845	60,434,864	ACAAAGUUGUACCUUUUGGA	73	45	84	67	Membrane-bound decoy receptor
1022	11	-	60,434,040	60,434,059	AUACUAUAUCCAAAGACCCU	78	37	85	67	Membrane-bound decoy receptor
1023	11	-	60,433,943	60,433,962	AUAAGCUGUUCAUUUAUGGA	74	36	87	66	Membrane-bound decoy receptor
1024	10	+	60,434,844	60,434,863	UACAAAGUUGUACCUUUUGG	69	47	80	65	Membrane-bound decoy receptor
1025	11	+	60,434,006	60,434,025	AAAAAUAUCUGAGUUCGAGG	85	42	69	65	Membrane-bound decoy receptor
1026	10	-	60,434,891	60,434,910	UUGACAUUGUGCUUUGGUAC	83	32	77	64	Membrane-bound decoy receptor
1027	11	-	60,434,039	60,434,058	UACUAUAUCCAAAGACCCUU	79	31	82	64	Membrane-bound decoy receptor
1028	11	-	60,434,034	60,434,053	UAUCCAAAGACCCUUGGGGA	67	44	82	64	Membrane-bound decoy receptor
1029	11	+	60,434,003	60,434,022	CACAAAAAUAUCUGAGUUCG	79	31	79	63	Membrane-bound decoy receptor
1030	11	-	60,433,947	60,433,966	GGAUAUAAGCUGUUCAUUUA	79	21	90	63	Membrane-bound decoy receptor
1031	11	-	60,433,942	60,433,961	UAAGCUGUUCAUUUAUGGAA	71	43	76	63	Membrane-bound decoy receptor
1032	11	+	60,434,028	60,434,047	GACCCUUCCCCAAGGGUCUU	79	21	86	62	Membrane-bound decoy receptor
1033	11	-	60,433,987	60,434,006	UGUGUUUAAAGUCUUGCCUG	71	50	64	62	Membrane-bound decoy receptor
1034	11	-	60,433,981	60,434,000	UAAAGUCUUGCCUGAGGUCU	77	43	62	61	Membrane-bound decoy receptor
1035	11	-	60,434,033	60,434,052	AUCCAAAGACCCUUGGGGAA	64	45	70	60	Membrane-bound decoy receptor
1036	11	+	60,434,051	60,434,070	AUAUAGUAUAUAUGCAUCAU	68	46	64	59	Membrane-bound decoy receptor
1037	10	+	60,434,841	60,434,860	GAAUACAAAGUUGUACCUUU	74	24	74	57	Membrane-bound decoy receptor
1038	10	-	60,434,859	60,434,878	UAUGAUUUUCUCCCUCCAAA	56	33	80	56	Membrane-bound decoy receptor
1039	11	+	60,433,968	60,433,987	CACUGUUUUUCCAAGACCUC	73	40	57	56	Membrane-bound decoy receptor

FIG. 29C

SEQ ID NO:	Genomic cut coordinate	Exon	CDS cut position	CDS cut position %	Strand	Start coordinate	End coordinate	crRNA	GC content	PAM
1040	190,604,156	4	93	5.4	+	190,604,140	190,604,159	ACUGGGGACUAGACACCAUG	55	AGG
1041	190,604,267	4	204	11.9	+	190,604,251	190,604,270	CAGCUGGCCUUACUCUGAUC	55	TGG
1042	190,604,283	4	220	12.8	+	190,604,267	190,604,286	GAUCUGGUAUUGGACUAGGC	50	AGG
1043	190,604,329	4	266	15.5	-	190,604,327	190,604,346	CCUUACUAAUGCGGUUCUCG	50	GGG
1044	190,609,068	5	424	24.8	-	190,609,066	190,609,085	AUGCACUGGGAGUUUCAUGG	50	GGG
1045	190,609,069	5	425	24.8	-	190,609,067	190,609,086	UAUGCACUGGGAGUUUCAUG	45	GGG
1046	190,609,109	5	465	27.1	+	190,609,093	190,609,112	AUAUAGAAUAUGGCAUUCAG	30	AGG
1047	190,609,151	5	507	29.6	-	190,609,149	190,609,168	AUAGUCGGUUUGACACUGGA	45	AGG
1048	190,609,155	5	511	29.8	-	190,609,153	190,609,172	AGUGAUAGUCGGUUUGACAC	45	TGG
1049	190,620,317	6	580	33.9	-	190,620,315	190,620,334	GAAACUCAAGUUCAUACCUU	35	CGG
1050	190,623,410	7	770	45	+	190,623,394	190,623,413	GUGGUCUAUGAGAAAGAACC	45	AGG
1051	190,627,343	8	796	46.5	+	190,627,327	190,627,346	GGAGCUACUCAUUCCCUGUA	50	CGG
1052	190,627,345	8	798	46.6	-	190,627,343	190,627,362	AAACUAAAAUAGACCGUACA	30	GGG
1053	190,627,398	8	851	49.7	+	190,627,382	190,627,401	GAGGUUUGGUGGACCAUUGA	50	TGG
1054	190,627,444	8	897	52.4	+	190,627,428	190,627,447	UUGAUGUCACCAUUAACGAA	35	AGG
1055	190,629,417	9	970	56.6	-	190,629,415	190,629,434	GCUGCGCUUGAGAUCCUCAG	60	AGG
1056	190,604,376	4	313	18.3	-	190,604,374	190,604,393	GCCAGUGUCAUUGAGGAGAG	55	TGG
1057	190,609,176	5	532	31.1	+	190,609,160	190,609,179	ACCGACUAUCACUUGGUAUA	40	TGG
1058	190,620,435	6	698	40.7	+	190,620,419	190,620,438	ACUCUGACUGUAAAGGUAGU	40	AGG
1059	190,604,383	4	320	18.7	-	190,604,381	190,604,400	UAUAGUUGCCAGUGUCAUUG	40	AGG
1060	190,627,387	8	840	49	+	190,627,371	190,627,390	AUUCUCGCAAUGAGGUUUGG	45	TGG
1061	190,604,263	4	200	11.7	-	190,604,261	190,604,280	UCCAAUACCAGAUCAGAGUA	40	AGG
1062	190,604,288	4	225	13.1	+	190,604,272	190,604,291	GGUAUUGGACUAGGCAGGAC	55	CGG
1063	190,604,251	4	188	11	-	190,604,249	190,604,268	UCAGAGUAAGGCCAGCUGAA	50	TGG
1064	190,627,384	8	837	48.9	+	190,627,368	190,627,387	UGGAUUCUCGCAAUGAGGUU	45	TGG
1065	190,604,375	4	312	18.2	-	190,604,373	190,604,392	CCAGUGUCAUUGAGGAGAGU	50	GGG
1066	190,604,289	4	226	13.2	+	190,604,273	190,604,292	GUAUUGGACUAGGCAGGACC	55	GGG
1067	190,604,408	4	345	20.1	+	190,604,392	190,604,411	GCAACUAUACCUGCAUGUUA	40	AGG
1068	190,620,412	6	675	39.4	+	190,620,396	190,620,415	GACGUACGUUUCAUCUCACC	50	AGG
1069	190,629,457	9	1010	59	+	190,629,441	190,629,460	UGUCAUGCUAGAAGUGCCAA	45	AGG
1070	190,604,192	4	129	7.5	-	190,604,190	190,604,209	AGUGGGCACUUGAUGCGAGC	60	TGG
1071	190,604,357	4	294	17.2	+	190,604,341	190,604,360	GUAAGGAGAAAGAUGUGCUG	45	TGG
1072	190,604,209	4	146	8.5	-	190,604,207	190,604,226	UCAAGAAGUGUUCAAAGAGU	35	GGG
1073	190,609,169	5	525	30.6	+	190,609,153	190,609,172	GUGUCAAACCGACUAUCACU	45	TGG
1074	190,623,380	7	740	43.2	-	190,623,378	190,623,397	CCACAUGAUCAUUAGGUGAA	40	TGG
1075	190,629,414	9	967	56.5	+	190,629,398	190,629,417	CAUCAAGAAAGUUACCUCUG	40	AGG
1076	190,604,326	4	263	15.4	-	190,604,324	190,604,343	UACUAAUGCGGUUCUCGGGG	55	AGG
1077	190,604,323	4	260	15.2	-	190,604,321	190,604,340	UAAUGCGGUUCUCGGGGAGG	60	CGG
1078	190,627,346	8	799	46.6	-	190,627,344	190,627,363	AAAACUAAAAUAGACCGUAC	30	AGG
1079	190,620,428	6	691	40.3	+	190,620,412	190,620,431	CACCAGGACUCUGACUGUAA	50	AGG
1080	190,620,316	6	579	33.8	-	190,620,314	190,620,333	AAACUCAAGUUCAUACCUUC	35	GGG
1081	190,620,312	6	575	33.6	+	190,620,296	190,620,315	UUUAAUAAUGUAAUACCCGA	25	AGG
1082	190,604,312	4	249	14.5	-	190,604,310	190,604,329	UCGGGGAGGCGGAAGUUAAU	55	TGG
1083	190,620,339	6	602	35.1	-	190,620,337	190,620,356	UAUUUGAAAUUAAGGCAAUG	25	AGG
1084	190,609,081	5	437	25.5	-	190,609,079	190,609,098	CUAUAUACAGUUUAUGCACU	30	GGG
1085	190,604,298	4	235	13.7	+	190,604,282	190,604,301	UAGGCAGGACCGGGACCUUG	65	AGG
1086	190,604,340	4	277	16.2	+	190,604,324	190,604,343	CCCCGAGAACCGCAUUAGUA	55	AGG
1087	190,620,419	6	682	39.8	-	190,620,417	190,620,436	UACCUUUACAGUCAGAGUCC	45	TGG
1088	190,604,330	4	267	15.6	-	190,604,328	190,604,347	UCCUUACUAAUGCGGUUCUC	45	GGG
1089	190,604,386	4	323	18.9	+	190,604,370	190,604,389	CCCACUCUCCUCAAUGACAC	55	TGG

FIG. 30A

SEQ ID NO:	Genomic cut coordinate	Exon	CDS cut position	CDS cut position %	Strand	Start coordinate	End coordinate	crRNA	GC content	PAM
1090	190,609,070	5	426	24.9	-	190,609,068	190,609,087	UUAUGCACUGGGAGUUUCAU	40	GGG
1091	190,604,279	4	216	12.6	+	190,604,263	190,604,282	CUCUGAUCUGGUAUUGGACU	45	AGG
1092	190,620,390	6	653	38.1	+	190,620,374	190,620,393	GUUGUUACAUAUCCAGAAAA	30	TGG
1093	190,604,371	4	308	18	-	190,604,369	190,604,388	UGUCAUUGAGGAGAGUGGGC	55	CGG
1094	190,604,173	4	110	6.4	-	190,604,171	190,604,190	CUGGCUCAUCUUCAAACACU	45	TGG
1095	190,604,331	4	268	15.6	-	190,604,329	190,604,348	CUCCUUACUAAUGCGGUUCU	45	CGG
1096	190,609,071	5	427	24.9	-	190,609,069	190,609,088	UUUAUGCACUGGGAGUUUCA	40	TGG
1097	190,609,166	5	522	30.5	-	190,609,164	190,609,183	ACCAUAUACCAAGUGAUAGU	35	CGG
1098	190,609,026	5	382	22.3	+	190,609,010	190,609,029	CAGCAAAGUUGCAUUUCCCU	45	TGG
1099	190,604,250	4	187	10.9	-	190,604,248	190,604,267	CAGAGUAAGGCCAGCUGAAU	50	GGG
1100	190,609,082	5	438	25.6	-	190,609,080	190,609,099	UCUAUAUACAGUUUAUGCAC	30	TGG
1101	190,604,273	4	210	12.3	+	190,604,257	190,604,276	GCCUUACUCUGAUCUGGUAU	45	TGG
1102	190,604,210	4	147	8.6	-	190,604,208	190,604,227	UUCAAGAAGUGUUCAAAGAG	35	TGG
1103	190,604,296	4	233	13.6	-	190,604,294	190,604,313	UAAUUGGCUCCUCAAGGUCC	50	CGG
1104	190,623,391	7	751	43.8	+	190,623,375	190,623,394	CCAUUCACCUAAUGAUCAUG	40	TGG
1105	190,604,338	4	275	16.1	-	190,604,336	190,604,355	CAUCUUUCUCCUUACUAAUG	35	CGG
1106	190,564,324	3	35	2	+	190,564,308	190,564,327	GUAGUGAGUCUCUACUUUUA	35	TGG
1107	190,604,160	4	97	5.7	-	190,604,158	190,604,177	AAACACUUGGAUUUGCCUCA	40	TGG
1108	190,604,302	4	239	14	-	190,604,300	190,604,319	GGAAGUUAAUUGGCUCCUCA	45	AGG
1109	190,604,251	4	188	11	+	190,604,235	190,604,254	UACAGCACAGCCCAUUCAGC	55	TGG
1110	190,627,400	8	853	49.8	-	190,627,398	190,627,417	AUCAGGUUUUUUUCCAUCAA	30	TGG
1111	190,623,354	7	714	41.7	-	190,623,352	190,623,371	ACAGGGGGCACUGCAUUUUU	50	TGG
1112	190,609,031	5	387	22.6	-	190,609,029	190,609,048	UCUUUUUGAACAACUUCCAA	30	GGG
1113	190,620,391	6	654	38.2	-	190,620,389	190,620,408	UGAAACGUACGUCCAUUUUC	40	TGG
1114	190,627,417	8	870	50.8	-	190,627,415	190,627,434	ACAUCAAUAGUGAUGUCAUC	35	AGG
1115	190,609,132	5	488	28.5	+	190,609,116	190,609,135	AUCACUUGUCCAAAUGUAGA	35	TGG
1116	190,623,387	7	747	43.6	-	190,623,385	190,623,404	UCAUAGACCACAUGAUCAUU	35	AGG
1117	190,609,130	5	486	28.4	-	190,609,128	190,609,147	GGAAAAUAUCCAUCUACAUU	30	TGG
1118	190,609,032	5	388	22.7	-	190,609,030	190,609,049	GUCUUUUUGAACAACUUCCA	35	AGG
1119	190,604,363	4	300	17.5	+	190,604,347	190,604,366	AGAAAGAUGUGCUGUGGUUC	45	CGG
1120	190,620,354	6	617	36	+	190,620,338	190,620,357	AUUGCCUUAAUUUCAAAUAA	20	TGG
1121	190,629,462	9	1015	59.3	-	190,629,460	190,629,479	UGCUUUGGCAACUUCGCCUU	50	TGG
1122	190,629,477	9	1030	60.1	-	190,629,475	190,629,494	CUGCUUCACCUUGGCUGCUU	55	TGG
1123	190,645,737	11	1240	72.4	+	190,645,721	190,645,740	UGUAUCCUAUGCAAGGAAUG	40	CGG
1124	190,645,771	11	1274	74.4	+	190,645,755	190,645,774	UUUGUAUUACUGACCCUCCG	45	TGG
1125	190,645,773	11	1276	74.5	-	190,645,771	190,645,790	AUUCUCCAAAACUCCACGGA	45	GGG
1126	190,645,774	11	1277	74.5	-	190,645,772	190,645,791	CAUUCUCCAAAACUCCACGG	50	AGG
1127	190,645,832	11	1335	77.9	+	190,645,816	190,645,835	UUGACCGAGACAGUCUGCCU	55	GGG
1128	190,645,833	11	1336	78	+	190,645,817	190,645,836	UGACCGAGACAGUCUGCCUG	60	GGG
1129	190,645,834	11	1337	78.1	+	190,645,818	190,645,837	GACCGAGACAGUCUGCCUGG	65	GGG
1130	190,648,386	12	1394	81.4	-	190,648,384	190,648,403	UGGGGCUUAGAACAACCAGG	55	AGG
1131	190,648,413	12	1421	83	+	190,648,397	190,648,416	AGCCCCAACUACGUGCUCCA	60	GGG
1132	190,648,467	12	1475	86.1	+	190,648,451	190,648,470	CUAGAAAAUAUGGCCUCUCG	45	GGG
1133	190,648,469	12	1477	86.2	-	190,648,467	190,648,486	GACGUUGAUGUUGCCCCGAG	60	AGG
1134	190,648,404	12	1412	82.4	-	190,648,402	190,648,421	UUCCCUGGAGCACGUAGUUG	55	GGG
1135	190,648,389	12	1397	81.6	-	190,648,387	190,648,406	AGUUGGGGCUUAGAACAACC	50	AGG
1136	190,645,730	11	1233	72	+	190,645,714	190,645,733	AUAUUUAUGUAUCCUAUGCA	25	AGG
1137	190,648,517	12	1525	89	+	190,648,501	190,648,520	CAAAGCUGUGAAGGAAACGA	45	AGG
1138	190,648,466	12	1474	86	+	190,648,450	190,648,469	CCUAGAAAAUAUGGCCUCUC	45	GGG
1139	190,648,508	12	1516	88.5	+	190,648,492	190,648,511	AGUACAGUACAAAGCUGUGA	40	AGG

FIG. 30B

SEQ ID NO:	Genomic cut coordinate	Exon	CDS cut position	CDS cut position %	Strand	Start coordinate	End coordinate	crRNA	GC content	PAM
1140	190,648,412	12	1420	82.9	+	190,648,396	190,648,415	AAGCCCCAACUACGUGCUCC	60	AGG
1141	190,644,361	10	1165	68	+	190,644,345	190,644,364	AGAGAUGGUCCUAUUUUACC	40	GGG
1142	190,648,433	12	1441	84.1	-	190,648,431	190,648,450	GCCAGCCUUGAGCUCCAGGA	65	GGG
1143	190,645,825	11	1328	77.5	-	190,645,823	190,645,842	UUCCCCCAGGCAGACUGUCU	60	CGG
1144	190,645,779	11	1282	74.8	+	190,645,763	190,645,782	ACUGACCCUCCGUGGAGUUU	55	TGG
1145	190,648,406	12	1414	82.5	-	190,648,404	190,648,423	GGUUCCCUGGAGCACGUAGU	60	TGG
1146	190,645,777	11	1280	74.7	-	190,645,775	190,645,794	AUUCAUUCUCCAAAACUCCA	35	CGG
1147	190,645,831	11	1334	77.9	+	190,645,815	190,645,834	UUUGACCGAGACAGUCUGCC	55	TGG
1148	190,645,731	11	1234	72	-	190,645,729	190,645,748	UUCUUCCGCAUUCCUUGCAU	45	AGG
1149	190,644,360	10	1164	68	+	190,644,344	190,644,363	UAGAGAUGGUCCUAUUUUAC	35	CGG
1150	190,648,465	12	1473	86	+	190,648,449	190,648,468	GCCUAGAAAAUAUGGCCUCU	45	CGG
1151	190,644,368	10	1172	68.4	-	190,644,366	190,644,385	CAUCUGUUCCAAAAUGAGCC	45	CGG
1152	190,648,534	12	1542	90	+	190,648,518	190,648,537	CGAAGGUGAAAGAGCUGAAG	50	AGG
1153	190,644,359	10	1163	67.9	-	190,644,357	190,644,376	CAAAAUGAGCCCGGUAAAAU	40	AGG
1154	190,648,457	12	1465	85.5	+	190,648,441	190,648,460	CAAGGCUGGCCUAGAAAAUA	45	TGG
1155	190,648,455	12	1463	85.4	-	190,648,453	190,648,472	CCCGAGAGGCCAUAUUUUCU	50	AGG
1156	190,648,382	12	1390	81.1	+	190,648,366	190,648,385	UCAGAAAAGCAGACGCCUCC	55	TGG
1157	190,648,405	12	1413	82.5	-	190,648,403	190,648,422	GUUCCCUGGAGCACGUAGUU	55	GGG
1158	190,644,371	10	1175	68.6	+	190,644,355	190,644,374	CUAUUUUACCGGGCUCAUUU	40	TGG
1159	190,644,392	10	1196	69.8	+	190,644,376	190,644,395	GGAACAGAUGAAACCAUUUU	35	AGG
1160	190,648,434	12	1442	84.2	-	190,648,432	190,648,451	GGCCAGCCUUGAGCUCCAGG	70	AGG
1161	190,648,535	12	1543	90.1	+	190,648,519	190,648,538	GAAGGUGAAAGAGCUGAAGA	45	GGG
1162	190,648,419	12	1427	83.3	-	190,648,417	190,648,436	CCAGGAGGGCUUGGGUUCCC	70	TGG
1163	190,648,427	12	1435	83.8	-	190,648,425	190,648,444	CUUGAGCUCCAGGAGGGCUU	60	GGG
1164	190,648,443	12	1451	84.7	+	190,648,427	190,648,446	GCCCUCCUGGAGCUCAAGGC	70	TGG
1165	190,648,430	12	1438	83.9	+	190,648,414	190,648,433	CCAGGGAACCCAAGCCCUCC	70	TGG
1166	190,648,439	12	1447	84.5	+	190,648,423	190,648,442	CCAAGCCCUCCUGGAGCUCA	65	AGG
1167	190,648,428	12	1436	83.8	-	190,648,426	190,648,445	CCUUGAGCUCCAGGAGGGCU	65	TGG
1168	190,648,571	12	1579	92.2	+	190,648,555	190,648,574	CACGGUCAUUAAAUGGAAAG	40	GGG
1169	190,648,603	12	1611	94	+	190,648,587	190,648,606	AGUAUCCACAGGGCAGGUUC	55	TGG
1170	190,648,564	12	1572	91.8	+	190,648,548	190,648,567	CGGUGCUCACGGUCAUUAAA	50	TGG
1171	190,648,589	12	1597	93.2	-	190,648,587	190,648,606	GAACCUGCCCUGUGGAUACU	55	TGG
1172	190,648,597	12	1605	93.7	+	190,648,581	190,648,600	AAUCCAAGUAUCCACAGGGC	50	AGG
1173	190,648,544	12	1552	90.6	+	190,648,528	190,648,547	AGAGCUGAAGAGGGCUAAGA	50	CGG
1174	190,648,597	12	1605	93.7	-	190,648,595	190,648,614	UGCUUCCAGAACCUGCCCUG	60	TGG
1175	190,648,569	12	1577	92.1	+	190,648,553	190,648,572	CUCACGGUCAUUAAAUGGAA	40	AGG
1176	190,648,553	12	1561	91.1	+	190,648,537	190,648,556	GAGGGCUAAGACGGUGCUCA	60	CGG
1177	190,648,592	12	1600	93.4	+	190,648,576	190,648,595	GGAAAAAUCCAAGUAUCCAC	40	AGG
1178	190,648,619	12	1627	95	+	190,648,603	190,648,622	GUUCUGGAAGCAGCUGCAGG	60	TGG
1179	190,648,570	12	1578	92.1	+	190,648,554	190,648,573	UCACGGUCAUUAAAUGGAAA	35	GGG
1180	190,648,616	12	1624	94.8	+	190,648,600	190,648,619	CAGGUUCUGGAAGCAGCUGC	60	AGG
1181	190,644,265	10	1069	62.4	+	190,644,249	190,644,268	GCCAGCUCCAAGAUACACAG	55	TGG
1182	190,644,278	10	1082	63.2	+	190,644,262	190,644,281	UACACAGUGGAACUGGCUUG	50	TGG
1183	190,644,298	10	1102	64.3	-	190,644,296	190,644,315	AAUCACCACUAGCAGGACUG	50	TGG
1184	190,644,261	10	1065	62.2	-	190,644,259	190,644,278	GCCAGUUCCACUGUGUAUCU	50	TGG
1185	190,629,493	9	1046	61.1	+	190,629,477	190,629,496	GCAGCCAAGGUGAAGCAGAA	55	AGG
1186	190,629,480	9	1033	60.3	+	190,629,464	190,629,483	CGAAGUUGCCAAAGCAGCCA	55	AGG
1187	190,644,305	10	1109	64.7	-	190,644,303	190,644,322	CAAUGAGAAUCACCACUAGC	45	AGG
1188	190,644,304	10	1108	64.7	+	190,644,288	190,644,307	UGGAGCCACAGUCCUGCUAG	60	TGG
1189	190,644,271	10	1075	62.8	+	190,644,255	190,644,274	UCCAAGAUACACAGUGGAAC	45	TGG

FIG. 30C

SEQ ID NO:	Genomic cut coordinate	Exon	CDS cut position	CDS cut position %	Strand	Start coordinate	End coordinate	crRNA	GC content	PAM
1190	190,644,284	10	1088	63.5	+	190,644,268	190,644,287	GUGGAACUGGCUUGUGGUUU	50	TGG
1191	190,644,255	10	1059	61.8	-	190,644,253	190,644,272	UCCACUGUGUAUCUUGGAGC	50	TGG
1192	190,644,335	10	1139	66.5	-	190,644,333	190,644,352	CCAUCUCUAGCCAGUAAACA	45	TGG
1193	190,644,346	10	1150	67.1	+	190,644,330	190,644,349	CCAUGUUUACUGGCUAGAGA	45	TGG
1194	190,644,336	10	1140	66.5	+	190,644,320	190,644,339	UUGUUGUUUACCAUGUUUAC	30	TGG
1195	190,648,668	12	1676	97.8	+	190,648,652	190,648,671	CGGUCUAGCAGUGAUGAGCA	55	GGC
1196	190,648,648	12	1656	96.7	+	190,648,632	190,648,651	CAGUGAAGAAAAGUCCCAGG	50	CGC
1197	190,648,667	12	1675	97.8	+	190,648,651	190,648,670	GCGGUCUAGCAGUGAUGAGC	60	AGG
1198	190,648,651	12	1659	96.8	-	190,648,649	190,648,668	UCAUCACUGCUAGACCGCCU	55	GGC
1199	190,648,645	12	1653	96.5	+	190,648,629	190,648,648	UGCCAGUGAAGAAAAGUCCC	50	AGG
1200	190,648,652	12	1660	96.9	-	190,648,650	190,648,669	CUCAUCACUGCUAGACCGCC	60	TGG
1201	190,648,680	12	1688	98.5	-	190,648,678	190,648,697	UUUUCAAAGAUGAAUACGAG	30	AGG
1202	190,648,636	12	1644	96	-	190,648,634	190,648,653	CGCCUGGGACUUUUCUUCAC	55	TGG
1203	190,648,631	12	1639	95.7	-	190,648,629	190,648,648	GGGACUUUUCUUCACUGGCA	50	TGG

FIG. 30D

SEQ ID NO:	MIT	CFD	Elevation	CFD	OffTarget #	Azimuth	DeepSpCas9	CrispScan	CFD	Lindel	inDelphi	Frameshift	Precision	Graf Motifs	Bioscore	ON_OFF	OFF_FS	ON_FS	Interference predictions
1040	81	91	49	74	103	71	65	52	53	89	86	88	49	OK	87	68	81	75	Knockout
1041	88	95	57	80	56	42	38	41	40	88	91	89	61	OK	91	60	85	70	Knockout
1042	86	93	53	77	66	60	48	33	47	82	86	84	58	OK	63	62	81	69	Knockout
1043	95	97	53	82	21	58	46	27	44	85	78	82	55	OK	49	63	82	69	Knockout
1044	89	82	61	71	172	70	65	69	68	86	90	88	59	OK	58	69	79	76	Knockout
1045	87	81	59	69	204	63	52	48	54	81	85	83	52	OK	58	61	76	69	Knockout
1046	85	75	58	66	258	67	53	43	54	89	89	89	58	OK	60	60	77	70	Knockout
1047	92	94	42	76	44	63	65	56	61	88	89	88	64	OK	56	69	82	75	Knockout
1048	93	96	53	81	35	59	61	44	55	77	87	82	59	OK	61	68	81	72	Knockout
1049	74	89	60	74	238	49	44	50	48	86	89	87	47	TT	50	61	81	70	Knockout
1050	73	87	60	73	160	55	70	63	63	76	81	79	52	OK	59	69	76	72	Knockout
1051	80	91	59	77	79	53	61	43	52	89	88	88	63	OK	78	65	83	73	Knockout
1052	81	89	50	73	217	66	44	34	48	92	90	91	61	OK	75	61	82	71	Knockout
1053	76	88	58	73	156	39	38	58	45	89	86	92	62	OK	68	59	83	70	Knockout
1054	89	92	59	80	101	66	48	48	54	90	86	86	53	OK	62	67	83	73	Knockout
1055	78	90	55	74	102	71	63	72	69	86	90	86	63	OK	70	72	81	77	Knockout
1056	59	72	56	62	262	57	49	59	55	87	87	87	61	OK	57	59	75	68	Knockout
1057	91	97	53	80	31	36	33	39	36	85	91	88	64	OK	75	58	84	68	Knockout
1058	80	85	59	75	129	51	51	36	46	83	84	83	63	OK	58	60	79	68	Knockout
1059	79	88	60	76	120	60	56	36	51	75	81	78	57	OK	56	63	77	68	Knockout
1060	80	84	51	72	87	54	37	36	42	87	88	91	63	OK	76	57	81	68	Knockout
1061	77	89	61	76	120	51	54	33	48	84	83	84	54	OK	74	61	80	68	Knockout
1062	78	90	47	72	108	55	50	52	52	75	80	77	44	OK	61	62	74	67	Knockout
1063	68	80	61	70	201	54	58	26	46	87	82	85	65	OK	61	58	77	67	Knockout
1064	89	95	51	78	57	43	39	50	44	77	79	78	43	OK	76	61	78	67	Knockout
1065	63	80	61	68	216	57	53	52	54	77	78	78	48	OK	66	61	73	67	Knockout
1066	80	92	47	73	78	64	62	45	57	74	70	72	44	OK	61	65	73	67	Knockout
1067	84	91	59	78	75	43	38	42	41	81	84	82	47	OK	68	59	80	67	Knockout
1068	90	96	52	79	37	58	32	32	41	75	85	80	49	OK	59	60	79	67	Knockout
1069	71	75	60	69	205	64	41	39	48	83	83	83	48	OK	55	58	76	67	Knockout
1070	80	83	43	75	77	49	34	22	35	90	91	91	46	OK	58	55	83	67	Knockout
1071	58	70	61	63	329	65	60	40	55	74	86	80	62	OK	68	59	71	66	Knockout
1072	60	78	53	64	228	54	46	59	53	81	84	82	52	OK	64	58	73	66	Knockout
1073	98	98	47	80	26	66	56	26	50	59	70	64	53	OK	72	65	72	65	Knockout
1074	71	80	59	70	160	51	38	24	38	89	87	88	63	OK	45	54	79	65	Knockout
1075	45	71	39	52	298	66	51	46	54	88	90	89	65	OK	59	53	70	65	Knockout
1076	95	97	42	78	25	58	44	43	48	73	65	69	49	OK	49	63	74	65	Knockout
1077	86	82	36	71	63	55	42	32	60	60	67	64	50	OK	47	65	67	65	Knockout
1078	88	89	50	76	138	56	21	40	39	77	85	81	48	OK	71	57	78	65	Knockout
1079	70	79	62	70	215	51	29	52	44	75	83	79	47	OK	58	57	75	65	Knockout
1080	69	88	59	72	181	44	27	30	34	88	85	87	48	TT	57	53	79	64	Knockout
1081	78	83	55	72	205	59	16	32	36	89	82	86	46	OK	54	54	79	64	Knockout
1082	88	95	46	77	63	29	7	55	30	79	92	85	60	OK	64	53	81	64	Knockout
1083	56	65	70	64	409	64	35	21	40	86	88	87	55	OK	59	52	75	64	Knockout
1084	74	87	60	74	170	49	29	28	35	81	82	82	51	OK	56	54	78	64	Knockout
1085	70	88	34	64	122	57	58	70	62	72	59	65	47	TT	60	63	65	64	Knockout
1086	96	98	50	82	14	40	29	30	33	78	70	74	54	OK	52	58	78	63	Knockout
1087	75	86	55	72	121	58	52	24	45	67	77	72	51	OK	57	58	72	63	Knockout
1088	89	95	52	79	48	31	11	44	29	79	84	81	62	TT	49	54	80	63	Knockout
1089	71	86	59	72	192	55	43	38	45	85	78	72	58	OK	58	59	72	63	Knockout

FIG. 30E

SEQ ID NO:	MIT	CFD	Elevation	CCT	Offtarget #	Azimuth	DeepSpCas9	CrisprScan	CFD	Lindel	inDelphi	Frameshift	Precision	Graf Motifs	Bioscore	CCT	CFD	Offtarget #	Interpretation predictions
1090	71	85	60	72	132	45	16	41	34	78	88	83	60	OK	58	53	78	63	Knockout
1091	83	89	60	77	134	51	42	45	46	66	68	67	43	OK	65	62	72	63	Knockout
1092	50	73	65	63	337	49	35	42	42	81	82	82	52	OK	57	52	72	62	Knockout
1093	58	73	49	60	271	62	41	37	47	80	77	78	44	OK	59	53	69	62	Knockout
1094	60	79	58	66	304	41	32	44	39	84	81	82	57	OK	56	52	74	62	Knockout
1095	95	95	49	80	53	30	5	35	23	79	85	82	60	TT	50	51	81	62	Knockout
1096	70	79	60	70	185	42	14	26	27	88	91	89	62	TT	42	49	79	62	Knockout
1097	82	88	61	77	90	53	44	34	44	56	73	65	62	OK	71	60	71	62	Knockout
1098	64	81	62	69	215	51	37	46	45	75	69	72	45	OK	59	57	70	62	Knockout
1099	81	90	53	75	141	34	20	77	44	70	60	65	53	OK	61	59	70	61	Knockout
1100	76	85	60	74	158	47	47	15	36	73	72	72	46	OK	55	55	73	61	Knockout
1101	86	93	60	80	62	41	17	38	32	70	68	69	51	OK	78	56	74	60	Knockout
1102	60	79	65	68	249	47	28	17	31	80	85	82	56	OK	63	49	75	60	Knockout
1103	71	81	53	68	141	61	51	43	52	59	63	61	50	OK	60	60	65	60	Knockout
1104	83	86	61	77	123	61	48	28	46	49	63	56	53	OK	62	61	66	59	Knockout
1105	55	71	62	63	306	50	27	31	36	80	78	79	53	OK	52	49	71	59	Knockout
1106	75	85	60	73	126	16	10	33	20	81	89	85	61	TT	57	47	79	59	Knockout
1107	57	72	44	58	328	54	38	22	38	80	82	81	44	OK	68	48	69	59	Knockout
1108	73	86	61	73	167	62	21	25	36	72	59	66	48	OK	52	54	69	58	Knockout
1109	75	87	49	70	143	53	32	5	30	71	75	73	49	OK	61	50	72	58	Knockout
1110	64	79	65	69	257	35	8	36	24	79	85	82	63	OK	61	46	76	58	Knockout
1111	71	83	53	69	181	24	3	56	25	75	86	80	63	TT	38	47	75	58	Knockout
1112	45	62	69	58	1312	57	21	37	38	75	74	74	49	OK	60	46	66	57	Knockout
1113	86	93	49	76	56	24	6	4	11	79	90	84	61	TT	58	44	80	57	Knockout
1114	60	78	59	66	214	45	22	30	32	75	72	74	50	OK	56	49	70	57	Knockout
1115	65	79	60	68	220	42	21	9	24	75	75	76	59	OK	69	46	71	56	Knockout
1116	72	85	61	73	161	40	20	28	29	63	71	67	49	TT	52	51	70	56	Knockout
1117	65	82	65	71	297	35	11	8	18	68	83	75	50	TT	69	45	73	55	Knockout
1118	43	75	54	57	343	50	12	20	27	77	83	80	59	OK	55	42	69	55	Knockout
1119	54	78	58	63	400	36	26	38	34	63	71	67	48	TT	55	49	65	55	Knockout
1120	44	66	61	57	434	26	7	32	18	79	84	82	57	OK	62	38	69	52	Knockout
1121	89	96	57	81	81	30	22	67	40	60	40	50	59	TT	46	60	65	57	Knockout or soluble decoy receptor
1122	66	82	53	67	245	18	25	65	36	63	47	55	56	TT	33	52	61	53	Knockout or soluble decoy receptor
1123	75	85	61	74	133	66	57	48	58	72	81	76	58	OK	60	66	75	69	Membrane-bound decoy receptor
1124	91	93	50	78	64	63	47	43	51	81	84	83	60	OK	66	69	80	71	Membrane-bound decoy receptor
1125	84	86	61	78	109	67	50	52	56	78	87	82	52	OK	71	67	80	72	Membrane-bound decoy receptor
1126	78	90	53	74	142	73	71	48	64	84	90	87	61	OK	71	69	80	76	Membrane-bound decoy receptor
1127	83	93	48	75	78	55	52	44	50	88	86	86	56	GGC	69	63	80	70	Membrane-bound decoy receptor
1128	74	91	46	70	103	57	57	55	56	87	88	86	58	OK	69	53	79	71	Membrane-bound decoy receptor
1129	71	86	49	69	104	75	66	52	64	81	81	81	48	OK	69	67	75	71	Membrane-bound decoy receptor
1130	74	84	59	72	196	79	64	59	67	81	74	78	49	OK	68	70	75	72	Membrane-bound decoy receptor
1131	86	93	46	75	74	64	65	36	55	84	86	85	58	OK	68	65	80	72	Membrane-bound decoy receptor
1132	85	93	57	79	77	66	47	46	53	84	88	86	53	OK	63	66	82	72	Membrane-bound decoy receptor
1133	90	95	42	76	43	63	43	76	61	82	89	85	59	OK	66	69	81	74	Membrane-bound decoy receptor
1134	90	94	47	77	102	52	48	55	52	72	83	77	47	OK	63	64	77	69	Membrane-bound decoy receptor
1135	85	91	51	75	104	66	65	46	59	82	74	78	57	OK	70	67	72	68	Membrane-bound decoy receptor
1136	69	80	61	70	286	65	58	21	48	86	86	86	64	OK	56	59	78	68	Membrane-bound decoy receptor
1137	68	71	53	64	313	70	73	52	65	70	77	73	65	OK	62	65	69	67	Membrane-bound decoy receptor
1138	74	88	60	74	144	38	20	61	40	82	91	86	67	TT	64	57	80	67	Membrane-bound decoy receptor
1139	54	75	56	62	346	59	69	28	49	83	85	85	54	OK	62	55	74	66	Membrane-bound decoy receptor

FIG. 30F

SEQ ID NO:	MIT	CFD	Elevation	CFD	Offtarget #	Azimuth	DeepSpCas9	CrispScan	CFD	Lindel	inDelphi	Frameshift	Precision	Graf Motifs	Bioscore	CFD_OOF	CFD_Ins	CFD_Del	Interference predictions
1140	82	94	56	81	68	43	40	34	39	72	77	74	41	OK	66	60	76	65	Membrane-bound decoy receptor
1141	80	88	56	75	139	52	26	35	38	78	88	83	60	OK	71	56	79	65	Membrane-bound decoy receptor
1142	59	71	46	56	328	58	62	71	64	76	74	75	56	OK	71	60	65	65	Membrane-bound decoy receptor
1143	72	85	39	65	186	55	32	45	44	86	87	87	49	OK	71	55	76	65	Membrane-bound decoy receptor
1144	89	93	46	76	66	31	27	40	33	79	92	86	65	TT	71	54	81	65	Membrane-bound decoy receptor
1145	86	96	50	77	84	36	34	46	37	74	84	79	62	OK	72	57	78	65	Membrane-bound decoy receptor
1146	54	72	38	65	349	67	40	19	42	93	91	90	64	OK	66	53	77	65	Membrane-bound decoy receptor
1147	82	93	45	73	72	34	37	16	29	89	89	89	55	GGC	69	51	81	64	Membrane-bound decoy receptor
1148	75	83	61	73	133	52	37	43	44	77	66	72	45	OK	55	59	73	63	Membrane-bound decoy receptor
1149	73	87	56	73	137	35	8	46	30	87	86	86	59	TT	71	51	80	63	Membrane-bound decoy receptor
1150	68	85	61	71	154	53	24	23	33	82	82	82	48	TT	63	52	77	62	Membrane-bound decoy receptor
1151	59	81	60	67	374	58	25	15	33	84	86	86	56	GGC	63	50	76	62	Membrane-bound decoy receptor
1152	59	70	64	64	277	55	45	37	46	69	80	74	54	OK	63	55	69	61	Membrane-bound decoy receptor
1153	84	93	53	77	100	30	10	25	22	79	88	84	58	OK	65	49	80	61	Membrane-bound decoy receptor
1154	66	76	57	64	365	29	34	39	34	60	91	85	62	OK	59	49	75	61	Membrane-bound decoy receptor
1155	80	90	61	77	87	35	5	18	19	82	92	87	63	TT	56	48	82	61	Membrane-bound decoy receptor
1156	83	87	53	74	170	46	43	27	39	73	60	66	52	OK	71	57	70	60	Membrane-bound decoy receptor
1157	82	94	45	77	81	30	16	37	28	74	75	75	53	OK	63	52	76	60	Membrane-bound decoy receptor
1158	86	94	51	77	66	29	9	19	17	84	89	87	57	TT	70	47	82	60	Membrane-bound decoy receptor
1159	60	82	66	69	279	32	6	33	24	77	89	83	59	TT	64	46	76	59	Membrane-bound decoy receptor
1160	50	69	41	53	349	58	53	36	49	68	71	70	54	OK	71	51	62	57	Membrane-bound decoy receptor
1161	26	50	38	36	1192	66	65	47	59	69	81	75	59	OK	63	48	57	57	Membrane-bound decoy receptor
1162	60	69	40	56	348	32	28	57	39	66	82	75	57	OK	55	46	65	57	Membrane-bound decoy receptor
1163	54	71	43	56	433	37	54	52	48	73	57	65	52	TT	66	52	61	56	Membrane-bound decoy receptor
1164	37	62	41	47	721	42	47	27	39	81	87	84	58	OK	57	43	65	56	Membrane-bound decoy receptor
1165	60	77	38	56	347	36	36	28	33	76	70	74	50	OK	66	46	66	55	Membrane-bound decoy receptor
1166	24	60	48	34	563	44	48	49	47	70	75	72	46	OK	65	40	63	51	Membrane-bound decoy receptor
1167	24	42	19	26	1239	24	28	38	30	72	74	73	45	OK	66	29	51	44	Membrane-bound decoy receptor
1168	71	87	60	73	124	59	24	53	45	76	65	81	56	OK	69	59	77	66	Membrane-bound decoy receptor or wildtype-like
1169	70	87	60	72	179	38	47	40	42	72	82	77	49	TT	64	57	75	64	Membrane-bound decoy receptor or wildtype-like
1170	89	96	53	79	93	22	9	36	23	88	91	89	61	OK	63	51	84	64	Membrane-bound decoy receptor or wildtype-like
1171	75	87	49	70	157	43	24	29	32	83	92	88	58	OK	56	51	79	63	Membrane-bound decoy receptor or wildtype-like
1172	55	77	52	61	224	54	44	28	42	79	90	84	56	OK	59	52	73	63	Membrane-bound decoy receptor or wildtype-like
1173	53	70	55	59	387	49	57	60	55	64	76	70	53	OK	62	57	65	62	Membrane-bound decoy receptor or wildtype-like
1174	23	73	22	35	346	74	66	46	62	62	88	85	57	OK	66	51	62	62	Membrane-bound decoy receptor or wildtype-like
1175	89	87	61	76	92	50	22	48	40	71	79	71	47	OK	77	58	73	62	Membrane-bound decoy receptor or wildtype-like
1176	87	92	42	74	87	62	54	59	56	62	41	51	63	OK	70	66	62	61	Membrane-bound decoy receptor or wildtype-like
1177	54	78	38	67	247	56	51	24	44	72	73	73	43	OK	54	55	70	61	Membrane-bound decoy receptor or wildtype-like
1178	40	66	43	50	480	58	54	46	53	72	72	72	49	OK	65	52	61	58	Membrane-bound decoy receptor or wildtype-like
1179	59	79	60	66	193	48	16	29	29	63	69	66	47	OK	69	46	66	54	Membrane-bound decoy receptor or wildtype-like
1180	39	85	37	47	452	49	53	64	55	66	46	56	59	OK	72	51	41	52	Membrane-bound decoy receptor or wildtype-like
1181	75	85	59	73	185	80	78	45	68	85	90	87	65	OK	63	71	80	76	Soluble decoy receptor
1182	72	85	53	70	151	63	59	40	54	89	92	91	51	TT	62	62	80	72	Soluble decoy receptor
1183	74	87	53	71	133	68	63	47	59	85	91	88	58	OK	69	65	80	73	Soluble decoy receptor
1184	76	88	61	75	143	38	23	37	33	61	89	84	55	OK	59	54	80	64	Soluble decoy receptor
1185	59	72	53	61	308	60	43	37	47	84	79	81	57	OK	48	54	71	63	Soluble decoy receptor
1186	64	83	59	69	138	57	36	31	41	81	76	78	51	OK	58	55	73	63	Soluble decoy receptor
1187	86	92	51	76	101	59	23	30	34	72	74	73	64	OK	62	55	75	61	Soluble decoy receptor
1188	74	83	44	67	160	61	47	53	54	64	53	55	46	OK	62	60	63	60	Soluble decoy receptor
1189	76	86	58	73	176	43	36	7	29	72	64	68	50	OK	67	51	71	57	Soluble decoy receptor

FIG. 30G

SEQ ID NO:	MIT	CFD	Elevation	Off	Offtarget #	Azimuth	DeepSpCas9	CrisprScan	Cfd	Lindel	InDelphi	Frameshift	Precision	Graf Motifs	Bioscore				Interference predictions
1190	69	82	53	66	249	30	31	54	38	63	70	66	50	TT	56	51	66	56	Soluble decoy receptor
1191	70	85	60	72	179	46	49	17	37	65	61	63	50	OK	40	55	62	54	Soluble decoy receptor
1192	73	87	60	73	396	53	43	34	43	63	76	80	57	OK	73	58	76	65	Soluble or membrane-bound decoy receptor
1193	61	82	56	66	414	48	24	21	31	61	61	61	51	OK	69	49	74	59	Soluble or membrane-bound decoy receptor
1194	64	83	60	70	224	36	6	14	16	76	67	82	60	TT	77	43	76	56	Soluble or membrane-bound decoy receptor
1195	84	93	58	78	67	57	63	45	54	67	60	66	59	OK	50	66	63	75	Wildtype-like
1196	59	78	58	65	267	70	61	74	71	72	80	76	51	OK	43	69	70	71	Wildtype-like
1197	86	93	53	78	57	46	50	39	45	64	66	66	55	OK	49	61	62	70	Wildtype-like
1198	92	94	44	77	66	50	57	49	55	64	56	61	48	GGC	42	66	69	64	Wildtype-like
1199	61	76	61	66	241	57	67	29	51	70	82	76	58	OK	44	59	71	64	Wildtype-like
1200	93	94	41	77	66	38	21	25	28	80	74	77	59	OK	35	52	77	61	Wildtype-like
1201	73	84	59	72	233	54	13	32	36	66	77	71	52	OK	47	54	72	60	Wildtype-like
1202	62	83	51	65	130	36	13	43	31	74	90	82	58	OK	52	48	74	59	Wildtype-like
1203	73	84	61	73	153	43	24	37	35	71	70	71	47	OK	54	54	72	59	Wildtype-like

FIG. 30H

SEQ ID NO:	Genomic cut coordinate	Exon	Strand	Start coordinate	End coordinate	crRNA	GC content	PAM
1204	22547487	3	-	22547484	22547503	AAAAGCUAUUCACUUACCUG	35	AGG
1205	22582132	4	+	22582116	22582135	CCAGAGCGCUGUGAUGACUG	60	GGG
1206	22582148	4	+	22582132	22582151	ACUGGGGACUAGAUACCAUG	50	AGG
1207	22582185	4	-	22582182	22582201	AGUGGGCACUUGAUGCGAGC	60	TGG
1208	22582256	4	-	22582253	22582272	UCCAAUACCAGAUCAGAGUA	40	AGG
1209	22582259	4	+	22582243	22582262	CAGCUGGCCUUACUCUGAUC	55	TGG
1210	22582275	4	+	22582259	22582278	GAUCUGGUAUUGGACGAGGC	55	AGG
1211	22582281	4	+	22582265	22582284	GUAUUGGACGAGGCAGGACC	60	GGG
1212	22582319	4	-	22582316	22582335	UACUAAUGCGGUUGUCAGGG	50	AGG
1213	22582368	4	-	22582365	22582384	CCCGUGUCAUUGAGGAGGGU	60	GGG
1214	22582372	4	-	22582369	22582388	GUUGCCCGUGUCAUUGAGGA	55	GGG
1215	22582373	4	-	22582370	22582389	AGUUGCCCGUGUCAUUGAGG	55	AGG
1216	22582376	4	-	22582373	22582392	UAUAGUUGCCCGUGUCAUUG	45	AGG
1217	22582378	4	+	22582362	22582381	CCCACCCUCCUCAAUGACAC	60	GGG
1218	22582399	4	-	22582396	22582415	AUCAGGCUACCUUAACAUGC	45	AGG
1219	22582400	4	+	22582384	22582403	GCAACUAUACCUGCAUGUUA	40	AGG
1220	22585908	5	-	22585905	22585924	AUGCAGUGGGAGUUUCAUGG	50	AGG
1221	22585938	5	+	22585922	22585941	CAUAGACUGUAUAUAGAGUA	30	CGG
1222	22585991	5	-	22585988	22586007	AUAGUUGGUUUGACAGUGGG	45	AGG
1223	22585994	5	-	22585991	22586010	GUGAUAGUUGGUUUGACAGU	40	GGG
1224	22585995	5	-	22585992	22586011	AGUGAUAGUUGGUUUGACAG	40	TGG
1225	22586015	5	+	22585999	22586018	ACCAACUAUCACUUGGUACA	40	TGG
1226	22597719	6	+	22597703	22597722	UAGGACUCUAACUGUAAAGG	40	TGG
1227	22599398	7	-	22599395	22599414	UCAUUGGGUGAAUAGAUCUG	40	AGG
1228	22599435	7	+	22599419	22599438	GUGGUCUACGAGAAAGAACC	50	GGG
1229	22601632	8	+	22601616	22601635	CCUGAAGGACGCUCGCAAUG	60	AGG
1230	22601637	8	+	22601621	22601640	AGGACGCUCGCAAUGAGGUU	55	TGG
1231	22601640	8	+	22601624	22601643	ACGCUCGCAAUGAGGUUUGG	55	TGG
1232	22601651	8	+	22601635	22601654	GAGGUUUGGUGGACCAUUGA	50	CGG
1233	22599395	7	-	22599392	22599411	UUGGGUGAAUAGAUCUGAGG	45	AGG
1234	22601598	8	-	22601595	22601614	AAGUAAAAUAGACUGUACAG	30	GGG
1235	22601697	8	+	22601681	22601700	UUGAUGUAACUGUUAAUGAA	25	AGG
1236	22597700	6	+	22597684	22597703	GGCGUAUCUUCCAUCUGACU	50	AGG
1237	22582369	4	-	22582366	22582385	GCCCGUGUCAUUGAGGAGGG	65	TGG
1238	22585911	5	-	22585908	22585927	UCUAUGCAGUGGGAGUUUCA	45	TGG
1239	22597642	6	+	22597626	22597645	AUAGCCUUGGUUUCAAACAA	35	TGG
1240	22547431	3	+	22547415	22547434	UUGACAGGAUGGGACUUCUG	50	TGG
1241	22547473	3	-	22547470	22547489	UACCUGAGGCAUCACUCUGC	55	AGG
1242	22582244	4	-	22582241	22582260	UCAGAGUAAGGCCAGCUGAA	50	TGG
1243	22582271	4	+	22582255	22582274	CUCUGAUCUGGUAUUGGACG	50	AGG
1244	22582280	4	+	22582264	22582283	GGUAUUGGACGAGGCAGGAC	60	CGG
1245	22586020	5	+	22586004	22586023	CUAUCACUUGGUACAUGGUA	40	AGG
1246	22597636	6	-	22597633	22597652	AUCUCCAUUGUUUGAAACCA	35	AGG
1247	22601654	8	-	22601651	22601670	AUCUGGCUUUUUUCCGUCAA	40	TGG
1248	22582122	4	-	22582119	22582138	CCCCAGUCAUCACAGCGCUC	65	TGG
1249	22582316	4	-	22582313	22582332	UAAUGCGGUUGUCAGGGAGG	55	CGG
1250	22582322	4	-	22582319	22582338	CCUUACUAAUGCGGUUGUCA	45	GGG
1251	22582332	4	+	22582316	22582335	CCCUGACAACCGCAUUAGUA	50	AGG
1252	22599434	7	+	22599418	22599437	UGUGGUCUACGAGAAAGAAC	45	CGG
1253	22582166	4	-	22582163	22582182	CUGGCUCAUCUUCAAACACU	45	TGG

FIG. 31A

SEQ ID NO:	Genomic cut coordinate	Exon	Strand	Start coordinate	End coordinate	crRNA	GC content	PAM
1254	22582202	4	-	22582199	22582218	UCAAGAAGUGUUCAAAGAGU	35	GGG
1255	22582305	4	-	22582302	22582321	UCAGGGAGGCGGAAGUUAAU	50	TGG
1256	22586008	5	+	22585992	22586011	CUGUCAAACCAACUAUCACU	40	TGG
1257	22597716	6	+	22597700	22597719	GACUAGGACUCUAACUGUAA	40	AGG
1258	22599413	7	-	22599410	22599429	UCGUAGACCACAAGAUCAUU	40	GGG
1259	22599414	7	-	22599411	22599430	CUCGUAGACCACAAGAUCAU	45	TGG
1260	22582131	4	+	22582115	22582134	UCCAGAGCGCUGUGAUGACU	55	GGG
1261	22582349	4	+	22582333	22582352	GUAAGGAGAAAGAUGUGCUC	45	TGG
1262	22585921	5	-	22585918	22585937	CUAUAUACAGUCUAUGCAGU	35	GGG
1263	22585922	5	-	22585919	22585938	UCUAUAUACAGUCUAUGCAG	35	TGG
1264	22597679	6	+	22597663	22597682	UUGUUACAUAUCCAGAAAAU	25	GGG
1265	22582130	4	+	22582114	22582133	UUCCAGAGCGCUGUGAUGAC	55	TGG
1266	22582243	4	-	22582240	22582259	CAGAGUAAGGCCAGCUGAAU	50	GGG
1267	22582265	4	+	22582249	22582268	GCCUUACUCUGAUCUGGUAU	45	TGG
1268	22582323	4	-	22582320	22582339	UCCUUACUAAUGCGGUUGUC	45	AGG
1269	22582377	4	+	22582361	22582380	ACCCACCCUCCUCAAUGACA	55	CGG
1270	22586006	5	-	22586003	22586022	ACCAUGUACCAAGUGAUAGU	40	TGG
1271	22597723	6	+	22597707	22597726	ACUCUAACUGUAAAGGUGGU	40	AGG
3421	22599380	7	-	22599377	22599396	UGAGGAGGCAAUGCGUCUUU	50	TGG
3422	22601599	8	-	22601596	22601615	AAAGUAAAAUAGACUGUACA	25	GGG
3423	22601622	8	-	22601619	22601638	CCUCAUUGCGAGCGUCCUUC	60	AGG
3424	22582153	4	-	22582150	22582169	AAACACUUGGAUCUGCCUCA	45	TGG
3425	22597600	6	+	22597584	22597603	UUUAAUAAUGUGAUACCUGA	25	AGG
3426	22597680	6	-	22597677	22597696	UGGAAGAUACGCCCAUUUUC	45	TGG
3427	22601600	8	-	22601597	22601616	GAAAGUAAAAUAGACUGUAC	30	AGG
3428	22547481	3	+	22547465	22547484	AUCCUGCAGAGUGAUGCCUC	55	AGG
3429	22582243	4	+	22582227	22582246	UACAGCACAGCCCAUUCAGC	55	TGG
3430	22582331	4	-	22582328	22582347	CAUCUUUCUCCUUACUAAUG	35	CGG
3431	22582364	4	-	22582361	22582380	UGUCAUUGAGGAGGGUGGGU	55	CGG
3432	22585871	5	-	22585868	22585887	UCUUUCUGAACCACUUCCAG	45	AGG
3433	22597678	6	+	22597662	22597681	GUUGUUACAUAUCCAGAAAA	30	TGG
3434	22599416	7	+	22599400	22599419	CUAUUCACCCAAUGAUCUUG	40	TGG
3435	22601681	8	-	22601678	22601697	AUUAACAGUUACAUCAAUAC	25	TGG
3436	22597605	6	-	22597602	22597621	AAACUCAAGUUCAUGCCUUC	40	AGG
3437	22597629	6	+	22597613	22597632	CUUGAGUUUUCUUAUAGCCU	35	TGG
3438	22601671	8	-	22601668	22601687	ACAUCAAUACUGGUGUCAUC	40	TGG
3439	22547457	3	+	22547441	22547460	GUGAUGAGUCUCUACUUCUA	40	TGG
3440	22582289	4	-	22582286	22582305	UAAUUGGCUCCUCCAGGUCC	55	CGG
3441	22585970	5	-	22585967	22585986	GGAAAGAAUCCAUCUACAUU	35	TGG
3442	22547458	3	+	22547442	22547461	UGAUGAGUCUCUACUUCUAU	35	GGG
3443	22597700	6	-	22597697	22597716	CAGUUAGAGUCCUAGUCAGA	45	TGG
3444	22582290	4	+	22582274	22582293	GAGGCAGGACCGGGACCUGG	75	AGG
3445	22585971	5	+	22585955	22585974	AUCACAUGUCCAAAUGUAGA	35	TGG
3446	22582203	4	-	22582200	22582219	UUCAAGAAGUGUUCAAAGAG	35	TGG
3447	22582295	4	-	22582292	22582311	GGAAGUUAAUUGGCUCCUCC	50	AGG
3448	22585865	5	+	22585849	22585868	CAGCAAAGUUGCAUUUCCUC	45	TGG
3449	22585871	5	+	22585855	22585874	AGUUGCAUUUCCUCUGGAAG	45	TGG
3450	22601617	8	+	22601601	22601620	AGUCUAUUUUACUUUCCUGA	30	AGG
3451	22582287	4	+	22582271	22582290	GACGAGGCAGGACCGGGACC	75	TGG
3452	22601575	8	+	22601559	22601578	UAACUUGUUUUUUUUAGGAG	25	AGG

FIG. 31B

SEQ ID NO:	Genomic cut coordinate	Exon	Strand	Start coordinate	End coordinate	crRNA	GC content	PAM
3453	22604397	9	+	22604381	22604400	UGUCAUGCUAGAAAUGCCAA	40	AGG
3454	22604420	9	+	22604404	22604423	AGAGGUUGACAAAGCAGCCA	50	AGG
3455	22604402	9	+	22604386	22604405	UGCUAGAAAUGCCAAAGGAG	45	AGG
3456	22604427	9	-	22604424	22604443	AUUACCUUUCUGCUUCACCU	40	TGG
3457	22604403	9	-	22604400	22604419	UGCUUUGUCAACCUCUCCUU	45	TGG
3458	22604354	9	+	22604338	22604357	CAUCAAAAAAGUUUCUGCUG	35	AGG
3459	22613528	11	+	22613512	22613531	AUCUUACGCAAGGAACGCUG	50	AGG
3460	22613559	11	+	22613543	22613562	UUUGUGUUACUGACCCUCCG	50	TGG
3461	22613562	11	-	22613559	22613578	AUUCUCCAAAACUCCACGGA	45	GGG
3462	22613563	11	-	22613560	22613579	CAUUCUCCAAAACUCCACGG	50	AGG
3463	22613614	11	-	22613611	22613630	UUCCCCCAGGUAGACUGUCA	55	CGG
3464	22613620	11	+	22613604	22613623	UUGACCGUGACAGUCUACCU	50	GGG
3465	22613621	11	+	22613605	22613624	UGACCGUGACAGUCUACCUG	55	GGG
3466	22613622	11	+	22613606	22613625	GACCGUGACAGUCUACCUGG	60	GGG
3467	22613627	11	-	22613624	22613643	GUGAAAUACCUACUUCCCCC	50	AGG
3468	22613619	11	+	22613603	22613622	UUUGACCGUGACAGUCUACC	50	TGG
3469	22613567	11	+	22613551	22613570	ACUGACCCUCCGUGGAGUUU	55	TGG
3470	22612148	10	+	22612132	22612151	GGAGAUGGUCUUAUUUUACC	40	GGG
3471	22613518	11	+	22613502	22613521	AUAUUUAUGUAUCUUACGCA	25	AGG
3472	22612156	10	-	22612153	22612172	CAUCUGUUCCAAAAUGAGCC	45	CGG
3473	22613566	11	-	22613563	22613582	AUUCAUUCUCCAAAACUCCA	35	CGG
3474	22612147	10	+	22612131	22612150	UGGAGAUGGUCUUAUUUUAC	35	CGG
3475	22612158	10	+	22612142	22612161	UUAUUUUACCGGGCUCAUUU	35	TGG
3476	22613489	11	+	22613473	22613492	CUUCCUUUUGCUAGAUGGAA	40	AGG
3477	22612133	10	+	22612117	22612136	CCACGUUUACUGGCUGGAGA	55	TGG
3478	22612179	10	+	22612163	22612182	GGAACAGAUGAAACCAUUUU	35	AGG
3479	22613580	11	+	22613564	22613583	GGAGUUUUGGAGAAUGAAUU	35	TGG
3480	22612182	10	-	22612179	22612198	CUUUCAUUACUCACCUAAAA	30	TGG
3481	22612123	10	-	22612120	22612139	CCAUCUCCAGCCAGUAAACG	55	TGG
3482	22612127	10	+	22612111	22612130	UGUUUACCACGUUUACUGGC	45	TGG
3483	22612093	10	-	22612090	22612109	CAAUGAGAAUCACUACCAGC	45	AGG
3484	22612123	10	+	22612107	22612126	UUGUUGUUUACCACGUUUAC	35	TGG
3485	22612088	10	+	22612072	22612091	UUUUGGAGCUACAGUCCUGC	50	TGG
3486	22612052	10	+	22612036	22612055	GAUAGCUCCAAGAUACACAG	45	TGG
3487	22612049	10	-	22612046	22612065	GCUAAUUCCACUGUGUAUCU	40	TGG
3488	22612065	10	+	22612049	22612068	UACACAGUGGAAUUAGCAUG	40	TGG
3489	22604433	9	+	22604417	22604436	GCAGCCAAGGUGAAGCAGAA	55	AGG
3490	22612071	10	+	22612055	22612074	GUGGAAUUAGCAUGUGGUUU	40	TGG

FIG. 31C

SEQ ID NO:	MIT	CFD	Off-Target	OffTarget #	Azimuth	DeepSpCas9	CrisprScan	Off-	Lindel	inDelphi	Frameshift	Precision	Graf motifs	OR-OffT	OffT-KO	OR-OffT-KO	Interference predictions
1204	76	88	82	155	70	59	45	58	81	83	82	47	OK	70	82	74	Knockout
1205	74	87	81	158	69	68	56	64	82	86	84	60	OK	72	82	76	Knockout
1206	87	91	89	98	73	74	52	66	90	88	89	51	OK	78	89	82	Knockout
1207	92	93	93	99	49	34	22	35	89	91	90	46	OK	64	91	73	Knockout
1208	81	91	86	93	51	54	33	46	84	83	84	54	OK	66	85	72	Knockout
1209	80	92	86	118	42	38	41	40	88	91	89	61	OK	63	88	72	Knockout
1210	89	96	93	70	58	50	42	50	79	86	82	57	OK	71	87	75	Knockout
1211	78	89	84	97	60	57	50	56	74	71	73	42	OK	70	78	71	Knockout
1212	88	92	90	52	58	54	39	50	77	73	75	55	OK	70	82	72	Knockout
1213	75	89	82	104	56	50	62	56	75	77	76	45	OK	69	79	71	Knockout
1214	84	92	88	79	60	55	54	56	79	70	75	56	OK	72	81	73	Knockout
1215	87	92	90	62	57	53	50	53	77	73	75	48	OK	71	82	73	Knockout
1216	91	94	93	40	59	48	39	49	76	81	79	57	OK	71	86	73	Knockout
1217	73	86	81	178	62	47	55	55	73	81	77	57	OK	68	79	71	Knockout
1218	89	94	92	64	55	61	17	44	88	92	90	57	OK	68	91	75	Knockout
1219	90	95	93	53	45	40	42	42	82	84	83	46	OK	67	88	73	Knockout
1220	75	84	80	170	76	70	65	70	90	94	92	59	OK	75	86	81	Knockout
1221	76	86	81	146	50	47	81	59	84	81	82	55	OK	70	82	74	Knockout
1222	74	85	80	129	55	59	79	64	81	84	82	63	OK	72	81	75	Knockout
1223	82	90	86	87	54	54	61	56	68	78	73	51	OK	71	79	72	Knockout
1224	79	92	86	98	66	57	50	58	68	85	76	59	OK	72	81	73	Knockout
1225	87	93	90	72	61	59	27	49	90	92	91	64	OK	69	90	77	Knockout
1226	83	90	87	86	65	74	66	68	75	80	77	58	OK	77	82	77	Knockout
1227	80	88	84	133	73	73	64	70	86	93	89	61	OK	77	87	81	Knockout
1228	83	92	88	75	56	68	64	63	81	86	84	52	OK	75	86	78	Knockout
1229	97	98	98	36	62	50	53	55	83	82	83	54	OK	76	90	78	Knockout
1230	93	97	95	30	49	48	53	50	79	80	79	44	OK	72	87	75	Knockout
1231	92	95	94	29	57	45	49	50	89	96	92	63	OK	72	93	79	Knockout
1232	86	94	90	89	42	40	66	49	87	94	91	63	OK	70	90	77	Knockout
1233	65	78	72	219	66	63	79	69	80	82	81	41	OK	70	76	74	Knockout
1234	61	77	69	280	73	69	59	67	79	89	84	57	OK	68	76	73	Knockout
1235	65	81	73	226	57	58	44	53	91	89	90	63	OK	63	82	72	Knockout
1236	86	94	90	57	60	32	31	41	80	82	81	45	OK	66	85	71	Knockout
1237	73	83	78	142	49	47	66	54	79	75	77	57	OK	66	78	70	Knockout
1238	76	86	81	122	45	30	36	37	87	95	91	62	TT	59	86	70	Knockout
1239	74	86	80	141	47	51	43	47	74	90	82	64	OK	63	81	70	Knockout
1240	63	81	72	193	67	45	67	60	68	81	74	58	OK	66	73	69	Knockout
1241	78	89	84	114	54	49	27	43	77	82	80	46	OK	63	82	69	Knockout
1242	73	81	77	176	54	58	26	46	87	82	85	65	OK	61	81	69	Knockout
1243	92	94	93	63	51	48	48	49	67	64	65	43	OK	71	79	69	Knockout
1244	85	87	76	136	50	51	54	52	77	82	80	43	OK	64	78	69	Knockout
1245	69	86	78	105	40	53	56	50	83	80	81	48	OK	64	79	69	Knockout
1246	66	81	74	215	55	42	41	46	84	90	87	60	OK	60	80	69	Knockout
1247	87	92	90	131	35	1	49	28	88	89	89	58	OK	59	89	69	Knockout
1248	82	91	87	131	47	46	15	36	82	79	80	40	OK	61	83	68	Knockout
1249	73	79	76	123	62	47	81	63	66	64	65	53	OK	70	71	68	Knockout
1250	88	92	90	54	55	38	34	42	70	72	71	49	OK	66	80	68	Knockout
1251	97	98	98	27	40	29	31	33	77	72	75	54	OK	65	86	68	Knockout
1252	75	89	82	110	49	50	49	49	76	72	74	44	OK	66	78	68	Knockout
1253	69	86	78	187	44	33	44	40	86	82	84	56	OK	59	81	67	Knockout

FIG. 31D

SEQ ID NO:	MIT	CFD	OFF	OffTarget #	Azimuth	DeepSpCas9	CrisprScan	ON	Lindel	inDelphi	Frameshift	Precision	Graf motifs	ON	OFF	FD	OVERALL	Interference predictions
1254	61	77	69	227	51	43	59	51	80	84	82	52	OK	60	75		67	Knockout
1255	86	89	88	90	25	12	44	27	80	92	86	60	OK	57	87		67	Knockout
1256	89	95	92	76	55	50	27	44	58	70	64	51	OK	68	78		67	Knockout
1257	84	92	88	63	50	37	44	44	60	76	68	51	OK	66	78		67	Knockout
1258	90	97	94	37	42	20	40	34	69	76	73	50	TT	64	83		67	Knockout
1259	89	95	92	43	43	25	45	38	64	78	71	61	OK	65	82		67	Knockout
1260	80	91	86	115	47	31	42	40	75	70	72	46	OK	63	79		66	Knockout
1261	61	78	70	258	49	57	29	45	82	85	83	49	OK	57	76		66	Knockout
1262	74	88	81	101	57	37	37	44	73	75	74	52	OK	62	78		66	Knockout
1263	79	87	83	112	62	63	37	54	65	67	61	51	OK	68	72		66	Knockout
1264	54	75	65	351	43	37	58	46	85	88	87	58	OK	55	76		66	Knockout
1265	82	90	86	116	41	30	31	34	78	72	75	61	OK	60	80		65	Knockout
1266	81	92	87	128	34	20	77	44	69	60	64	53	OK	65	75		65	Knockout
1267	90	94	92	57	42	20	41	34	68	67	67	51	OK	63	80		65	Knockout
1268	96	96	96	33	33	13	42	29	67	70	69	60	OK	63	82		65	Knockout
1269	77	83	80	157	60	54	22	45	76	62	69	41	OK	63	75		65	Knockout
1270	80	91	86	95	48	45	27	40	57	80	69	65	OK	63	77		65	Knockout
1271	76	88	82	108	54	48	35	46	62	74	68	70	OK	64	75		65	Knockout
3421	89	92	91	88	33	12	50	32	73	72	73	42	TT	61	82		65	Knockout
3422	52	73	63	445	62	42	26	43	91	89	90	60	OK	53	76		65	Knockout
3423	94	97	96	34	29	4	29	21	79	80	79	48	TT	58	87		65	Knockout
3424	68	79	74	190	61	53	24	46	69	76	73	46	OK	60	73		64	Knockout
3425	72	79	76	222	57	13	33	34	83	81	82	48	OK	55	79		64	Knockout
3426	87	94	91	52	23	6	14	15	81	91	86	62	TT	53	88		64	Knockout
3427	67	76	72	250	56	24	41	40	74	85	80	48	OK	56	76		64	Knockout
3428	33	63	48	558	60	59	62	60	79	79	79	44	OK	54	64		63	Knockout
3429	79	90	85	107	53	32	8	30	71	75	73	49	OK	57	79		63	Knockout
3430	58	71	65	270	50	33	44	42	83	81	82	53	OK	53	73		63	Knockout
3431	50	68	59	337	59	31	44	45	83	85	84	52	OK	52	71		63	Knockout
3432	69	79	74	207	62	54	47	54	58	62	60	45	OK	64	67		63	Knockout
3433	80	81	71	225	45	26	37	36	81	83	82	52	OK	53	76		63	Knockout
3434	70	85	78	134	53	41	20	38	73	74	73	46	TT	58	75		63	Knockout
3435	72	87	80	170	46	19	24	30	74	83	79	58	OK	55	79		63	Knockout
3436	70	86	78	186	36	14	23	24	83	86	84	50	TT	51	81		62	Knockout
3437	73	85	79	163	40	22	18	27	84	79	82	43	GGC	53	80		62	Knockout
3438	77	89	83	109	44	26	14	28	68	81	74	54	OK	56	79		62	Knockout
3439	77	88	83	111	35	21	40	32	67	73	70	61	OK	57	76		61	Knockout
3440	64	81	73	173	60	49	45	51	55	62	58	51	OK	62	65		61	Knockout
3441	74	89	82	144	39	19	6	21	75	84	79	50	TT	51	80		61	Knockout
3442	74	87	81	136	44	19	27	30	66	71	69	43	OK	55	75		60	Knockout
3443	51	55	53	402	46	43	51	47	77	86	82	50	OK	50	67		60	Knockout
3444	32	58	45	573	60	66	61	62	68	55	62	50	OK	57	53		59	Knockout
3445	69	83	76	169	43	24	9	25	73	80	76	63	OK	51	76		59	Knockout
3446	39	76	58	271	45	28	21	31	81	85	83	56	OK	44	70		57	Knockout
3447	66	87	77	128	54	25	25	35	56	48	52	57	OK	56	64		54	Knockout
3448	60	78	69	218	44	24	41	36	59	57	58	47	OK	53	63		54	Knockout
3449	59	82	71	203	48	31	39	39	61	44	53	51	OK	55	62		54	Knockout
3450	50	67	59	350	57	9	10	25	81	78	79	44	OK	42	69		54	Knockout
3451	61	78	70	252	44	37	39	40	51	51	51	47	OK	55	60		53	Knockout
3452	34	49	42	754	52	4	31	26	76	68	72	55	OK	34	57		46	Knockout

FIG. 31E

SEQ ID NO:	MIT	CFD	COF	OffTarget #	Azimuth	DeepSpCas9	CrisprScan	CM	Lindel	inDelphi	Frameshift	Precision	Graf motifs	ON - OFF	OFF - ES	OVERALL	Interference predictions
3453	66	81	74	185	67	42	37	49	76	76	76	45	OK	61	75	66	Knockout or soluble decoy receptor
3454	57	77	67	275	54	58	33	48	78	82	80	50	OK	58	74	65	Knockout or soluble decoy receptor
3455	57	74	66	282	64	60	54	59	65	61	63	48	OK	62	64	63	Knockout or soluble decoy receptor
3456	43	78	61	547	51	62	13	42	76	87	81	65	OK	51	71	61	Knockout or soluble decoy receptor
3457	63	82	73	203	28	35	48	37	57	57	57	46	TT	55	65	55	Knockout or soluble decoy receptor
3458	60	76	68	267	62	29	30	40	42	49	45	61	OK	54	67	51	Knockout or soluble decoy receptor
3459	94	98	96	21	64	69	46	60	87	85	86	51	OK	78	91	81	Membrane-bound decoy receptor
3460	90	93	92	80	65	56	44	55	82	83	83	65	OK	73	87	76	Membrane-bound decoy receptor
3461	83	92	88	100	67	50	52	56	80	88	84	51	OK	72	86	76	Membrane-bound decoy receptor
3462	86	91	89	87	73	71	48	64	85	90	88	61	OK	76	88	80	Membrane-bound decoy receptor
3463	84	91	88	119	64	50	45	53	80	79	79	48	OK	70	83	73	Membrane-bound decoy receptor
3464	92	97	95	50	52	63	45	53	79	87	83	59	OK	74	89	77	Membrane-bound decoy receptor
3465	84	94	89	71	63	61	50	58	81	79	80	48	OK	73	84	76	Membrane-bound decoy receptor
3466	86	92	89	76	76	68	56	66	77	74	75	44	OK	78	82	77	Membrane-bound decoy receptor
3467	82	89	86	109	60	73	38	57	79	66	73	56	OK	71	79	72	Membrane-bound decoy receptor
3468	91	95	93	50	39	31	22	31	88	90	89	65	OK	62	91	71	Membrane-bound decoy receptor
3469	85	94	90	71	33	30	46	36	78	92	85	65	TT	63	87	70	Membrane-bound decoy receptor
3470	81	90	86	120	47	16	38	34	80	90	85	60	OK	60	85	68	Membrane-bound decoy receptor
3471	83	88	86	166	60	27	26	38	79	82	81	55	OK	62	83	68	Membrane-bound decoy receptor
3472	75	83	79	175	58	25	15	33	85	88	87	56	GGC	56	83	66	Membrane-bound decoy receptor
3473	60	73	67	285	67	40	18	42	89	91	90	64	OK	54	78	66	Membrane-bound decoy receptor
3474	72	85	79	160	32	3	37	24	86	90	88	59	TT	51	83	63	Membrane-bound decoy receptor
3475	83	87	85	100	25	9	19	18	84	89	87	57	TT	51	86	63	Membrane-bound decoy receptor
3476	68	73	71	233	45	16	38	33	83	76	80	48	OK	52	75	61	Membrane-bound decoy receptor
3477	81	88	85	91	54	20	28	34	61	57	59	50	OK	59	72	59	Membrane-bound decoy receptor
3478	56	82	69	294	32	5	31	23	75	88	81	60	TT	46	75	58	Membrane-bound decoy receptor
3479	50	73	62	346	31	8	42	27	83	89	86	57	OK	44	74	58	Membrane-bound decoy receptor
3480	73	86	80	165	15	3	18	12	78	83	81	52	OK	46	80	57	Membrane-bound decoy receptor
3481	90	95	93	80	64	63	34	54	79	72	75	58	OK	73	84	74	Membrane-bound or soluble decoy receptor
3482	92	95	94	43	50	36	5	30	85	91	88	66	OK	62	91	71	Membrane-bound or soluble decoy receptor
3483	83	93	88	98	59	43	23	42	67	65	66	50	OK	65	77	65	Membrane-bound or soluble decoy receptor
3484	92	93	93	67	26	5	22	18	72	82	77	60	TT	55	85	62	Membrane-bound or soluble decoy receptor
3485	72	82	77	154	47	38	13	33	75	73	74	45	OK	55	75	61	Membrane-bound or soluble decoy receptor
3486	78	88	83	114	76	78	42	65	85	91	88	65	OK	74	86	79	Soluble decoy receptor
3487	75	89	82	120	37	28	21	29	81	90	85	55	OK	55	84	65	Soluble decoy receptor
3488	41	87	64	149	65	60	45	57	71	81	76	51	OK	60	70	65	Soluble decoy receptor
3489	38	73	56	290	60	43	40	48	82	78	80	57	OK	52	68	61	Soluble decoy receptor
3490	66	82	74	189	36	35	41	37	80	67	63	51	TT	56	69	58	Soluble decoy receptor

FIG. 31F

SEQ ID NO:	Exon	Strand	Start coordinate	End coordinate	crRNA	Off	On	Frameshift	Overall	Interference predictions
1272	5	-	30,467,004	30,467,023	ACGGUUGGUUUGACACUGGG	88	72	85	82	Knockout
1273	4	+	30,464,029	30,464,048	ACUGGGGACUAGAUACCAUG	89	66	89	81	Knockout
1274	6	+	30,479,986	30,480,005	CCGGACUCUGACUGUAAAGG	92	68	76	79	Knockout
1275	4	+	30,464,013	30,464,032	CCAGAACGCUGCGAUGACUG	88	61	83	78	Knockout
1276	5	-	30,467,007	30,467,026	GUGACGGUUGGUUUGACACU	91	59	84	78	Knockout
1277	8	-	30,484,739	30,484,758	AUUAACAGUUACGUCCAGAG	90	58	82	77	Knockout
1278	4	-	30,464,293	30,464,312	GUCAGGCUACCUUAACAUGC	93	46	89	76	Knockout
1279	5	-	30,467,008	30,467,027	AGUGACGGUUGGUUUGACAC	93	55	81	76	Knockout
1280	6	+	30,479,842	30,479,861	CUAGGGUUGUCGUAAAAUAG	95	46	86	76	Knockout
1281	8	+	30,484,742	30,484,761	UGGACGUAACUGUUAAUGAA	84	54	89	75	Knockout
1282	3	+	30,428,093	30,428,112	UCAUGCCUCAGGUAAGUGAA	81	53	90	74	Knockout
1283	4	+	30,464,259	30,464,278	CCUACCCUCCUCAAUGACAC	88	57	78	74	Knockout
1284	5	-	30,466,858	30,466,877	UGCAACUUUGCUGCAAUACG	91	48	84	74	Knockout
1285	6	+	30,479,983	30,480,002	CAGCCGGACUCUGACUGUAA	92	51	79	74	Knockout
1286	8	+	30,484,696	30,484,715	GAGAUUUGGUGGACCAUUGA	88	41	92	74	Knockout
1287	4	+	30,464,156	30,464,175	GAUCUGGUAUUGGACUAGGC	90	46	84	73	Knockout
1288	4	-	30,464,266	30,464,285	GUUGCCCGUGUCAUUGAGGA	84	59	76	73	Knockout
1289	4	-	30,464,267	30,464,286	AGUUGCCCGUGUCAUUGAGG	90	52	78	73	Knockout
1290	4	-	30,464,270	30,464,289	UAUAGUUGCCCGUGUCAUUG	90	50	79	73	Knockout
1291	5	+	30,467,015	30,467,034	ACCAACCGUCACUUGGUAUA	93	36	90	73	Knockout
1292	5	-	30,467,019	30,467,038	ACCAUAUACCAAGUGACGGU	94	55	69	73	Knockout
1293	5	-	30,467,023	30,467,042	GCUUACCAUAUACCAAGUGA	75	60	84	73	Knockout
1294	6	-	30,479,976	30,479,995	CAGAGUCCGGCUGAGAUGGA	71	65	83	73	Knockout
1295	8	+	30,484,685	30,484,704	ACUCUCGCAAUGAGAUUUGG	88	46	85	73	Knockout
1296	8	+	30,484,722	30,484,741	AAAGCCAGAUGACACCACUC	86	52	81	73	Knockout
1297	4	-	30,464,079	30,464,098	AGUGGGCACUUGAUGCGAGC	92	35	90	72	Knockout
1298	4	+	30,464,162	30,464,181	GUAUUGGACUAGGCAGGACC	86	57	72	72	Knockout
1299	4	+	30,464,281	30,464,300	GCAACUAUACCUGCAUGUUA	90	42	83	72	Knockout
1300	3	+	30,428,082	30,428,101	AUCCUGCAAAGUCAUGCCUC	78	54	82	71	Knockout
1301	4	-	30,464,213	30,464,232	UACUAAUGCGGUUCUCAGGG	88	52	75	71	Knockout

FIG. 32A

SEQ ID NO:	Exon	Strand	Start coordinate	End coordinate	crRNA	OOF	On	Frameshift	On-target	Interference predictions
1302	10	+	30,500,105	30,500,124	GAUAGCUCCAAGAUACACAG	85	68	86	80	Soluble decoy receptor
1303	9	+	30,487,166	30,487,185	UCAUGCUAGAAAUGCCAAAG	80	65	84	77	Soluble decoy receptor
1304	10	-	30,500,152	30,500,171	GAUCACCACUAGCAGGACUG	82	60	88	77	Soluble decoy receptor
1305	10	+	30,500,118	30,500,137	UACACAGUGGAACUGGCAUG	70	58	89	72	Soluble decoy receptor
1306	9	+	30,487,187	30,487,206	GGAGGUUGACAAACCAGCCA	79	50	82	70	Soluble decoy receptor
1307	10	-	30,500,103	30,500,122	GUGUAUCUUGGAGCUAUCAC	87	52	70	70	Soluble decoy receptor
1308	9	+	30,487,169	30,487,188	UGCUAGAAAUGCCAAAGGGG	75	61	72	69	Soluble decoy receptor
1309	9	-	30,487,183	30,487,202	UGGUUUGUCAACCUCCCCUU	83	50	71	68	Soluble decoy receptor
1310	10	-	30,500,115	30,500,134	GCCAGUUCCACUGUGUAUCU	86	35	85	68	Soluble decoy receptor
1311	10	-	30,500,159	30,500,178	CAAUGAGGAUCACCACUAGC	90	41	70	67	Soluble decoy receptor
1312	10	-	30,500,174	30,500,193	AGACAUGGUAAAUGACAAUG	70	59	69	66	Soluble decoy receptor
1313	10	+	30,500,144	30,500,163	UGGAGCCACAGUCCUGCUAG	80	54	57	64	Soluble decoy receptor
1314	9	+	30,487,081	30,487,100	AGACUCUAACAGAAGAUGAA	61	48	80	63	Soluble decoy receptor
1315	9	+	30,487,200	30,487,219	CCAGCCAAGGUGAAACAGAA	65	46	79	63	Soluble decoy receptor
1316	9	+	30,487,164	30,487,183	UGUCAUGCUAGAAAUGCCAA	63	42	77	61	Soluble decoy receptor
1317	9	-	30,487,207	30,487,226	AUUACCUUUCUGUUUCACCU	65	38	81	61	Soluble decoy receptor
1318	9	+	30,487,165	30,487,184	GUCAUGCUAGAAAUGCCAAA	51	43	82	59	Soluble decoy receptor
1319	10	+	30,500,111	30,500,130	UCCAAGAUACACAGUGGAAC	77	32	67	59	Soluble decoy receptor
1320	9	-	30,487,203	30,487,222	CCUUUCUGUUUCACCUUGGC	63	24	83	57	Soluble decoy receptor
1321	9	+	30,487,121	30,487,140	CAUCAAGAAAGUUACUGCUG	65	51	48	55	Soluble decoy receptor
1322	10	+	30,500,124	30,500,143	GUGGAACUGGCAUGUGGUUU	12	43	65	40	Soluble decoy receptor

FIG. 32B

SEQ ID NO:	Exon	Strand	Start coordinate	End coordinate	crRNA	OOF	On	Frameshift	On-target	Interference predictions
1323	11	-	30,501,651	30,501,670	CAUUCUCCAAAACUCCACGG	86	64	87	79	Membrane-bound decoy receptor
1324	11	+	30,501,695	30,501,714	UUGACCGAGACAGUCUACCU	93	53	83	77	Membrane-bound decoy receptor
1325	11	+	30,501,697	30,501,716	GACCGAGACAGUCUACCUGG	86	66	79	77	Membrane-bound decoy receptor
1326	11	+	30,501,696	30,501,715	UGACCGAGACAGUCUACCUG	88	58	82	76	Membrane-bound decoy receptor
1327	11	+	30,501,634	30,501,653	UUUGUAUUACUGACCCUCCG	90	51	83	74	Membrane-bound decoy receptor
1328	11	-	30,501,650	30,501,669	AUUCUCCAAAACUCCACGGA	85	56	82	74	Membrane-bound decoy receptor
1329	10	+	30,500,180	30,500,199	CAUUUACCAUGUCUACUGGC	89	36	90	72	Membrane-bound decoy receptor
1330	11	+	30,501,593	30,501,612	AUAUUUAUGUAUCCUAUGCA	82	48	87	72	Membrane-bound decoy receptor
1331	11	-	30,501,702	30,501,721	UUCCCCCAGGUAGACUGUCU	83	46	86	72	Membrane-bound decoy receptor
1332	11	+	30,501,694	30,501,713	UUUGACCGAGACAGUCUACC	92	31	88	71	Membrane-bound decoy receptor
1333	11	-	30,501,715	30,501,734	CUGAAACACCUACUUCCCCC	82	57	71	70	Membrane-bound decoy receptor
1334	11	+	30,501,642	30,501,661	ACUGACCCUCCGUGGAGUUU	90	33	86	69	Membrane-bound decoy receptor
1335	10	+	30,500,200	30,500,219	UGGAGAUGGUCCUAUUUUAC	88	28	87	68	Membrane-bound decoy receptor
1336	10	+	30,500,201	30,500,220	GGAGAUGGUCCUAUUUUACC	87	37	82	68	Membrane-bound decoy receptor
1337	10	-	30,500,222	30,500,241	CAUCUGUUCCAAAAUGAGCC	79	33	86	66	Membrane-bound decoy receptor
1338	11	+	30,501,564	30,501,583	GUUCCUUUUGCUAGAUGGGA	76	42	79	66	Membrane-bound decoy receptor
1339	10	-	30,500,189	30,500,208	CCAUCUCCAGCCAGUAGACA	79	44	71	65	Membrane-bound decoy receptor
1340	10	-	30,500,213	30,500,232	CAAAAUGAGCCCGGUAAAAU	90	22	84	65	Membrane-bound decoy receptor
1341	10	+	30,500,211	30,500,230	CUAUUUUACCGGGCUCAUUU	85	17	87	63	Membrane-bound decoy receptor
1342	11	-	30,501,654	30,501,673	AUUCAUUCUCCAAAACUCCA	58	42	90	63	Membrane-bound decoy receptor
1343	11	-	30,501,608	30,501,627	UUCUUCAGCAUUCCUUGCAU	68	41	70	60	Membrane-bound decoy receptor
1344	10	-	30,500,248	30,500,267	CUUCCAUUACUCACCUAAAA	81	16	81	59	Membrane-bound decoy receptor
1345	10	+	30,500,176	30,500,195	UUGUCAUUUACCAUGUCUAC	71	30	70	57	Membrane-bound decoy receptor
1346	10	+	30,500,186	30,500,205	CCAUGUCUACUGGCUGGAGA	68	43	59	57	Membrane-bound decoy receptor
1347	10	+	30,500,232	30,500,251	GGAACAGAUGAAACCAUUUU	68	23	81	57	Membrane-bound decoy receptor
1348	11	+	30,501,655	30,501,674	GGAGUUUUGGAGAAUGAAUU	57	27	86	57	Membrane-bound decoy receptor

FIG. 32C

SEQ ID NO:	Exon	Strand	Start coordinate	End coordinate	crRNA	OOF	ON	Frameshift	OVERALL	Interference predictions
1349	7	+	79,687,223	79,687,242	UCAUUGGGUGAGUAGAUCUG	83	72	93	83	Knockout
1350	5	+	79,703,302	79,703,321	AUGCACUGGGAGUUUCAUGG	79	69	92	80	Knockout
1351	5	+	79,703,215	79,703,234	AGUGAUGGUUGGUUUGACAC	91	60	81	78	Knockout
1352	5	+	79,703,219	79,703,238	AUGGUUGGUUUGACACUGGA	80	64	87	77	Knockout
1353	8	-	79,685,121	79,685,140	CCUGAAGGAUGCCCGCAAUG	93	60	78	77	Knockout
1354	6	+	79,689,758	79,689,777	CAGAGUCCUAGUGAGAUGGA	74	66	86	76	Knockout
1355	7	-	79,687,199	79,687,218	GUAGUCUACGAGAAAGAACC	83	60	85	76	Knockout
1356	8	-	79,685,113	79,685,132	AUGCCCGCAAUGAGGUUUGG	88	49	92	76	Knockout
1357	5	+	79,703,365	79,703,384	UGCAACUUUGCUGCAAUACG	93	48	84	75	Knockout
1358	7	+	79,687,226	79,687,245	UUGGGUGAGUAGAUCUGAGG	71	71	83	75	Knockout
1359	8	+	79,685,106	79,685,125	UGGUCCACCAAACCUCAUUG	92	54	80	75	Knockout
1360	8	-	79,685,102	79,685,121	GAGGUUUGGUGGACCAUUGA	88	45	92	75	Knockout
1361	5	+	79,703,200	79,703,219	GCUUACCAUAUACCAAGUGA	86	54	82	74	Knockout
1362	8	-	79,685,116	79,685,135	AGGAUGCCCGCAAUGAGGUU	93	51	79	74	Knockout
1363	8	+	79,685,107	79,685,126	GGUCCACCAAACCUCAUUGC	95	49	78	74	Knockout
1364	8	-	79,685,056	79,685,075	UUGAUGUAACUGUCAAUGAA	80	48	91	73	Knockout
1365	5	-	79,703,208	79,703,227	ACCAACCAUCACUUGGUAUA	92	33	91	72	Knockout
1366	8	+	79,685,142	79,685,161	AAGUAAAAUAGACUGUACAA	69	64	84	72	Knockout
1367	5	+	79,703,289	79,703,308	CUAUAUAUAGUCUAUGCACU	86	43	85	71	Knockout
1368	5	+	79,703,204	79,703,223	ACCAUAUACCAAGUGAUGGU	84	53	76	71	Knockout
1369	6	-	79,689,767	79,689,786	GGCGUACCUUCCAUCUCACU	88	41	82	70	Knockout
1370	9	-	79,682,295	79,682,314	AGAAGAUGAAACGAGAACUC	74	55	82	70	Knockout
1371	5	+	79,703,299	79,703,318	UCUAUGCACUGGGAGUUUCA	83	33	92	69	Knockout
1372	5	+	79,703,288	79,703,307	UCUAUAUAUAGUCUAUGCAC	83	43	81	69	Knockout
1373	6	-	79,689,825	79,689,844	AUAGCCUUGGUUUCAAACAA	77	49	81	69	Knockout
1374	6	+	79,689,818	79,689,837	AUCUCCAUUGUUUGAAACCA	75	44	87	69	Knockout
1375	6	-	79,689,788	79,689,807	UUGUUACAUAUCCAGAAAAC	69	51	88	69	Knockout
1376	6	+	79,689,754	79,689,773	CAGUCAGAGUCCUAGUGAGA	74	54	80	69	Knockout
1377	6	-	79,689,748	79,689,767	UAGGACUCUGACUGUGAAGG	72	71	65	69	Knockout
1378	4	+	79,707,885	79,707,904	AUCAGGCUACCUUAACAUGC	69	44	90	68	Knockout

FIG. 33A

SEQ ID NO:	Exon	Strand	Start coordinate	End coordinate	crRNA	OOF	GH	Frameshift	OOF&GH	Interference predictions
1379	10	-	79,673,450	79,673,469	GAUAGCUCCAAGAUACACAG	86	65	88	80	Soluble decoy receptor
1380	10	+	79,673,403	79,673,422	GAUCACUACCAGCAGCACUG	76	62	92	77	Soluble decoy receptor
1381	9	-	79,682,220	79,682,239	UCAUGCUAGAAAUGCCAAAG	74	65	84	74	Soluble decoy receptor
1382	10	-	79,673,437	79,673,456	UACACAGUGGAAUUAGCAUG	80	57	76	71	Soluble decoy receptor
1383	10	+	79,673,381	79,673,400	AAACAUGGUAAACAACAAUG	68	59	83	70	Soluble decoy receptor
1384	9	+	79,682,203	79,682,222	UGGUUUGUCAACCUCCCCUU	86	50	71	69	Soluble decoy receptor
1385	9	-	79,682,199	79,682,218	GGAGGUUGACAAACCAGCCA	76	50	82	69	Soluble decoy receptor
1386	9	-	79,682,217	79,682,236	UGCUAGAAAUGCCAAAGGGG	72	61	72	68	Soluble decoy receptor
1387	9	-	79,682,221	79,682,240	GUCAUGCUAGAAAUGCCAAA	69	43	82	65	Soluble decoy receptor
1388	10	+	79,673,440	79,673,459	GCUAAUUCCACUGUGUAUCU	81	29	85	65	Soluble decoy receptor
1389	9	-	79,682,222	79,682,241	UGUCAUGCUAGAAAUGCCAA	72	42	77	64	Soluble decoy receptor
1390	9	-	79,682,186	79,682,205	CCAGCCAAGGUGAAACAGAA	68	46	79	64	Soluble decoy receptor
1391	9	+	79,682,179	79,682,198	AUUACCUUUCUGUUUCACCU	65	38	82	61	Soluble decoy receptor
1392	10	-	79,673,431	79,673,450	GUGGAAUUAGCAUGUGGUUU	79	37	64	60	Soluble decoy receptor
1393	9	+	79,682,183	79,682,202	CCUUUCUGUUUCACCUUGGC	67	24	83	58	Soluble decoy receptor
1394	9	-	79,682,180	79,682,199	AAGGUGAAACAGAAAGGUAA	46	55	69	57	Soluble decoy receptor
1395	9	-	79,682,265	79,682,284	CAUCAAAAAAGUUACUGCUG	67	44	47	53	Soluble decoy receptor
1396	10	-	79,673,414	79,673,433	UUUUGGAGCCACAGUGCUGC	72	33	54	53	Soluble decoy receptor

FIG. 33B

SEQ ID NO:	Exon	Strand	Start coordinate	End coordinate	crRNA	OOF	GH	Frameshift	OOF&GH	Interference predictions
1397	11	+	79,671,659	79,671,678	CAUUCUCCAAAACUCCACGG	86	64	86	79	Membrane-bound decoy receptor
1398	11	+	79,671,660	79,671,679	AUUCUCCAAAACUCCACGGA	87	56	84	76	Membrane-bound decoy receptor
1399	11	-	79,671,676	79,671,695	UUUGUGUUACUGACCCUCCG	89	55	83	75	Membrane-bound decoy receptor
1400	11	-	79,671,615	79,671,634	UUGACCGUGACAGUCUGCCU	88	49	84	74	Membrane-bound decoy receptor
1401	11	-	79,671,707	79,671,726	AUCUUACGCAAGGAAUGCUG	83	58	78	73	Membrane-bound decoy receptor
1402	11	-	79,671,614	79,671,633	UGACCGUGACAGUCUGCCUG	79	55	86	73	Membrane-bound decoy receptor
1403	11	-	79,671,613	79,671,632	GACCGUGACAGUCUGCCUGG	76	64	78	73	Membrane-bound decoy receptor
1404	11	+	79,671,595	79,671,614	GUGAGAUACCUACUUCCCCC	87	63	70	73	Membrane-bound decoy receptor
1405	11	-	79,671,668	79,671,687	ACUGACCCUCCGUGGAGUUU	89	36	85	70	Membrane-bound decoy receptor
1406	11	+	79,671,608	79,671,627	UUCCCCCAGGCAGACUGUCA	79	53	80	70	Membrane-bound decoy receptor
1407	10	-	79,673,375	79,673,394	UGUUUACCAUGUUUACUGGC	85	30	89	68	Membrane-bound decoy receptor
1408	10	+	79,673,366	79,673,385	CCAUCUCCAGCCAGUAAACA	83	41	80	68	Membrane-bound decoy receptor
1409	11	-	79,671,717	79,671,736	AUAUUUAUGUAUCUUACGCA	86	36	81	68	Membrane-bound decoy receptor
1410	11	-	79,671,616	79,671,635	UUUGACCGUGACAGUCUGCC	89	29	88	68	Membrane-bound decoy receptor
1411	10	+	79,673,333	79,673,352	CAUCUGUUCCAAAAUGAGCC	81	33	87	67	Membrane-bound decoy receptor
1412	10	-	79,673,354	79,673,373	GGAGAUGGUCUUAUUUUACC	80	34	85	66	Membrane-bound decoy receptor
1413	11	+	79,671,656	79,671,675	AUUCAUUCUCCAAAACUCCA	84	42	90	65	Membrane-bound decoy receptor
1414	10	-	79,673,355	79,673,374	UGGAGAUGGUCUUAUUUUAC	77	24	88	63	Membrane-bound decoy receptor
1415	10	-	79,673,344	79,673,363	UUAUUUUACCGGGCUCAUUU	85	18	87	63	Membrane-bound decoy receptor
1416	11	+	79,671,740	79,671,759	ACUCUUUCCCAUCUGGCAAA	61	41	87	63	Membrane-bound decoy receptor
1417	11	+	79,671,733	79,671,752	AUAUCAUACUCUUUCCCAUC	83	30	72	62	Membrane-bound decoy receptor
1418	10	+	79,673,307	79,673,326	CGUUCAUUACUCACCUAAAA	87	13	80	60	Membrane-bound decoy receptor
1419	10	-	79,673,379	79,673,398	UUGUUGUUUACCAUGUUUAC	76	18	82	59	Membrane-bound decoy receptor
1420	10	-	79,673,323	79,673,342	GGAACAGAUGAAACCAUUUU	72	23	81	58	Membrane-bound decoy receptor
1421	11	-	79,671,750	79,671,769	CUUUCUUCCUUUUGCCAGAU	59	27	88	58	Membrane-bound decoy receptor
1422	11	-	79,671,655	79,671,674	GGAGUUUUGGAGAAUGAAUU	62	27	86	58	Membrane-bound decoy receptor
1423	10	-	79,673,369	79,673,388	CCAUGUUUACUGGCUGGAGA	73	33	61	56	Membrane-bound decoy receptor
1424	11	-	79,671,751	79,671,770	UCUUUCUUCCUUUUGCCAGA	47	19	87	51	Membrane-bound decoy receptor

FIG. 33C

SEQ ID NO:	Genomic cut coordinate	Exon	CDS cut position	CDS cut position %	Strand	Start coordinate	End coordinate	crRNA	GC content	PAM
1425	99128997	2	240	15.9	+	99128981	99129000	UUGACUUAAUUCCUCGAGAU	35	AGG
1426	99128944	2	187	12.4	-	99128942	99128961	GUUGUGUAUAACUUUGUCUG	35	TGG
1427	99128997	2	240	15.9	-	99128995	99129014	CAUACAAACGGCCUAUCUCG	50	AGG
1428	99105232	1	27	1.8	+	99105216	99105235	CGGUCGCUGCUCCGCGUCCC	80	CGG
1429	99129030	2	273	18.1	+	99129014	99129033	GUGCACCCUCUUCAAAAACU	45	GGG
1430	99105254	1	49	3.2	+	99105238	99105257	GCUGCUCCUCCUCGUGCUGG	70	CGG
1431	99128907	2	150	9.9	+	99128891	99128910	AUUUUACUUGUGUGACAGAU	30	GGG
1432	99105252	1	47	3.1	-	99105250	99105269	CCGCCGCCGCCGCCAGCACG	90	AGG
1433	99105249	1	44	2.9	-	99105247	99105266	CCGCCGCCGCCAGCACGAGG	85	AGG
1434	99105257	1	52	3.4	+	99105241	99105260	GCUCCUCCUCGUGCUGGCGG	75	CGG
1435	99105238	1	33	2.2	-	99105236	99105255	AGCACGAGGAGGAGCAGCCG	70	GGG
1436	99129009	2	252	16.7	-	99129007	99129026	GAAGAGGGUGCACAUACAAA	45	CGG
1437	99128879	2	122	8.1	-	99128877	99128896	UAAAAUUGUCUUUUGUACAG	25	AGG
1438	99129061	2	304	20.1	+	99129045	99129064	UACAACAUAUUGCUGCAAUC	35	AGG
1439	99128876	2	119	7.9	-	99128874	99128893	AAUUGUCUUUUGUACAGAGG	35	TGG
1440	99128906	2	149	9.9	+	99128890	99128909	AAUUUUACUUGUGUGACAGA	30	TGG
1441	99105290	1	85	5.6	+	99105274	99105293	GGCGGCGGCGCUGCUCCCGG	90	GGG
1442	99105232	1	27	1.8	-	99105230	99105249	AGGAGGAGCAGCCGGGGACG	75	CGG
1443	99105288	1	83	5.5	+	99105272	99105291	GCGGCGGCGGCGCUGCUCCC	90	GGG
1444	99105289	1	84	5.6	+	99105273	99105292	CGGCGGCGGCGCUGCUCCCG	90	GGG
1445	99129029	2	272	18	+	99129013	99129032	UGUGCACCCUCUUCAAAAAC	45	TGG
1446	99105239	1	34	2.2	-	99105237	99105256	CAGCACGAGGAGGAGCAGCC	70	GGG
1447	99129024	2	267	17.7	-	99129022	99129041	ACAGACCCAGUUUUUGAAGA	40	GGG
1448	99129025	2	268	17.7	-	99129023	99129042	CACAGACCCAGUUUUUGAAG	45	AGG
1449	99105251	1	46	3	+	99105235	99105254	CCGGCUGCUCCUCCUCGUGC	75	TGG
1450	99105296	1	91	6	+	99105280	99105299	GGCGCUGCUCCCGGGGGCGA	85	CGG
1451	99105260	1	55	3.6	+	99105244	99105263	CCUCCUCGUGCUGGCGGCGG	80	CGG
1452	99105240	1	35	2.3	-	99105238	99105257	CCAGCACGAGGAGGAGCAGC	70	CGG
1453	99105287	1	82	5.4	+	99105271	99105290	GGCGGCGGCGGCGCUGCUCC	90	CGG
1454	99105263	1	58	3.8	+	99105247	99105266	CCUCGUGCUGGCGGCGGCGG	85	CGG
1455	99132620	3	455	30.1	-	99132618	99132637	CUCGAUGGUGAAUGACAGUG	50	CGG
1456	99132659	3	494	32.7	-	99132657	99132676	UAAAAGGGCGAUCUAAUGAA	35	GGG
1457	99132660	3	495	32.7	-	99132658	99132677	AUAAAAGGGCGAUCUAAUGA	35	AGG
1458	99132722	3	557	36.8	+	99132706	99132725	AUUUAUGAUAUGACAACGUC	30	AGG
1459	99137938	4	654	43.3	+	99137922	99137941	AAGGUCGAUUUGGAGAAGUU	40	TGG
1460	99137993	4	709	46.9	-	99137991	99138010	CCACGAACGUUCUUCUCUAG	50	AGG
1461	99138004	4	720	47.6	+	99137988	99138007	CCUCUAGAGAAGAACGUUCG	50	TGG
1462	99138014	4	730	48.3	+	99137998	99138017	AGAACGUUCGUGGUUCCGUG	55	AGG
1463	99138066	4	782	51.7	-	99138064	99138083	UGUCUGCUGCUAUAAAUCCC	45	AGG
1464	99142559	5	829	54.8	+	99142543	99142562	UACUUGGACUCAGCUCUGGU	50	TGG
1465	99142581	5	851	56.3	+	99142565	99142584	GUGUCAGAUUAUCAUGAGCA	40	TGG
1466	99142659	5	929	61.4	+	99142643	99142662	CUUGCUCUGUCCACGGCGAG	65	CGG
1467	99144815	6	1057	69.9	+	99144799	99144818	CUGUAUUGCAGACUUAGGAC	45	TGG
1468	99144872	6	1114	73.7	+	99144856	99144875	UAUUGCUCCAAACCACAGAG	45	TGG
1469	99144873	6	1115	73.7	+	99144857	99144876	AUUGCUCCAAACCACAGAGU	45	GGG
1470	99146498	7	1144	75.7	-	99146496	99146515	GGAAUCAUCGAGAACUUCAG	45	GGG
1471	99146561	7	1207	79.8	+	99146545	99146564	ACGUGCUGACAUCUAUGCAA	45	TGG
1472	99146601	7	1247	82.5	+	99146585	99146604	AUUGCUCGACGAUGUUCCAU	45	TGG
1473	99146604	7	1250	82.7	+	99146588	99146607	GCUCGACGAUGUUCCAUUGG	55	TGG
1474	99149233	9	1440	95.2	+	99149217	99149236	GGUAUGCCAAUGGAGCAGCU	55	AGG

FIG. 34A

SEQ ID NO:	Genomic cut coordinate	Exon	CDS cut position	CDS cut position %	Strand	Start coordinate	End coordinate	crRNA	GC content	PAM
1475	99149248	9	1455	96.2	+	99149232	99149251	CAGCUAGGCUUACAGCAUUG	50	CGG
1476	99146562	7	1208	79.9	+	99146546	99146565	CGUGCUGACAUCUAUGCAAU	45	GGG
1477	99142652	5	922	61	+	99142636	99142655	GAUAAAACUUGCUCUGUCCA	40	CGG
1478	99132635	3	470	31.1	-	99132633	99132652	CCUCUUCAUUUGGCACUCGA	50	TGG
1479	99144854	6	1096	72.5	-	99144852	99144871	GUGGUUUGGAGCAAUAUCAA	40	TGG
1480	99132646	3	481	31.8	+	99132630	99132649	CCAUCGAGUGCCAAAUGAAG	50	AGG
1481	99142658	5	928	61.4	-	99142656	99142675	AUGGGCAAGACCGCUCGCCG	70	TGG
1482	99142626	5	896	59.3	+	99142610	99142629	AGAUACACAGUUACUGUGGA	40	AGG
1483	99142698	5	968	64	+	99142682	99142701	AUGGAGAUUGUUGGUACCCA	45	AGG
1484	99147745	8	1347	89.1	+	99147729	99147748	UUGUUUGUGAACAGAAGUUA	30	AGG
1485	99144845	6	1087	71.9	-	99144843	99144862	AGCAAUAUCAAUGGUAUCUG	35	TGG
1486	99132614	3	449	29.7	-	99132612	99132631	GGUGAAUGACAGUGCGGUUG	55	TGG
1487	99144810	6	1052	69.6	+	99144794	99144813	ACUUGCUGUAUUGCAGACUU	40	AGG
1488	99137943	4	659	43.6	+	99137927	99137946	CGAUUUGGAGAAGUUUGGAG	45	AGG
1489	99137913	4	629	41.6	+	99137897	99137916	AUUGUGUUACAAGAAAGCAU	30	TGG
1490	99142679	5	949	62.8	+	99142663	99142682	CGGUCUUGCCCAUCUUCACA	55	TGG
1491	99138060	4	776	51.3	+	99138044	99138063	UUACGUCAUGAAAACAUCCU	35	GGG
1492	99144742	6	984	65.1	-	99144740	99144759	AAAUCUCUAUGAGCAAUGGC	40	TGG
1493	99149223	9	1430	94.6	+	99149207	99149226	AGAGAAUGUUGGUAUGCCAA	40	TGG
1494	99132679	3	514	34	+	99132663	99132682	AGAUCGCCCUUUUAUUUCAG	40	AGG
1495	99147766	8	1368	90.5	+	99147750	99147769	GGCCAAAUAUCCCAAACAGA	45	TGG
1496	99137953	4	669	44.2	+	99137937	99137956	AAGUUUGGAGAGGAAAGUGG	45	CGG
1497	99147675	8	1277	84.5	-	99147673	99147692	CAAGAUCAUAAUAAGGCAGU	35	TGG
1498	99144883	6	1125	74.4	+	99144867	99144886	ACCACAGAGUGGGAACAAAA	45	AGG
1499	99142689	5	959	63.4	+	99142673	99142692	CAUCUUCACAUGGAGAUUGU	40	TGG
1500	99146499	7	1145	75.7	-	99146497	99146516	UGGAAUCAUCGAGAACUUCA	40	GGG
1501	99138059	4	775	51.3	+	99138043	99138062	GUUACGUCAUGAAAACAUCC	40	TGG
1502	99144746	6	988	65.3	-	99144744	99144763	UUUCAAAUCUCUAUGAGCAA	30	TGG
1503	99149212	9	1419	93.8	+	99149196	99149215	CUAAAAUUAUGAGAGAAUGU	25	TGG
1504	99137869	4	585	38.7	-	99137867	99137886	AUUGUUCUCUGAACAAGCAA	35	TGG
1505	99142622	5	892	59	+	99142606	99142625	AAACAGAUACACAGUUACUG	35	TGG
1506	99137954	4	670	44.3	+	99137938	99137957	AGUUUGGAGAGGAAAGUGGC	50	GGG
1507	99147765	8	1367	90.4	-	99147763	99147782	CACAGCUCUGCCAUCUGUUU	50	GGG
1508	99146543	7	1189	78.6	-	99146541	99146560	AUAGAUGUCAGCACGUUUGA	40	AGG
1509	99137955	4	671	44.4	+	99137939	99137958	GUUUGGAGAGGAAAGUGGCG	55	GGG
1510	99147700	8	1302	86.1	-	99147698	99147717	UCUUCAACUGAUGGGUCAGA	45	AGG
1511	99132645	3	480	31.7	-	99132643	99132662	AAUGAAGGGUCCUCUUCAUU	40	TGG
1512	99132674	3	509	33.7	-	99132672	99132691	UAGUACCCUCUGAAAUAAAA	30	GGG
1513	99132680	3	515	34.1	+	99132664	99132683	GAUCGCCCUUUUAUUUCAGA	40	GGG
1514	99147682	8	1284	84.9	-	99147680	99147699	GAAGGUACAAGAUCAUAAUA	30	AGG
1515	99138084	4	800	52.9	+	99138068	99138087	UUUAUAGCAGCAGACAAUAA	30	AGG
1516	99138018	4	734	48.5	-	99138016	99138035	UUUGAUAAAUCUCUGCCUCA	35	CGG
1517	99146576	7	1222	80.8	+	99146560	99146579	UGCAAUGGGCUUAGUAUUCU	40	GGG
1518	99149186	9	1393	92.1	-	99149184	99149203	AAUUUUAGCCAUUACUCUCA	30	AGG
1519	99132675	3	510	33.7	-	99132673	99132692	GUAGUACCCUCUGAAAUAAA	35	AGG
1520	99147766	8	1368	90.5	-	99147764	99147783	UCACAGCUCUGCCAUCUGUU	50	TGG
1521	99142595	5	865	57.2	-	99142593	99142612	UCUGUUUAAGUAAUCAAAAA	20	GGG
1522	99137919	4	635	42	+	99137903	99137922	UUACAAGAAAGCAUUGGCAA	35	AGG
1523	99146500	7	1146	75.8	-	99146498	99146517	AUGGAAUCAUCGAGAACUUC	40	AGG
1524	99144868	6	1110	73.4	-	99144866	99144885	UUUGUUCCCACUCUGUGGUU	45	TGG

FIG. 34B

SEQ ID NO:	Genomic cut coordinate	Exon	CDS cut position	CDS cut position %	Strand	Start coordinate	End coordinate	crRNA	GC content	PAM
1525	99137928	4	644	42.6	+	99137912	99137931	AGCAUUGGCAAAGGUCGAUU	45	TGG
1526	99132728	3	563	37.2	+	99132712	99132731	GAUAUGACAACGUCAGGUUC	45	TGG
1527	99146575	7	1221	80.8	+	99146559	99146578	AUGCAAUGGGCUUAGUAUUC	40	TGG
1528	99147757	8	1359	89.9	-	99147755	99147774	UGCCAUCUGUUUGGGAUAUU	40	TGG
1529	99142677	5	947	62.6	-	99142675	99142694	CAACAAUCUCCAUGUGAAGA	40	TGG
1530	99147708	8	1310	86.6	-	99147706	99147725	UUCUCAUUUCUUCAACUGAU	30	GGG
1531	99132734	3	569	37.6	+	99132718	99132737	ACAACGUCAGGUUCUGGCUC	55	AGG
1532	99149228	9	1435	94.9	-	99149226	99149245	UGUAAGCCUAGCUGCUCCAU	50	TGG
1533	99144786	6	1028	68	+	99144770	99144789	AAUAUCUUGGUAAAGAAGAA	25	TGG
1534	99147709	8	1311	86.7	-	99147707	99147726	UUUCUCAUUUCUUCAACUGA	30	TGG
1535	99132530	3	365	24.1	-	99132528	99132547	CUGCCAGUUCCACAGGACCA	60	AGG
1536	99132537	3	372	24.6	-	99132535	99132554	AUGACAGCUGCCAGUUCCAC	55	AGG
1537	99132532	3	367	24.3	+	99132516	99132535	AUCACCUGGCCUUGGUCCUG	60	TGG
1538	99132538	3	373	24.7	+	99132522	99132541	UGGCCUUGGUCCUGUGGAAC	60	TGG
1539	99132554	3	389	25.7	+	99132538	99132557	GAACUGGCAGCUGUCAUUGC	55	TGG
1540	99132525	3	360	23.8	-	99132523	99132542	AGUUCCACAGGACCAAGGCC	60	AGG
1541	99132524	3	359	23.7	+	99132508	99132527	GUAAAGUCAUCACCUGGCCU	50	TGG
1542	99129095	2	338	22.4	+	99129079	99129098	AAAAUAGAACUUCCAACUAC	30	TGG
1543	99132567	3	402	26.6	-	99132565	99132584	GAGAUGCAGACGAAGCACAC	55	TGG
1544	99132592	3	427	28.2	+	99132576	99132595	CUGCAUCUCACUCAUGUUGA	45	TGG
1545	99149286	9	1493	98.7	+	99149270	99149289	UCGCAACUCAGUCAACAGGA	50	AGG
1546	99149282	9	1489	98.5	+	99149266	99149285	AUUAUCGCAACUCAGUCAAC	40	AGG

FIG. 34C

SEQ ID NO:	MIT	CFD	Elevation	ccTop	Offtarget #	Azimuth	DeepSpCas9	CrisprScan	CRISTA	Lindel	InDelphi	Frameshift	Precision	Graf Motifs	Bioscore	GUIDE-SEQ	GUIDE-TAG	DISCOVER-Seq	Interference predictions
1425	87	93	56	79	86	42	29	44	38	87	86	87	60	OK	73	59	83	66	Knockout
1426	69	84	61	71	241	60	60	40	53	82	89	85	61	OK	55	62	78	70	Knockout
1427	90	88	41	76	73	65	65	31	54	83	84	83	52	OK	73	66	81	72	Knockout
1428	80	92	37	70	113	39	42	76	52	75	92	83	57	OK	45	61	77	66	Knockout
1429	76	89	64	76	111	52	34	50	45	74	79	75	55	OK	52	61	76	66	Knockout
1430	57	75	40	57	443	63	56	58	59	80	77	79	47	OK	49	58	68	65	Knockout
1431	66	75	59	67	266	50	15	53	39	86	86	86	55	OK	74	53	77	65	Knockout
1432	61	79	37	59	685	39	62	71	57	77	73	75	50	OK	51	58	67	64	Knockout
1433	81	91	39	70	166	41	62	73	59	69	55	62	43	OK	54	64	66	63	Knockout
1434	69	82	36	63	219	51	57	63	57	76	63	69	44	OK	38	60	66	63	Knockout
1435	46	72	34	51	496	57	56	51	55	77	82	80	48	OK	55	53	65	62	Knockout
1436	55	58	59	57	335	47	40	52	46	78	86	83	51	OK	68	52	70	62	Knockout
1437	55	66	63	61	386	52	16	28	33	82	94	88	59	OK	59	47	75	61	Knockout
1438	76	88	45	70	112	50	12	23	29	83	84	83	56	OK	53	49	77	61	Knockout
1439	34	59	53	49	1117	58	34	72	55	78	73	75	52	OK	66	52	62	60	Knockout
1440	62	77	59	66	297	53	8	24	28	86	87	87	51	OK	68	47	76	60	Knockout
1441	59	76	36	57	489	40	57	66	61	66	56	62	40	OK	43	59	59	60	Knockout
1442	52	60	32	46	745	46	48	66	53	72	83	77	56	OK	44	51	63	60	Knockout
1443	53	83	42	59	462	27	32	66	42	68	76	72	58	OK	42	51	66	58	Knockout
1444	63	83	36	61	335	34	41	63	53	68	56	62	38	OK	43	57	61	58	Knockout
1445	70	88	61	73	152	35	17	20	24	67	79	73	62	OK	48	49	73	57	Knockout
1446	38	62	32	44	569	42	38	59	46	82	80	81	57	GGC	51	45	63	57	Knockout
1447	60	71	58	63	296	54	22	45	40	65	68	67	56	OK	50	52	65	57	Knockout
1448	65	75	62	67	224	60	11	31	34	69	63	66	43	OK	54	51	67	56	Knockout
1449	65	81	40	62	255	46	45	29	40	69	64	66	44	OK	51	51	64	56	Knockout
1450	69	79	36	61	227	32	36	56	41	63	63	63	50	OK	37	51	62	55	Knockout
1451	72	83	38	64	203	40	44	67	57	49	26	36	64	OK	37	61	51	53	Knockout
1452	31	59	37	42	742	40	47	53	47	58	65	61	56	OK	51	45	52	50	Knockout
1453	33	71	39	44	822	17	33	56	35	56	63	59	46	OK	42	40	52	46	Knockout
1454	25	51	30	35	515	37	41	58	55	47	27	37	57	OK	40	45	36	42	Knockout
1455	69	82	65	72	180	73	73	64	77	86	80	83	56	OK	65	74	78	77	Membrane-bound decoy receptor
1456	80	85	48	71	124	59	60	52	57	86	82	84	65	OK	53	64	78	71	Membrane-bound decoy receptor
1457	81	89	54	75	98	53	37	27	39	70	80	75	57	OK	53	57	75	63	Membrane-bound decoy receptor
1458	85	91	52	76	100	37	21	41	33	74	75	74	55	OK	70	54	75	61	Membrane-bound decoy receptor
1459	70	83	58	70	150	42	46	57	48	83	85	89	74	OK	70	59	80	69	Membrane-bound decoy receptor
1460	91	96	39	75	35	57	26	41	41	83	85	84	44	OK	65	58	80	67	Membrane-bound decoy receptor
1461	96	89	42	79	45	44	58	41	48	87	93	90	64	TT	69	63	84	72	Membrane-bound decoy receptor
1462	94	87	34	75	28	71	64	45	60	87	92	89	60	OK	74	68	82	75	Membrane-bound decoy receptor
1463	63	90	58	70	134	59	65	40	55	80	87	83	58	OK	70	63	77	69	Membrane-bound decoy receptor
1464	68	86	47	67	141	57	70	35	54	85	87	86	53	OK	69	61	77	69	Membrane-bound decoy receptor
1465	80	90	60	77	104	55	49	40	48	74	61	67	65	OK	72	62	72	64	Membrane-bound decoy receptor
1466	89	95	42	75	71	60	40	63	54	83	90	87	60	OK	54	65	81	72	Membrane-bound decoy receptor
1467	84	91	58	78	105	51	53	44	49	74	79	77	56	OK	72	63	77	68	Membrane-bound decoy receptor
1468	68	82	61	70	172	72	61	37	57	90	89	90	56	OK	72	64	80	72	Membrane-bound decoy receptor
1469	47	77	61	62	316	62	65	56	61	83	87	85	51	OK	72	61	73	69	Membrane-bound decoy receptor
1470	79	87	54	73	106	70	41	48	53	75	84	79	56	OK	78	63	76	69	Membrane-bound decoy receptor
1471	82	92	60	78	81	57	57	36	50	90	86	88	50	OK	72	64	83	72	Membrane-bound decoy receptor
1472	91	95	51	79	29	49	49	58	52	81	80	80	44	OK	69	65	80	70	Membrane-bound decoy receptor
1473	95	96	49	81	16	53	64	37	51	83	88	86	60	OK	76	66	83	72	Membrane-bound decoy receptor
1474	83	92	61	79	81	66	65	43	59	75	70	73	58	OK	69	69	76	70	Membrane-bound decoy receptor

FIG. 34D

SEQ ID NO:	MIT	CFD	Elevation	GUIDE	Offtarget #	Azimuth	DeepSpCas9	CrispScan	CFD	Lindel	inDelphi	Frameshift	Precision	Graf Motifs	Bioscore	GUIDE	GUIDE	GUIDE	Transmembrane predictions
1475	86	91	53	77	84	69	63	58	63	87	91	89	58	OK	72	70	83	76	Membrane-bound decoy receptor
1476	82	89	59	78	77	53	32	39	41	87	90	89	56	OK	72	60	83	69	Membrane-bound decoy receptor
1477	67	85	62	71	147	63	51	29	47	85	84	85	56	OK	65	59	78	68	Membrane-bound decoy receptor
1478	92	91	48	77	75	48	24	36	36	92	91	92	61	OK	59	57	84	68	Membrane-bound decoy receptor
1479	73	88	61	74	206	53	37	56	56	63	72	68	66	OK	68	66	71	66	Membrane-bound decoy receptor
1480	81	89	53	74	83	57	49	39	48	78	76	77	43	OK	51	61	75	66	Membrane-bound decoy receptor
1481	92	87	42	77	58	62	43	38	48	73	71	72	51	OK	54	62	74	66	Membrane-bound decoy receptor
1482	65	80	55	67	207	56	54	29	46	84	86	86	62	OK	74	56	76	66	Membrane-bound decoy receptor
1483	67	90	52	70	171	59	53	72	61	75	56	65	54	OK	65	66	67	65	Membrane-bound decoy receptor
1484	59	78	64	67	304	46	30	48	41	85	91	88	54	OK	69	54	77	65	Membrane-bound decoy receptor
1485	69	82	62	71	191	68	53	35	51	68	79	73	61	OK	69	61	72	65	Membrane-bound decoy receptor
1486	59	86	49	68	104	50	64	69	61	80	73	86	50	OK	62	64	67	65	Membrane-bound decoy receptor
1487	59	85	46	63	170	61	41	52	51	76	83	80	59	TT	78	57	71	65	Membrane-bound decoy receptor
1488	65	78	70	71	190	53	43	46	47	80	76	78	46	OK	73	59	75	65	Membrane-bound decoy receptor
1489	51	72	59	61	287	59	66	34	53	79	78	79	43	OK	74	57	70	64	Membrane-bound decoy receptor
1490	89	89	53	74	94	55	33	21	36	77	86	81	50	OK	80	55	78	64	Membrane-bound decoy receptor
1491	61	87	51	66	129	61	40	35	45	77	84	81	59	TT	77	56	73	64	Membrane-bound decoy receptor
1492	75	86	59	73	176	49	51	12	37	80	84	82	64	OK	65	56	79	64	Membrane-bound decoy receptor
1493	71	83	59	71	201	61	56	53	56	69	59	64	51	OK	65	64	67	64	Membrane-bound decoy receptor
1494	78	86	59	74	107	60	6	30	33	78	85	82	56	OK	62	54	78	63	Membrane-bound decoy receptor
1495	48	74	68	63	349	63	47	31	46	76	83	79	49	OK	66	55	71	63	Membrane-bound decoy receptor
1496	40	53	41	45	566	60	57	87	68	77	76	76	42	OK	72	56	60	63	Membrane-bound decoy receptor
1497	71	80	56	69	175	51	38	43	44	72	81	77	52	OK	73	57	73	63	Membrane-bound decoy receptor
1498	53	68	65	62	412	48	32	46	42	84	85	85	54	OK	68	52	73	63	Membrane-bound decoy receptor
1499	58	79	61	66	207	48	23	37	36	85	90	86	61	TT	80	51	77	63	Membrane-bound decoy receptor
1500	75	85	59	73	140	53	17	27	32	79	83	81	63	TT	78	53	77	62	Membrane-bound decoy receptor
1501	62	92	57	70	79	51	44	4	30	83	89	86	57	OK	77	50	78	62	Membrane-bound decoy receptor
1502	63	76	61	67	298	54	20	40	38	83	81	82	46	OK	63	52	74	62	Membrane-bound decoy receptor
1503	53	65	69	62	358	57	42	13	37	83	88	87	56	OK	80	50	75	62	Membrane-bound decoy receptor
1504	36	81	38	51	203	56	51	38	48	85	87	87	51	OK	78	50	69	62	Membrane-bound decoy receptor
1505	53	67	51	57	367	61	65	31	52	72	81	77	58	OK	73	56	67	62	Membrane-bound decoy receptor
1506	47	69	47	54	427	46	57	41	48	81	87	84	61	OK	71	51	69	62	Membrane-bound decoy receptor
1507	66	85	52	68	282	25	12	60	32	80	86	83	49	TT	79	50	75	61	Membrane-bound decoy receptor
1508	63	82	56	67	117	41	35	37	38	71	88	80	58	OK	66	52	73	61	Membrane-bound decoy receptor
1509	62	70	43	58	295	60	50	34	48	79	75	77	46	OK	72	53	68	61	Membrane-bound decoy receptor
1510	69	80	48	65	182	56	34	40	43	85	81	73	51	OK	63	54	69	61	Membrane-bound decoy receptor
1511	75	87	53	72	141	35	16	49	33	74	84	79	48	TT	53	52	75	61	Membrane-bound decoy receptor
1512	49	77	64	63	229	38	31	42	37	81	87	84	58	OK	59	50	74	61	Membrane-bound decoy receptor
1513	72	87	58	72	103	56	3	37	32	75	80	78	47	OK	53	52	75	61	Membrane-bound decoy receptor
1514	74	86	61	74	177	42	42	45	43	83	66	84	58	OK	71	58	69	60	Membrane-bound decoy receptor
1515	59	79	64	67	304	42	28	36	35	74	82	78	57	OK	63	51	73	60	Membrane-bound decoy receptor
1516	60	77	46	57	280	66	37	29	44	78	76	77	46	OK	69	51	67	60	Membrane-bound decoy receptor
1517	73	87	60	73	140	32	6	39	26	70	86	78	60	TT	78	50	76	59	Membrane-bound decoy receptor
1518	65	78	62	68	252	45	12	13	23	88	81	85	51	OK	71	46	77	59	Membrane-bound decoy receptor
1519	49	82	46	59	158	34	24	38	32	86	86	86	60	OK	59	45	73	59	Membrane-bound decoy receptor
1520	62	72	46	60	369	29	34	24	29	86	88	87	53	TT	75	45	74	59	Membrane-bound decoy receptor
1521	46	74	65	62	459	47	12	36	32	79	82	80	58	OK	70	47	71	58	Membrane-bound decoy receptor
1522	56	69	64	63	319	65	42	40	49	81	82	81	46	OK	63	56	62	58	Membrane-bound decoy receptor
1523	83	92	54	76	101	32	16	41	30	69	69	69	44	TT	79	53	73	58	Membrane-bound decoy receptor
1524	58	79	53	63	266	40	23	50	38	87	72	69	48	OK	66	50	66	57	Membrane-bound decoy receptor

FIG. 34E

SEQ ID NO:	MIT	CFD	Elevation	OOF	Offtarget #	Azimuth	DeepSpCas9	CrisprScan	OOT	Lindel	inDelphi	Frameshift	Precision	Graf Motifs	Bioscore	OOT / OOT	OOT / ES	OOT/OOT1	Interference predictions
1525	89	93	52	79	81	39	20	35	31	57	65	61	41	OK	70	55	70	57	Membrane-bound decoy receptor
1526	87	94	53	78	62	43	37	33	38	58	46	52	54	TT	61	58	65	56	Membrane-bound decoy receptor
1527	82	91	55	76	97	20	7	26	48	65	86	75	56	TT	78	47	76	56	Membrane-bound decoy receptor
1528	71	84	64	73	194	15	2	51	23	69	74	72	66	TT	65	48	72	56	Membrane-bound decoy receptor
1529	67	81	62	70	232	46	12	16	25	67	76	71	59	OK	74	47	71	55	Membrane-bound decoy receptor
1530	41	56	65	54	483	42	5	37	28	85	83	84	68	OK	63	41	69	55	Membrane-bound decoy receptor
1531	77	88	47	71	101	44	53	27	41	61	47	49	58	OK	55	56	60	54	Membrane-bound decoy receptor
1532	29	27	42	33	3487	51	49	60	53	74	69	72	43	OK	71	43	62	52	Membrane-bound decoy receptor
1533	36	55	58	50	567	49	35	11	32	71	69	70	61	OK	65	41	60	50	Membrane-bound decoy receptor
1534	36	62	51	50	620	47	5	5	19	81	74	77	44	OK	58	34	64	49	Membrane-bound decoy receptor
1535	41	73	33	49	420	68	70	46	61	75	86	80	62	OK	44	55	65	64	Soluble decoy receptor
1536	70	86	53	70	179	53	49	58	53	64	70	67	48	OK	64	61	68	63	Soluble decoy receptor
1537	63	76	39	59	214	50	47	39	45	78	76	77	47	OK	50	52	68	61	Soluble decoy receptor
1538	74	88	53	72	199	36	41	51	43	65	61	63	52	OK	56	57	67	59	Soluble decoy receptor
1539	74	88	53	72	183	38	39	27	35	62	75	69	56	TT	67	53	70	58	Soluble decoy receptor
1540	68	88	46	67	194	52	46	35	44	62	59	61	53	GGC	44	56	64	57	Soluble decoy receptor
1541	64	87	53	68	186	50	51	20	40	60	64	62	55	GGC	43	54	65	57	Soluble decoy receptor
1542	68	81	59	69	225	50	22	17	30	73	66	69	49	OK	54	50	69	56	Soluble decoy receptor
1543	76	89	58	74	152	69	70	43	61	69	94	81	64	OK	69	67	63	75	Soluble or membrane-bound decoy receptor
1544	71	86	64	74	194	37	21	43	34	66	74	70	60	OK	66	54	72	59	Soluble or membrane-bound decoy receptor
1545	86	91	58	79	72	71	57	63	64	87	84	86	55	OK	51	71	62	76	Wildtype-like
1546	93	96	46	78	44	51	27	32	37	75	81	78	52	OK	54	58	78	64	Wildtype-like

FIG. 34F

SEQ ID NO:	Genomic cut coordinate	Exon	CDS cut position	CDS cut position %	Strand	Start coordinate	End coordinate	crRNA	GC content	PAM
1547	30606950	1	67	3.9	-	30606947	30606967	AACGUGCGGUGGGAUCGUGC	65	TGG
1548	30606960	1	77	4.5	-	30606957	30606977	CCGACUUCUGAACGUGCGGU	60	GGG
1549	30606961	1	78	4.6	-	30606958	30606978	CCCGACUUCUGAACGUGCGG	65	TGG
1550	30644774	2	122	7.2	+	30644757	30644777	AUGAUAGUCACUGACAACAA	35	CGG
1551	30644878	2	226	13	-	30644875	30644895	CUGUGGCUUCUCACAGAUGG	55	AGG
1552	30650331	3	325	19	-	30650328	30650348	UUCCAGAAUAAAGUCAUGGU	35	AGG
1553	30644902	2	250	15	+	30644885	30644905	GAAGCCACAGGAAGUCUGUG	55	TGG
1554	30644895	2	243	14	-	30644892	30644912	ACAGCCACACAGACUUCCUG	55	TGG
1555	30650329	3	323	19	-	30650326	30650346	CCAGAAUAAAGUCAUGGUAG	40	GGG
1556	30644910	2	258	15	+	30644893	30644913	AGGAAGUCUGUGUGGCUGUA	50	TGG
1557	30606972	1	89	5.2	+	30606955	30606975	CCACCGCACGUUCAGAAGUC	60	GGG
1558	30606933	1	50	2.9	-	30606930	30606950	UGCUGGCGAUACGCGUCCAC	65	AGG
1559	30606912	1	29	1.7	-	30606909	30606929	GGACGAUGUGCAGCGGCCAC	70	AGG
1560	30644890	2	238	14	+	30644873	30644893	CUCCAUCUGUGAGAAGCCAC	55	AGG
1561	30650396	3	390	23	-	30650393	30650413	CACAUGAAGAAAGUCUCACC	45	AGG
1562	30650335	3	329	19	-	30650332	30650352	CAUCUUCCAGAAUAAAGUCA	35	TGG
1563	30644881	2	229	13	-	30644878	30644898	UUCCUGUGGCUUCUCACAGA	50	TGG
1564	30650421	3	415	24	-	30650418	30650438	AUUGCACUCAUCAGAGCUAC	45	AGG
1565	30644836	2	184	11	-	30644833	30644853	GCAGGAUUUCUGGUUGUCAC	50	AGG
1566	30650330	3	324	19	-	30650327	30650347	UCCAGAAUAAAGUCAUGGUA	35	GGG
1567	30650320	3	314	18	-	30650317	30650337	AGUCAUGGUAGGGGAGCUUG	55	GGG
1568	30650373	3	367	22	+	30650356	30650376	UUCUCCAAAGUGCAUUAUGA	35	AGG
1569	30650455	3	449	26	+	30650438	30650458	GACAACAUCAUCUUCUCAGA	40	AGG
1570	30606928	1	45	2.6	+	30606911	30606931	GGCCGCUGCACAUCGUCCUG	70	TGG
1571	30606971	1	88	5.2	+	30606954	30606974	CCCACCGCACGUUCAGAAGU	60	CGG
1572	30644799	2	147	8.6	-	30644796	30644816	UCACAAAAUUUACACAGUUG	30	TGG
1573	30650314	3	308	18	-	30650311	30650331	GGUAGGGGAGCUUGGGGUCA	65	TGG
1574	30644833	2	181	11	-	30644830	30644850	GGAUUUCUGGUUGUCACAGG	50	TGG
1575	30650321	3	315	19	-	30650318	30650338	AAGUCAUGGUAGGGGAGCUU	50	GGG
1576	30644846	2	194	11	-	30644843	30644863	AGUUGCUCAUGCAGGAUUUC	45	TGG
1577	30650322	3	316	19	-	30650319	30650339	AAAGUCAUGGUAGGGGAGCU	50	TGG
1578	30606919	1	36	2.1	-	30606916	30606936	GUCCACAGGACGAUGUGCAG	60	CGG
1579	30650366	3	360	21	-	30650363	30650383	UUUUCCUUCAUAAUGCACUU	30	TGG
1580	30650340	3	334	20	+	30650323	30650343	CCCCUACCAUGACUUUAUUC	45	TGG
1581	30671755	4	572	34	-	30671752	30671772	GCUUCUGCUGCCGGUUAACG	60	CGG
1582	30671756	4	573	34	+	30671739	30671759	UCUACUGCUACCGCGUUAAC	50	CGG
1583	30671781	4	598	35	+	30671764	30671784	GCAGAAGCUGAGUUCAACCU	50	GGG
1584	30671798	4	615	36	+	30671781	30671801	CCUGGGAAACCGGCAAGACG	65	CGG
1585	30671808	4	625	37	+	30671791	30671811	CGGCAAGACGCGGAAGCUCA	65	TGG
1586	30671838	4	655	38	-	30671835	30671855	GCGGUCAUCUUCCAGGAUGA	55	TGG
1587	30671874	4	691	41	-	30671871	30671891	GUUGAUGUUGUUGGCACACG	50	TGG
1588	30671929	4	746	44	+	30671912	30671932	AUUGAGCUGGACACCCUGGU	55	GGG
1589	30671931	4	748	44	-	30671928	30671948	AAAGCGACCUUUCCCCACCA	55	GGG
1590	30672000	4	817	48	+	30671983	30672003	UUCAGAGCAGUUUGAGACAG	45	TGG
1591	30672024	4	841	49	+	30672007	30672027	AGUCAAGAUCUUUCCCUAUG	40	AGG
1592	30672165	4	982	58	-	30672162	30672182	UAGGUUGCCCUUGGCGUGGA	60	AGG
1593	30672169	4	986	58	+	30672152	30672172	AUCACCGCCUUCCACGCCAA	60	GGG
1594	30672194	4	1011	59	+	30672177	30672197	ACCUACAGGAGUACCUGACG	55	CGG
1595	30672196	4	1013	59	-	30672193	30672213	AGCUGAUGACAUGCCGCGUC	60	AGG
1596	30672210	4	1027	60	+	30672193	30672213	GACGCGGCAUGUCAUCAGCU	60	GGG

FIG. 35A

SEQ ID NO:	Genomic cut coordinate	Exon	CDS cut position	CDS cut position %	Strand	Start coordinate	End coordinate	crRNA	GC content	PAM
1597	30672213	4	1030	60	+	30672196	30672216	GCGGCAUGUCAUCAGCUGGG	65	AGG
1598	30672248	4	1065	63	+	30672231	30672251	UGGGCAGCUCCCUCGCCCGG	80	GGG
1599	30672252	4	1069	63	-	30672249	30672269	GUGGAGGUGAGCAAUCCCCC	65	GGG
1600	30672253	4	1070	63	-	30672250	30672270	UGUGGAGGUGAGCAAUCCCC	60	CGG
1601	30672268	4	1085	64	-	30672265	30672285	AUGGAGUGUGAUCACUGUGG	50	AGG
1602	30672271	4	1088	64	-	30672268	30672288	CACAUGGAGUGUGAUCACUG	50	TGG
1603	30672284	4	1101	65	+	30672267	30672287	ACAGUGAUCACACUCCAUGU	45	GGG
1604	30672287	4	1104	65	+	30672270	30672290	GUGAUCACACUCCAUGUGGG	55	AGG
1605	30672370	4	1187	70	-	30672367	30672387	GGGAAAGCCCAAAGUCACAC	55	AGG
1606	30672390	4	1207	71	-	30672387	30672407	CAGAGUAGGGUCCAGACGCA	60	GGG
1607	30672408	4	1225	72	+	30672391	30672411	UCUGGACCCUACUCUGUCUG	55	TGG
1608	30672427	4	1244	73	+	30672410	30672430	GUGGAUGACCUGGCUAACAG	55	TGG
1609	30672428	4	1245	73	+	30672411	30672431	UGGAUGACCUGGCUAACAGU	50	GGG
1610	30674120	5	1270	75	+	30674103	30674123	GGUGGGAACUGCAAGAUACA	50	TGG
1611	30674189	5	1339	79	-	30674186	30674206	CAGAGCCAUGGAGUAGACAU	50	CGG
1612	30674195	5	1345	79	+	30674178	30674198	GCAGACCGAUGUCUACUCCA	55	TGG
1613	30674238	5	1388	82	+	30674221	30674241	ACAUCUCGCUGUAAUGCAGU	45	GGG
1614	30688406	6	1419	83	-	30688403	30688423	CGCACCUUGGAACCAAAUGG	55	AGG
1615	30688435	6	1448	85	-	30688432	30688452	CCUUCAUGCUUUCGACACAG	50	GGG
1616	30688437	6	1450	85	-	30688434	30688454	GUCCUUCAUGCUUUCGACAC	50	AGG
1617	30688446	6	1459	86	+	30688429	30688449	CCCCUGUGUCGAAAGCAUGA	55	AGG
1618	30688469	6	1482	87	+	30688452	30688472	ACAACGUGUUGAGAGAUCGA	45	GGG
1619	30691452	7	1557	91	+	30691435	30691455	GUGAGACGUUGACUGAGUGC	55	TGG
1620	30691453	7	1558	91	+	30691436	30691456	UGAGACGUUGACUGAGUGCU	50	GGG
1621	30691468	7	1573	92	+	30691451	30691471	GUGCUGGGACCACGACCCAG	70	AGG
1622	30691492	7	1597	94	+	30691475	30691495	CCGUCUCACAGCCCAGUGUG	65	TGG
1623	30691492	7	1597	94	-	30691489	30691509	GAAGCGUUCUGCCACACACU	55	GGG
1624	30672131	4	948	56	+	30672114	30672134	AGGAGCGGAAGACGGAGUUG	60	GGG
1625	30672130	4	947	56	+	30672113	30672133	GAGGAGCGGAAGACGGAGUU	60	GGG
1626	30688493	6	1506	88	-	30688490	30688510	UGGUGGUUGAGCCAGAAGCU	55	GGG
1627	30691493	7	1598	94	-	30691490	30691510	UGAAGCGUUCUGCCACACAC	55	TGG
1628	30672312	4	1129	66	+	30672295	30672315	CAAGAUGCCCAUCGUGCACA	55	GGG
1629	30674143	5	1293	76	+	30674126	30674146	CUCCAGAAGUCCUAGAAUCC	50	AGG
1630	30688468	6	1481	87	+	30688451	30688471	GACAACGUGUUGAGAGAUCG	50	AGG
1631	30672111	4	928	55	+	30672094	30672114	ACUCCAGUUCCUGACGGCUG	60	AGG
1632	30688436	6	1449	85	-	30688433	30688453	UCCUUCAUGCUUUCGACACA	45	GGG
1633	30672283	4	1100	65	+	30672266	30672286	CACAGUGAUCACACUCCAUG	50	TGG
1634	30688419	6	1432	84	+	30688402	30688422	UCCAUUUGGUUCCAAGGUGC	50	GGG
1635	30672432	4	1249	73	+	30672415	30672435	UGACCUGGCUAACAGUGGGC	60	AGG
1636	30671949	4	766	45	+	30671932	30671952	GGGGAAAGGUCGCUUUGCUG	60	AGG
1637	30672184	4	1001	59	-	30672181	30672201	GCCGCGUCAGGUACUCCUGU	65	AGG
1638	30672027	4	844	50	-	30672024	30672044	CCAAGAGGCAUACUCCUCAU	50	AGG
1639	30672309	4	1126	66	-	30672306	30672326	CUUGAGGUCCCUGUGCACGA	60	TGG
1640	30672246	4	1063	62	-	30672243	30672263	GUGAGCAAUCCCCCGGGCGA	70	GGG
1641	30688413	6	1426	84	+	30688396	30688416	UGAGCCUCCAUUUGGUUCCA	50	AGG
1642	30674237	5	1387	81	+	30674220	30674240	GACAUCUCGCUGUAAUGCAG	50	TGG
1643	30671857	4	674	40	-	30671854	30671874	ACGUGGAGCUGAUGUCAGAG	55	CGG
1644	30688419	6	1432	84	-	30688416	30688436	ACAGGGGUGCUCCCGCACCU	70	TGG
1645	30672229	4	1046	61	+	30672212	30672232	UGGGAGGACCUGCGCAAGCU	65	GGG
1646	30672109	4	926	54	-	30672106	30672126	UCUUCCGCUCCUCAGCCGUC	65	AGG

FIG. 35B

SEQ ID NO:	Genomic cut coordinate	Exon	CDS cut position	CDS cut position %	Strand	Start coordinate	End coordinate	crRNA	GC content	PAM
1647	30672038	4	855	50	+	30672021	30672041	CCUAUGAGGAGUAUGCCUCU	50	TGG
1648	30672168	4	985	58	+	30672151	30672171	GAUCACCGCCUUCCACGCCA	65	AGG
1649	30672174	4	991	58	-	30672171	30672191	GUACUCCUGUAGGUUGCCCU	55	TGG
1650	30672105	4	922	54	+	30672088	30672108	GAACAUACUCCAGUUCCUGA	45	CGG
1651	30672143	4	960	56	+	30672126	30672146	CGGAGUUGGGGAAACAAUAC	50	TGG
1652	30672343	4	1160	68	-	30672340	30672360	AGGUUAGGUCGUUCUUCACG	50	AGG
1653	30672169	4	986	58	-	30672166	30672186	CCUGUAGGUUGCCCUUGGCG	65	TGG
1654	30672247	4	1064	62	-	30672244	30672264	GGUGAGCAAUCCCCCGGGCG	75	AGG
1655	30688409	6	1422	84	-	30688406	30688426	UCCCGCACCUUGGAACCAAA	55	TGG
1656	30672123	4	940	55	+	30672106	30672126	GACGGCUGAGGAGCGGAAGA	65	CGG
1657	30672391	4	1208	71	-	30672388	30672408	ACAGAGUAGGGUCCAGACGC	60	AGG
1658	30671930	4	747	44	+	30671913	30671933	UUGAGCUGGACACCCUGGUG	60	GGG
1659	30672247	4	1064	62	+	30672230	30672250	CUGGGCAGCUCCCUCGCCCG	80	GGG
1660	30691472	7	1577	93	-	30691469	30691489	GGGCUGUGAGACGGGCCUCU	70	GGG
1661	30672336	4	1153	68	-	30672333	30672353	GUCGUUCUUCACGAGGAUAU	45	TGG
1662	30672162	4	979	58	-	30672159	30672179	GUUGCCCUUGGCGUGGAAGG	65	CGG
1663	30671787	4	604	35	-	30671784	30671804	CCGCGUCUUGCCGGUUUCCC	70	AGG
1664	30671780	4	597	35	+	30671763	30671783	AGCAGAAGCUGAGUUCAACC	50	TGG
1665	30691466	7	1571	92	-	30691463	30691483	UGAGACGGGCCUCUGGGUCG	70	TGG
1666	30672308	4	1125	66	-	30672305	30672325	UUGAGGUCCCUGUGCACGAU	55	GGG
1667	30688418	6	1431	84	+	30688401	30688421	CUCCAUUUGGUUCCAAGGUG	50	CGG
1668	30688405	6	1418	83	+	30688388	30688408	AAAGAUUAUGAGCCUCCAUU	35	TGG
1669	30672403	4	1220	72	-	30672400	30672420	GGUCAUCCACAGACAGAGUA	50	GGG
1670	30672311	4	1128	66	+	30672294	30672314	CCAAGAUGCCCAUCGUGCAC	60	AGG
1671	30671896	4	713	42	-	30671893	30671913	UGGGCAGCAGCUCUGUGUUG	60	TGG
1672	30672325	4	1142	67	-	30672322	30672342	CGAGGAUAUUGGAGCUCUUG	50	AGG
1673	30671932	4	749	44	-	30671929	30671949	CAAAGCGACCUUUCCCCACC	60	AGG
1674	30674177	5	1327	78	-	30674174	30674194	GUAGACAUCGGUCUGCUUGA	50	AGG
1675	30671925	4	742	44	+	30671908	30671928	GCCCAUUGAGCUGGACACCC	65	TGG
1676	30672404	4	1221	72	-	30672401	30672421	AGGUCAUCCACAGACAGAGU	50	AGG
1677	30672417	4	1234	72	+	30672400	30672420	UACUCUGUCUGUGGAUGACC	50	TGG
1678	30671958	4	775	46	+	30671941	30671961	UCGCUUUGCUGAGGUCUAUA	45	AGG
1679	30672287	4	1104	65	-	30672284	30672304	GGCAUCUUGGGCCUCCCACA	65	TGG
1680	30674201	5	1351	79	+	30674184	30674204	CGAUGUCUACUCCAUGGCUC	55	TGG
1681	30672358	4	1175	69	-	30672355	30672375	AGUCACACAGGCAGCAGGUU	55	AGG
1682	30671838	4	655	38	+	30671821	30671841	CGAGCACUGUGCCAUCAUCC	60	TGG
1683	30672180	4	997	59	+	30672163	30672183	CCACGCCAAGGGCAACCUAC	65	AGG
1684	30672026	4	843	50	-	30672023	30672043	CAAGAGGCAUACUCCUCAUA	45	GGG
1685	30688494	6	1507	88	-	30688491	30688511	CUGGUGGUUGAGCCAGAAGC	60	TGG
1686	30691480	7	1585	93	-	30691477	30691497	CACACACUGGGCUGUGAGAC	60	GGG
1687	30671916	4	733	43	-	30671913	30671933	CACCAGGGUGUCCAGCUCAA	60	TGG
1688	30674210	5	1360	80	+	30674193	30674213	CUCCAUGGCUCUGGUGCUCU	60	GGG
1689	30691430	7	1535	90	-	30691427	30691447	UCAACGUCUCACACACCAUC	50	TGG
1690	30672209	4	1026	60	+	30672192	30672212	UGACGCGGCAUGUCAUCAGC	60	TGG
1691	30674153	5	1303	77	+	30674136	30674156	CCUAGAAUCCAGGAUGAAUU	40	TGG
1692	30688493	6	1506	88	+	30688476	30688496	GACCAGAAAUUCCCAGCUUC	50	TGG
1693	30674142	5	1292	76	-	30674139	30674159	CCAAAUUCAUCCUGGAUUCU	40	AGG
1694	30671928	4	745	44	+	30671911	30671931	CAUUGAGCUGGACACCCUGG	60	TGG
1695	30672103	4	920	54	-	30672100	30672120	GCUCCUCAGCCGUCAGGAAC	65	TGG
1696	30671935	4	752	44	+	30671918	30671938	CUGGACACCCUGGUGGGGAA	65	AGG

FIG. 35C

SEQ ID NO:	Genomic cut coordinate	Exon	CDS cut position	CDS cut position %	Strand	Start coordinate	End coordinate	crRNA	GC content	PAM
1697	30691513	7	1618	95	+	30691496	30691516	GGCAGAACGCUUCAGUGAGC	60	TGG
1698	30672226	4	1043	61	-	30672223	30672243	GGGAGCUGCCCAGCUUGCGC	75	AGG
1699	30672116	4	933	55	+	30672099	30672119	AGUUCCUGACGGCUGAGGAG	60	CGG
1700	30691473	7	1578	93	-	30691470	30691490	UGGGCUGUGAGACGGGCCUC	70	TGG
1701	30672228	4	1045	61	+	30672211	30672231	CUGGGAGGACCUGCGCAAGC	70	TGG
1702	30672390	4	1207	71	+	30672373	30672393	CUUUGGGCUUUCCCUGCGUC	60	TGG
1703	30671845	4	662	39	-	30671842	30671862	UGUCAGAGCGGUCAUCUUCC	55	AGG
1704	30672299	4	1116	66	-	30672296	30672316	CUGUGCACGAUGGGCAUCUU	55	GGG
1705	30671796	4	613	36	-	30671793	30671813	CAUGAGCUUCCGCGUCUUGC	60	CGG
1706	30672245	4	1062	62	+	30672228	30672248	AGCUGGGCAGCUCCCUCGCC	75	CGG
1707	30688484	6	1497	88	-	30688481	30688501	AGCCAGAAGCUGGGAAUUUC	50	TGG
1708	30674209	5	1359	80	+	30674192	30674212	ACUCCAUGGCUCUGGUGCUC	60	TGG
1709	30672129	4	946	56	+	30672112	30672132	UGAGGAGCGGAAGACGGAGU	60	TGG
1710	30671915	4	732	43	-	30671912	30671932	ACCAGGGUGUCCAGCUCAAU	55	GGG
1711	30691481	7	1586	93	-	30691478	30691498	CCACACACUGGGCUGUGAGA	60	CGG
1712	30671970	4	787	46	-	30671967	30671987	UGAAGUGUUCUGCUUCAGCU	45	TGG
1713	30671916	4	733	43	+	30671899	30671919	AGAGCUGCUGCCCAUUGAGC	60	TGG
1714	30672051	4	868	51	+	30672034	30672054	UGCCUCUUGGAAGACAGAGA	50	AGG
1715	30672246	4	1063	62	+	30672229	30672249	GCUGGGCAGCUCCCUCGCCC	80	GGG
1716	30674201	5	1351	79	-	30674198	30674218	UUCCCAGAGCACCAGAGCCA	60	TGG
1717	30672300	4	1117	66	-	30672297	30672317	CCUGUGCACGAUGGGCAUCU	60	TGG
1718	30674134	5	1284	75	-	30674131	30674151	AUCCUGGAUUCUAGGACUUC	45	TGG
1719	30691522	7	1627	96	+	30691505	30691525	CUUCAGUGAGCUGGAGCAUC	55	TGG
1720	30674150	5	1300	76	-	30674147	30674167	AACAUUCUCCAAAUUCAUCC	35	TGG
1721	30671764	4	581	34	-	30671761	30671781	UUGAACUCAGCUUCUGCUGC	50	CGG
1722	30672363	4	1180	69	-	30672360	30672380	CCCAAAGUCACACAGGCAGC	60	AGG
1723	30672373	4	1190	70	+	30672356	30672376	ACCUGCUGCCUGUGUGACUU	55	TGG
1724	30672374	4	1191	70	+	30672357	30672377	CCUGCUGCCUGUGUGACUUU	55	GGG
1725	30671660	4	477	28	-	30671657	30671677	AAUAUGACUAGCAACAAGUC	35	AGG
1726	30671701	4	518	30	-	30671698	30671718	CAACUCCCAGUGGUGGCAGG	65	AGG
1727	30671652	4	469	28	-	30671649	30671669	UAGCAACAAGUCAGGAUUGC	45	TGG
1728	30671683	4	500	29	+	30671666	30671686	CUAGUCAUAUUUCAAGUGAC	35	AGG
1729	30671708	4	525	31	-	30671705	30671725	GAUAUGGCAACUCCCAGUGG	55	TGG
1730	30671711	4	528	31	-	30671708	30671728	ACAGAUAUGGCAACUCCCAG	50	TGG
1731	30671704	4	521	31	-	30671701	30671721	UGGCAACUCCCAGUGGUGGC	65	AGG
1732	30671707	4	524	31	+	30671690	30671710	AUCAGCCUCCUGCCACCACU	60	GGG
1733	30671724	4	541	32	-	30671721	30671741	GAAGAUGAUGAUGACAGAUA	35	TGG
1734	30671706	4	523	31	+	30671689	30671709	CAUCAGCCUCCUGCCACCAC	65	TGG
1735	30691552	7	1657	97	+	30691535	30691555	CUCGGGGAGGAGCUGCUCGG	75	AGG
1736	30691536	7	1641	96	+	30691519	30691539	AGCAUCUGGACAGGCUCUCG	60	GGG
1737	30691527	7	1632	96	+	30691510	30691530	GUGAGCUGGAGCAUCUGGAC	60	AGG
1738	30691549	7	1654	97	+	30691532	30691552	GCUCUCGGGGAGGAGCUGCU	70	CGG
1739	30691571	7	1676	98	+	30691554	30691574	GAGGAGAAGAUUCCUGAAGA	45	CGG
1740	30691539	7	1644	97	+	30691522	30691542	AUCUGGACAGGCUCUCGGGG	65	AGG
1741	30691585	7	1690	99	-	30691582	30691602	GAGCUAUUUGGUAGUGUUUA	35	GGG
1742	30691535	7	1640	96	+	30691518	30691538	GAGCAUCUGGACAGGCUCUC	60	GGG
1743	30691534	7	1639	96	+	30691517	30691537	GGAGCAUCUGGACAGGCUCU	60	CGG
1744	30691586	7	1691	99	-	30691583	30691603	AGAGCUAUUUGGUAGUGUUU	35	AGG
1745	30691572	7	1677	98	-	30691569	30691589	GUGUUUAGGGAGCCGUCUUC	55	AGG

FIG. 35D

SEQ ID NO:	MIT	CFD	Elevation	CCTop	Offtarget #	Azimuth	DeepSpCas9	CrisprScan	CFD	Lindel	inDelphi	Frameshift	Precision	Graf Motifs	Bioscore	CCTop	CFD	CCTop11	Interference predictions
1547	98	99	42	80	11	54	55	36	46	79	85	82	47	OK	56	64	81	76	Knockout
1548	98	99	41	79	18	60	46	63	56	88	94	91	63	OK	52	68	85	75	Knockout
1549	98	98	43	80	24	54	46	22	41	84	90	87	53	OK	51	60	83	69	Knockout
1550	68	86	61	72	174	68	72	70	70	61	71	66	65	OK	59	71	69	69	Knockout
1551	61	82	55	66	251	59	53	62	58	75	84	80	57	OK	66	62	73	68	Knockout
1552	72	86	62	73	179	59	57	21	46	74	79	77	64	OK	58	60	75	65	Knockout
1553	58	74	44	59	343	73	70	36	60	87	84	86	60	OK	69	59	72	68	Knockout
1554	59	77	53	63	307	69	65	35	56	89	81	85	49	OK	62	59	74	68	Knockout
1555	73	82	61	72	173	63	50	50	54	72	76	74	50	OK	59	63	73	67	Knockout
1556	58	74	48	60	336	46	57	68	57	85	85	85	61	OK	70	58	72	67	Knockout
1557	89	95	43	76	36	51	26	52	43	81	85	83	56	OK	36	59	79	67	Knockout
1558	98	99	40	79	21	55	49	55	53	84	74	89	43	OK	63	66	74	67	Knockout
1559	88	93	44	75	102	46	51	60	52	73	67	70	50	OK	64	64	73	66	Knockout
1560	66	83	48	66	208	54	52	66	57	80	71	75	47	OK	59	61	70	66	Knockout
1561	79	88	60	76	171	61	50	28	46	79	79	74	46	OK	48	61	75	66	Knockout
1562	60	76	64	67	272	61	57	40	53	76	80	78	48	OK	63	60	72	66	Knockout
1563	54	73	53	60	345	48	51	46	48	85	81	88	50	OK	60	54	74	65	Knockout
1564	82	90	59	77	109	54	31	51	45	64	73	69	47	OK	47	61	73	64	Knockout
1565	58	76	45	60	266	49	41	51	47	82	87	84	60	OK	55	53	72	64	Knockout
1566	76	85	64	75	150	44	45	52	47	70	65	67	44	OK	59	61	71	63	Knockout
1567	71	81	53	68	179	62	50	58	57	65	63	64	54	TT	59	62	66	63	Knockout
1568	68	83	62	71	330	46	32	24	34	81	85	83	54	OK	62	53	77	63	Knockout
1569	62	78	64	68	238	59	22	23	35	78	89	84	50	OK	55	51	76	62	Knockout
1570	84	90	36	70	121	56	51	40	49	69	66	68	44	OK	66	59	69	62	Knockout
1571	93	94	47	76	40	55	22	38	38	85	77	71	56	OK	38	58	74	62	Knockout
1572	56	77	67	67	398	52	35	29	39	76	74	75	43	OK	54	53	71	60	Knockout
1573	51	69	42	54	390	39	38	68	48	76	80	78	51	OK	58	51	66	60	Knockout
1574	30	63	25	39	340	55	48	70	58	77	85	81	51	OK	58	48	60	59	Knockout
1575	71	86	56	71	149	37	39	55	44	66	58	62	54	TT	59	57	67	59	Knockout
1576	67	87	59	71	205	16	13	34	22	75	86	82	59	TT	48	46	76	58	Knockout
1577	68	81	42	64	201	44	22	48	38	69	70	70	61	OK	59	51	67	57	Knockout
1578	46	68	48	54	419	66	57	44	56	79	56	63	46	OK	65	55	58	57	Knockout
1579	58	72	59	63	414	45	11	8	21	86	90	88	60	TT	56	42	75	57	Knockout
1580	86	92	59	79	91	23	10	9	14	83	84	74	56	TT	67	46	76	56	Knockout
1581	95	96	42	78	61	63	67	46	59	80	70	75	60	OK	60	68	76	70	Membrane-bound decoy receptor
1582	98	98	40	79	34	43	49	45	46	77	71	74	63	OK	53	62	76	66	Membrane-bound decoy receptor
1583	55	88	59	67	206	67	71	59	66	80	89	84	58	OK	49	67	76	73	Membrane-bound decoy receptor
1584	90	93	43	75	100	62	61	48	57	74	74	74	45	OK	45	66	75	69	Membrane-bound decoy receptor
1585	90	92	47	76	56	53	44	56	51	79	80	79	45	OK	55	64	78	69	Membrane-bound decoy receptor
1586	71	86	59	72	128	54	65	43	54	79	82	80	56	OK	63	63	76	69	Membrane-bound decoy receptor
1587	85	94	47	75	100	56	47	61	55	75	79	77	56	OK	56	65	76	69	Membrane-bound decoy receptor
1588	68	87	53	69	210	64	54	68	62	77	81	79	65	OK	69	66	74	70	Membrane-bound decoy receptor
1589	77	89	44	70	91	71	70	71	71	68	76	72	68	OK	69	70	71	71	Membrane-bound decoy receptor
1590	72	79	64	72	225	59	41	71	57	79	93	86	61	OK	63	64	79	71	Membrane-bound decoy receptor
1591	72	84	60	72	148	57	43	47	49	83	88	85	63	OK	68	60	79	69	Membrane-bound decoy receptor
1592	84	93	35	71	62	50	63	74	62	80	67	73	67	OK	67	67	72	69	Membrane-bound decoy receptor
1593	96	97	37	75	61	61	57	77	65	78	75	77	44	OK	54	70	76	72	Membrane-bound decoy receptor
1594	90	94	58	81	46	74	65	46	62	84	79	82	41	OK	76	71	81	75	Membrane-bound decoy receptor
1595	97	98	46	80	32	45	35	66	49	79	81	80	49	OK	77	64	80	70	Membrane-bound decoy receptor
1596	84	93	58	78	55	60	54	46	53	80	84	82	54	OK	69	66	80	71	Membrane-bound decoy receptor

FIG. 35E

SEQ ID NO:	MIT	CFD	Elevation	CFD	Offtarget #	Azimuth	DeepSpCas9	CrisprScan	CFD	Lindel	inDelphi	Frameshift	Precision	Graf Motifs	Bioscore	CFD + CFD	CFD + CFD	CFD + CFD	Selected tracr predictions
1597	68	82	48	66	160	71	71	63	66	84	88	86	63	OK	78	67	76	73	Membrane-bound decoy receptor
1598	85	85	36	69	164	65	59	77	67	83	82	63	46	OK	69	68	76	73	Membrane-bound decoy receptor
1599	84	90	61	78	127	62	70	62	65	62	68	75	56	OK	64	72	77	73	Membrane-bound decoy receptor
1600	82	89	53	75	148	46	67	69	61	81	75	78	43	OK	64	68	76	71	Membrane-bound decoy receptor
1601	62	81	54	66	218	72	72	80	78	75	84	80	53	OK	73	72	73	74	Membrane-bound decoy receptor
1602	71	85	53	70	170	78	73	48	66	79	82	80	54	OK	69	69	75	72	Membrane-bound decoy receptor
1603	83	94	54	77	107	71	76	52	66	80	87	83	58	OK	65	71	80	75	Membrane-bound decoy receptor
1604	82	90	53	75	94	70	69	39	59	84	88	86	63	OK	51	67	80	73	Membrane-bound decoy receptor
1605	57	80	65	67	267	64	64	31	53	84	93	89	63	OK	75	60	78	70	Membrane-bound decoy receptor
1606	82	91	47	73	158	58	62	73	64	74	74	74	56	OK	61	69	74	71	Membrane-bound decoy receptor
1607	75	86	49	70	152	58	65	61	61	83	90	87	65	OK	61	66	78	73	Membrane-bound decoy receptor
1608	84	92	53	76	116	68	74	46	63	83	91	87	60	OK	59	69	82	75	Membrane-bound decoy receptor
1609	79	91	53	74	120	64	74	63	67	80	88	84	53	OK	64	71	79	75	Membrane-bound decoy receptor
1610	74	86	60	73	200	60	54	23	46	85	92	89	54	OK	82	59	81	69	Membrane-bound decoy receptor
1611	70	82	60	71	251	72	66	81	73	75	88	82	58	OK	71	72	76	75	Membrane-bound decoy receptor
1612	87	92	48	76	86	62	70	36	55	86	89	88	60	OK	74	66	82	73	Membrane-bound decoy receptor
1613	88	93	46	76	94	61	47	34	47	78	85	81	50	OK	60	61	79	68	Membrane-bound decoy receptor
1614	90	95	60	82	46	66	63	41	57	82	91	86	58	OK	63	69	84	75	Membrane-bound decoy receptor
1615	81	93	54	79	85	66	54	63	61	88	93	91	66	OK	69	70	85	77	Membrane-bound decoy receptor
1616	91	97	54	81	66	42	43	53	46	82	89	86	57	OK	60	63	83	71	Membrane-bound decoy receptor
1617	81	86	61	76	90	65	55	11	44	89	89	89	58	OK	75	60	83	70	Membrane-bound decoy receptor
1618	93	96	52	80	44	72	69	43	61	86	81	84	65	OK	70	71	82	75	Membrane-bound decoy receptor
1619	83	93	47	74	89	49	52	39	47	85	91	88	52	OK	71	60	81	70	Membrane-bound decoy receptor
1620	80	88	48	72	89	63	58	57	59	88	91	90	65	OK	71	66	81	74	Membrane-bound decoy receptor
1621	81	88	42	70	158	67	62	76	69	79	72	75	43	OK	71	70	73	72	Membrane-bound decoy receptor
1622	63	83	45	64	180	62	66	68	65	91	91	91	64	OK	78	65	77	73	Membrane-bound decoy receptor
1623	83	94	51	76	83	57	54	42	51	85	89	87	58	OK	79	63	82	71	Membrane-bound decoy receptor
1624	73	78	41	64	289	65	62	66	72	62	78	70	51	OK	58	68	67	69	Membrane-bound decoy receptor
1625	83	91	46	74	173	31	50	84	55	76	79	77	55	OK	58	65	76	69	Membrane-bound decoy receptor
1626	61	82	52	65	249	64	62	44	57	82	86	84	55	OK	76	61	74	69	Membrane-bound decoy receptor
1627	82	90	50	74	75	57	38	29	41	90	95	92	68	OK	78	58	83	69	Membrane-bound decoy receptor
1628	89	93	55	79	87	61	44	41	49	77	79	78	47	OK	68	64	79	69	Membrane-bound decoy receptor
1629	59	85	58	67	212	52	54	33	46	89	96	93	58	OK	62	57	80	69	Membrane-bound decoy receptor
1630	93	97	50	80	36	59	50	33	47	76	82	79	59	OK	63	64	79	69	Membrane-bound decoy receptor
1631	80	87	53	73	189	60	61	50	57	79	75	77	53	OK	57	65	75	69	Membrane-bound decoy receptor
1632	78	87	60	75	177	49	42	32	41	90	90	90	57	OK	68	58	82	69	Membrane-bound decoy receptor
1633	80	88	57	75	145	64	41	37	47	84	81	82	51	OK	63	61	79	68	Membrane-bound decoy receptor
1634	78	87	60	75	125	48	54	49	50	75	80	78	48	OK	64	63	76	68	Membrane-bound decoy receptor
1635	74	86	53	71	151	58	54	40	51	81	85	83	49	OK	67	61	77	68	Membrane-bound decoy receptor
1636	75	91	53	73	137	60	60	55	58	75	73	74	49	OK	63	66	73	68	Membrane-bound decoy receptor
1637	92	97	47	79	37	63	58	43	55	73	69	71	48	OK	69	67	75	68	Membrane-bound decoy receptor
1638	87	92	60	80	95	50	34	67	50	69	73	71	63	OK	62	65	75	67	Membrane-bound decoy receptor
1639	83	88	38	69	136	55	65	39	53	80	80	80	52	OK	63	61	74	67	Membrane-bound decoy receptor
1640	96	97	40	78	36	54	47	56	52	77	65	71	50	OK	55	65	74	67	Membrane-bound decoy receptor
1641	73	81	61	72	172	52	37	31	40	85	94	89	61	OK	63	56	81	67	Membrane-bound decoy receptor
1642	76	87	52	72	100	59	57	39	52	77	79	78	43	OK	61	62	75	67	Membrane-bound decoy receptor
1643	60	80	53	64	223	75	67	57	66	78	64	71	59	OK	62	65	68	67	Membrane-bound decoy receptor
1644	90	92	36	73	83	54	46	57	52	69	86	78	62	OK	64	62	75	67	Membrane-bound decoy receptor
1645	86	93	44	74	138	46	42	67	52	73	75	74	58	OK	57	63	74	67	Membrane-bound decoy receptor
1646	96	88	39	71	107	52	28	43	41	86	89	88	65	OK	62	56	79	67	Membrane-bound decoy receptor

FIG. 35F

SEQ ID NO:	MIT	CFD	Elevation	CFD	Offtarget #	Azimuth	DeepSpCas9	CrisprScan	CFD	Lindel	inDelphi	Frameshift	Precision	Graf Motifs	Bioscore	CFD	CFD	CFD	Membrane-bound decoy receptor
1647	82	92	58	77	88	58	46	37	47	74	79	77	43	TT	61	62	77	67	Membrane-bound decoy receptor
1648	84	92	40	72	82	57	57	29	48	81	78	79	50	OK	54	60	76	66	Membrane-bound decoy receptor
1649	80	93	53	76	76	52	60	54	55	76	61	68	47	OK	63	65	72	66	Membrane-bound decoy receptor
1650	73	82	52	69	158	65	61	20	49	82	78	80	43	OK	68	59	74	66	Membrane-bound decoy receptor
1651	76	91	54	74	124	50	30	41	40	79	69	84	57	OK	63	57	79	66	Membrane-bound decoy receptor
1652	96	96	43	76	26	63	58	31	51	64	74	69	48	OK	69	65	74	66	Membrane-bound decoy receptor
1653	82	88	40	70	92	57	61	46	55	70	78	74	45	OK	54	62	72	66	Membrane-bound decoy receptor
1654	89	97	43	76	61	47	34	56	46	75	77	76	45	OK	55	61	76	66	Membrane-bound decoy receptor
1655	79	90	47	72	80	56	17	32	35	90	89	90	57	OK	60	54	81	66	Membrane-bound decoy receptor
1656	67	82	51	67	230	52	59	65	59	68	75	72	59	OK	58	63	69	66	Membrane-bound decoy receptor
1657	80	88	41	70	134	50	63	45	53	71	80	76	60	OK	61	61	73	66	Membrane-bound decoy receptor
1658	86	93	53	67	200	63	48	91	64	68	62	65	48	OK	69	66	66	66	Membrane-bound decoy receptor
1659	68	81	31	60	283	46	60	72	59	76	74	75	45	OK	56	60	68	65	Membrane-bound decoy receptor
1660	65	82	61	69	224	49	38	56	48	75	82	79	48	TT	71	59	74	65	Membrane-bound decoy receptor
1661	93	96	52	80	33	38	20	38	32	73	69	81	58	OK	71	56	81	65	Membrane-bound decoy receptor
1662	58	85	34	59	139	57	47	87	64	78	68	73	60	OK	70	61	66	65	Membrane-bound decoy receptor
1663	83	94	43	73	64	37	32	71	47	71	79	75	61	OK	46	60	74	65	Membrane-bound decoy receptor
1664	71	85	55	70	184	52	47	17	39	84	86	85	54	OK	49	54	79	65	Membrane-bound decoy receptor
1665	85	89	38	71	96	49	55	56	53	65	77	71	50	OK	71	62	71	65	Membrane-bound decoy receptor
1666	80	94	50	75	78	46	33	78	52	65	73	69	55	OK	73	53	72	65	Membrane-bound decoy receptor
1667	71	84	60	72	179	47	39	51	46	80	78	79	44	OK	64	59	75	65	Membrane-bound decoy receptor
1668	76	89	56	74	131	43	19	41	34	83	87	85	51	TT	63	54	79	64	Membrane-bound decoy receptor
1669	44	79	60	61	244	55	53	52	53	82	76	79	55	OK	61	57	70	64	Membrane-bound decoy receptor
1670	90	93	53	79	82	47	37	36	40	73	73	73	40	OK	68	59	76	64	Membrane-bound decoy receptor
1671	49	69	40	53	419	56	63	65	61	76	82	79	57	OK	52	57	66	64	Membrane-bound decoy receptor
1672	83	88	60	77	132	51	40	43	45	70	72	71	47	TT	57	61	74	64	Membrane-bound decoy receptor
1673	74	85	48	69	113	48	37	46	44	78	80	79	57	OK	68	56	74	64	Membrane-bound decoy receptor
1674	70	84	48	67	89	48	46	38	44	76	86	81	53	OK	61	56	74	64	Membrane-bound decoy receptor
1675	70	85	58	71	191	49	65	37	50	64	75	69	56	OK	70	61	70	64	Membrane-bound decoy receptor
1676	49	84	62	66	279	55	61	35	50	72	74	73	49	OK	63	58	69	63	Membrane-bound decoy receptor
1677	80	87	59	75	126	51	54	32	46	68	66	67	46	OK	67	60	71	63	Membrane-bound decoy receptor
1678	79	87	61	76	101	41	18	35	31	81	82	82	55	OK	78	53	79	63	Membrane-bound decoy receptor
1679	63	81	53	66	188	51	41	42	45	77	83	80	51	OK	67	55	73	63	Membrane-bound decoy receptor
1680	81	91	60	77	84	48	55	27	43	65	65	65	50	OK	72	60	71	62	Membrane-bound decoy receptor
1681	60	82	46	63	262	42	44	46	44	78	79	79	48	OK	67	53	71	62	Membrane-bound decoy receptor
1682	73	90	48	70	130	51	52	22	42	68	82	75	58	OK	62	56	73	62	Membrane-bound decoy receptor
1683	65	94	37	65	75	55	27	44	42	83	74	78	47	OK	67	54	72	62	Membrane-bound decoy receptor
1684	80	94	55	76	75	46	26	52	41	65	70	67	48	OK	68	59	72	62	Membrane-bound decoy receptor
1685	59	78	45	61	245	48	36	54	46	73	83	78	59	OK	70	53	69	62	Membrane-bound decoy receptor
1686	61	79	53	64	301	50	14	52	39	82	77	80	59	OK	73	52	72	61	Membrane-bound decoy receptor
1687	60	79	52	64	211	48	31	63	47	71	74	72	53	OK	54	56	68	61	Membrane-bound decoy receptor
1688	62	80	52	65	278	41	24	51	39	71	69	80	60	TT	80	52	72	61	Membrane-bound decoy receptor
1689	87	95	46	76	66	47	29	29	35	70	74	72	51	OK	71	55	74	61	Membrane-bound decoy receptor
1690	94	97	41	77	26	49	21	23	31	67	80	73	46	OK	69	54	75	61	Membrane-bound decoy receptor
1691	61	80	62	68	257	32	18	32	27	83	86	84	54	OK	64	48	76	60	Membrane-bound decoy receptor
1692	66	86	61	71	166	37	37	16	30	78	82	80	46	TT	71	50	76	60	Membrane-bound decoy receptor
1693	63	81	64	69	236	29	6	18	16	90	94	92	63	TT	62	44	81	60	Membrane-bound decoy receptor
1694	59	79	41	60	246	59	51	54	55	71	61	66	50	OK	69	57	63	60	Membrane-bound decoy receptor
1695	77	88	61	75	162	37	44	41	41	68	60	64	43	OK	68	58	70	60	Membrane-bound decoy receptor
1696	48	65	40	51	331	54	42	62	53	79	76	78	46	OK	59	52	64	60	Membrane-bound decoy receptor

FIG. 35G

SEQ ID NO:	MIT	CFD	Elevation	COF	Offtarget #	Azimuth	DeepSpCas9	CrisprScan	CCT	Lindel	inDelphi	Frameshift	Precision	Graf Motifs	Bioscore	COF	CFD	Offtarget	Membrane/decoy predictions
1697	64	82	49	65	185	44	22	29	29	84	90	87	46	OK	59	47	76	60	Membrane-bound decoy receptor
1698	82	87	38	68	203	45	45	34	41	66	69	67	48	OK	68	55	68	59	Membrane-bound decoy receptor
1699	61	79	49	63	198	62	67	54	61	58	61	55	56	OK	62	62	59	59	Membrane-bound decoy receptor
1700	64	83	33	60	403	26	28	59	38	78	80	79	48	OK	71	49	70	59	Membrane-bound decoy receptor
1701	76	89	35	67	192	39	19	48	35	72	77	74	59	OK	68	51	71	59	Membrane-bound decoy receptor
1702	81	88	48	72	141	34	24	43	34	68	74	71	57	OK	61	53	72	59	Membrane-bound decoy receptor
1703	78	86	48	71	102	38	33	29	33	59	79	69	64	TT	57	52	70	58	Membrane-bound decoy receptor
1704	80	93	54	76	93	35	16	61	37	55	66	61	72	TT	59	57	68	58	Membrane-bound decoy receptor
1705	80	70	38	63	338	32	15	30	26	81	92	86	63	TT	47	44	75	58	Membrane-bound decoy receptor
1706	66	76	39	60	292	34	16	54	35	80	76	78	55	OK	56	48	69	58	Membrane-bound decoy receptor
1707	61	81	61	68	275	19	11	25	18	80	94	87	66	TT	58	43	77	58	Membrane-bound decoy receptor
1708	65	79	44	63	204	29	42	25	32	69	92	80	69	OK	60	47	71	58	Membrane-bound decoy receptor
1709	64	83	48	65	267	44	45	53	47	35	53	59	43	OK	56	56	62	57	Membrane-bound decoy receptor
1710	81	91	52	75	94	34	29	69	44	47	57	52	56	OK	68	59	63	57	Membrane-bound decoy receptor
1711	62	75	49	62	292	52	33	33	39	74	62	68	46	OK	73	51	65	56	Membrane-bound decoy receptor
1712	62	80	51	64	160	49	41	34	41	71	57	64	63	OK	67	53	64	56	Membrane-bound decoy receptor
1713	77	85	46	70	218	47	54	29	40	61	54	58	47	OK	55	55	64	56	Membrane-bound decoy receptor
1714	39	60	69	56	542	61	48	27	45	65	67	66	53	OK	64	51	61	56	Membrane-bound decoy receptor
1715	58	80	37	58	363	40	42	42	41	64	65	65	50	OK	56	50	61	55	Membrane-bound decoy receptor
1716	46	68	38	51	409	54	61	39	51	56	65	61	50	OK	72	51	56	54	Membrane-bound decoy receptor
1717	73	86	54	71	143	30	19	34	28	63	57	60	67	OK	63	49	66	53	Membrane-bound decoy receptor
1718	67	80	49	65	184	32	21	25	26	65	72	68	51	TT	76	46	67	53	Membrane-bound decoy receptor
1719	68	83	53	68	219	37	33	36	35	56	48	52	60	OK	53	52	60	52	Membrane-bound decoy receptor
1720	29	58	57	48	###	46	22	7	20	76	84	80	59	OK	71	34	64	49	Membrane-bound decoy receptor
1721	58	78	49	62	259	49	37	26	37	46	46	46	59	OK	49	50	54	48	Membrane-bound decoy receptor
1722	17	60	6	28	###	53	34	21	36	85	78	82	59	OK	72	32	56	48	Membrane-bound decoy receptor
1723	9	29	6	15	###	29	16	25	24	73	85	79	56	TT	56	20	47	40	Membrane-bound decoy receptor
1724	7	35	3	12	###	28	25	48	34	71	76	73	48	TT	74	21	43	40	Membrane-bound decoy receptor
1725	72	90	59	74	141	56	44	42	47	85	83	89	56	OK	59	61	83	70	Soluble decoy receptor
1726	52	72	46	57	292	56	53	66	58	84	90	87	55	OK	52	58	72	67	Soluble decoy receptor
1727	78	89	60	76	151	43	33	41	39	80	92	86	60	TT	43	57	81	67	Soluble decoy receptor
1728	67	83	57	69	151	50	34	46	43	81	87	84	64	OK	62	56	77	65	Soluble decoy receptor
1729	74	89	59	74	106	64	51	62	62	77	75	76	53	OK	51	68	75	71	Soluble or membrane-bound decoy receptor
1730	73	86	60	73	133	72	52	39	54	88	87	88	48	OK	57	64	80	72	Soluble or membrane-bound decoy receptor
1731	69	83	59	70	202	48	51	43	47	80	74	77	61	OK	64	59	74	65	Soluble or membrane-bound decoy receptor
1732	59	78	44	60	247	51	46	53	50	74	68	71	56	OK	51	55	66	60	Soluble or membrane-bound decoy receptor
1733	47	70	60	59	528	56	49	54	53	69	64	66	44	OK	59	56	63	59	Soluble or membrane-bound decoy receptor
1734	52	79	48	60	401	40	50	41	44	42	43	42	60	OK	52	52	61	49	Soluble or membrane-bound decoy receptor
1735	71	82	37	63	209	62	64	76	69	91	97	94	73	OK	49	66	79	79	Wildtype-like
1736	82	88	49	73	134	53	58	45	52	85	83	84	48	OK	56	62	79	70	Wildtype-like
1737	69	84	53	69	257	51	51	63	55	80	75	78	43	OK	57	62	73	67	Wildtype-like
1738	59	77	33	56	264	54	37	58	50	87	84	85	71	OK	54	53	71	64	Wildtype-like
1739	39	67	63	56	603	63	58	61	61	71	80	76	55	OK	61	58	66	64	Wildtype-like
1740	62	86	36	68	136	59	43	49	50	79	71	75	45	OK	48	59	71	64	Wildtype-like
1741	78	84	60	74	160	27	16	52	32	81	90	86	56	TT	39	53	80	64	Wildtype-like
1742	62	81	45	63	237	38	32	62	44	84	89	87	63	TT	62	53	75	64	Wildtype-like
1743	65	81	49	65	240	45	56	45	49	74	79	77	44	TT	51	57	71	63	Wildtype-like
1744	64	76	82	67	235	27	34	37	33	79	86	82	48	TT	40	50	75	61	Wildtype-like
1745	84	93	49	79	64	31	9	46	29	71	71	71	47	TT	51	54	75	60	Wildtype-like

FIG. 35H

SEQ ID NO:	Genomic cut coordinate	Exon	CDS cut position %	crRNA	GC content	PAM
1746	154405710	1	5.7	CCAAGGCGCUGCCCUGCGCA	75	GGG
1747	154429250	2	9.9	CAGCGUGACUCUGACCUGCC	65	CGG
1748	154429252	2	10	GCGUGACUCUGACCUGCCCG	70	GGG
1749	154429253	2	10.1	CGUGACUCUGACCUGCCCGG	70	GGG
1750	154429283	2	12.2	CCUGAGCACCCAGUGAACAG	60	TGG
1751	154429380	2	19.1	UCGGUGCAGCUCCACGACUC	65	TGG
1752	154429380	2	19.1	AUGAAUAGUUUCCAGAGUCG	40	TGG
1753	154429416	2	21.7	AGUGCACAGUCCCAGCUGGG	65	CGG
1754	154430560	3	29.2	GUCAGGGAUGGGGUGCUCCG	70	AGG
1755	154430579	3	30.6	CACCCCAUCCCCUGACGACAA	60	AGG
1756	154429301	2	13.5	UCACUGGGUGCUCAGGAAGC	60	CGG
1757	154405697	1	4.8	CUGCGCAGGGCAGCGCCUUG	75	GGG
1758	154429404	2	20.8	AACUAUUCAUGCUACCGGGC	50	CGG
1759	154429417	2	21.7	ACCGGGCCCGGCCGCCCAGCU	85	GGG
1760	154430545	3	28.1	UCAGCAAUGUUGUUUGUGAG	40	TGG
1761	154429400	2	20.5	UGGAAACUAUUCAUGCUACC	40	GGG
1762	154430492	3	24.4	GGAGAGCUGGGGGCUCCUCGG	75	GGG
1763	154430530	3	27.1	UCACAAACAACAUUGCUGAG	40	GGG
1764	154405643	1	0.9	AGCCAGCAGCGCGCAGCCGA	75	CGG
1765	154429251	2	10	AGCGUGACUCUGACCUGCCC	65	GGG
1766	154429345	2	16.6	GAUGGGCUGGCAUGGGAAGG	65	AGG
1767	154430547	3	28.3	AGCAAUGUUGUUUGUGAGUG	40	GGG
1768	154430571	3	30	CAGCCUUUGUCGUCAGGGAU	55	GGG
1769	154434539	4	34	GCACGGCUCCUGGAAGUCUU	60	CGG
1770	154405693	1	4.5	CGGGAGCGGCGCUGGCCCCA	85	AGG
1771	154405698	1	4.8	CCUGCGCAGGGCAGCGCCUU	75	GGG
1772	154429224	2	8	GGCGUGCUGACCAGUCUGCC	70	AGG
1773	154429253	2	10.1	UUCCGGCUCUACCCCCGGGC	75	AGG
1774	154429286	2	12.4	AGACAAUGCCACUGUUCACU	45	GGG
1775	154429308	2	14	GUGCUCAGGAAGCCGGCUGC	70	AGG
1776	154429328	2	15.4	AGGCUCCCACCCCAGCAGAU	65	GGG
1777	154430513	3	25.9	GAGGGGGCUCUUCCGGAAGC	70	AGG
1778	154430546	3	28.2	CAGCAAUGUUGUUUGUGAGU	40	GGG
1779	154429338	2	16.1	CCCAGCAGAUGGGCUGGCAU	65	GGG
1780	154429419	2	21.9	GCAAGUGCACAGUCCCAGCU	60	GGG
1781	154430491	3	24.3	GAGAGCUGGGGCUCCUCGGG	75	GGG
1782	154430576	3	30.3	GAGCACAGCCUUUGUCGUCA	55	GGG
1783	154405652	1	1.6	GGCCGUCGGCUGCGCGCUGC	85	TGG
1784	154405667	1	2.6	CGCUCCCGGCGCGGCCAGCA	85	GGG
1785	154405674	1	3.1	GCUGCCCUGCUGGCCGCGCC	85	GGG
1786	154429223	2	8	CACGCUGUCUCCUGGCAGAC	65	TGG
1787	154429322	2	15	GCCAGCCCAUCUGCUGGGGU	70	GGG
1788	154429436	2	23.1	UGGGACUGUGCACUUGCUGG	60	TGG
1789	154430554	3	28.8	UUGUUUGUGAGUGGGGUCCU	50	CGG
1790	154430572	3	30.1	ACAGCCUUUGUCGUCAGGGA	55	TGG
1791	154430504	3	25.2	CUUCCGGAAGCAGGAGAGCU	60	GGG
1792	154430570	3	29.9	AGCCUUUGUCGUCAGGGAUG	55	GGG
1793	154429440	2	23.4	ACUGUGCACUUGCUGGUGGA	55	TGG
1794	154429262	2	10.7	GACCUGCCCGGGGGUAGAGC	75	CGG
1795	154429327	2	15.4	CCCAUGCCAGCCCAUCUGCU	65	GGG

FIG. 36A

SEQ ID NO:	Genomic cut coordinate	Exon	CDS cut position %	crRNA	GC content	PAM
1796	154429342	2	16.4	GCAGAUGGGCUGGCAUGGGA	65	AGG
1797	154429420	2	22	AGCAAGUGCACAGUCCCAGC	60	TGG
1798	154430505	3	25.3	UCUUCCGGAAGCAGGAGAGC	60	TGG
1799	154405679	1	3.5	CCUGCUGGCCGCGCCGGGAG	85	CGG
1800	154429294	2	13	CCACUGUUCACUGGGUGCUC	60	AGG
1801	154429332	2	15.7	UCCCACCCCAGCAGAUGGGC	70	TGG
1802	154429399	2	20.5	CUGGAAACUAUUCAUGCUAC	40	CGG
1803	154430503	3	25.2	UUCCGGAAGCAGGAGAGCUG	60	GGG
1804	154405673	1	3.1	GGCUGCCCUGCUGGCCGCGC	85	CGG
1805	154405681	1	3.6	CUUGGGGCCAGCGCCGCUCC	80	CGG
1806	154405709	1	5.6	CCCAAGGCGCUGCCCUGCGC	80	AGG
1807	154429337	2	16.1	CCCCAGCAGAUGGGCUGGCA	70	TGG
1808	154429407	2	21	UCCCAGCUGGGCGGCCGGCC	85	CGG
1809	154429416	2	21.7	UACCGGGCCGGCCGCCCAGC	85	TGG
1810	154430493	3	24.4	AGGAGAGCUGGGGCUCCUCG	70	GGG
1811	154430529	3	27	CACAAACAACAUUGCUGAGG	45	GGG
1812	154430591	3	31.4	GACGACAAAGGCUGUGCUCU	55	TGG
1813	154405676	1	3.3	GGCCAGCGCCGCUCCCGGCG	90	CGG
1814	154429309	2	14.1	CUGGGGUGGGAGCCUGCAGC	75	CGG
1815	154429361	2	17.8	AAGGAGGCUGCUGCUGAGGU	60	CGG
1816	154430532	3	27.2	ACUCACAAACAACAUUGCUG	40	AGG
1817	154429412	2	21.4	CACAGUCCCAGCUGGGCGGC	75	CGG
1818	154430596	3	31.8	CAAAGGCUGUGCUCUUGGUG	55	AGG
1819	154405699	1	4.9	CCCUGCGCAGGGCAGCGCCU	80	TGG
1820	154429433	2	22.9	AGCUGGGACUGUGCACUUGC	60	TGG
1821	154430531	3	27.1	CUCACAAACAACAUUGCUGA	40	GGG
1822	154429323	2	15.1	UGCCAGCCCAUCUGCUGGGG	70	TGG
1823	154429326	2	15.3	CCAUGCCAGCCCAUCUGCUG	65	GGG
1824	154430495	3	24.6	GCAGGAGAGCUGGGGCUCCU	70	CGG
1825	154430520	3	26.4	CAUUGCUGAGGGGGCUCUUC	60	CGG
1826	154429327	2	15.4	CAGGCUCCCACCCCAGCAGA	70	TGG
1827	154430577	3	30.4	AGAGCACAGCCUUUGUCGUC	55	AGG
1828	154429328	2	15.4	UCCCAUGCCAGCCCAUCUGC	65	TGG
1829	154430512	3	25.8	AGCCCCAGCUCUCCUGCUUC	65	CGG
1830	154405668	1	2.7	CCGCUCCCGGCGCGGCCAGC	90	AGG
1831	154405664	1	2.4	CGCGCUGCUGGCUGCCCUGC	80	TGG
1832	154430494	3	24.5	CAGGAGAGCUGGGGCUCCUC	70	GGG
1833	154429357	2	17.5	UGGGAAGGAGGCUGCUGCUG	65	AGG
1834	154405685	1	3.9	GGCCGCGCCGGGAGCGGCGC	95	TGG
1835	154434602	4	38.5	CUGCCAGUUAGCAGUCCCGG	65	AGG
1836	154434603	4	38.5	UGCCAGUUAGCAGUCCCGGA	60	GGG
1837	154434638	4	41	GACACUACUGGCGACGCACA	60	TGG
1838	154434652	4	42	UGUGCGUCGCCAGUAGUGUC	60	GGG
1839	154434686	4	44.4	ACAGAUUCCACAACCCUGAA	45	AGG
1840	154435046	5	49.5	CAGGUGACACUGAGCCAGCG	65	GGG
1841	154435100	5	53.3	ACUCAUCUUUCUACAGACUA	35	CGG
1842	154435119	5	54.7	ACGGUUUGAGCUCAGAUAUC	45	GGG
1843	154435127	5	55.2	AGCUCAGAUAUCGGGCUGAA	50	CGG
1844	154436010	6	60.3	GUCAUCCACGACGCCUGGAG	65	CGG
1845	154436017	6	60.8	ACGACGCCUGGAGCGGCCUG	75	AGG

FIG. 36B

SEQ ID NO:	Genomic cut coordinate	Exon	CDS cut position %	crRNA	GC content	PAM
1846	154436084	6	65.5	GUGGAGCGAGUGGAGCCCGG	75	AGG
1847	154436096	6	66.4	ACCUGUCCAAGGCGUGCCCA	65	TGG
1848	154435007	5	46.7	GUGACUGUGAUGUUGGCAGG	55	CGG
1849	154436045	6	62.8	GGUGCAGCUUCGUGCCCAGG	70	AGG
1850	154435045	5	49.4	AGGUGACACUGAGCCAGCGG	65	GGG
1851	154436004	6	59.8	UCAGGCCGCUCCAGGCGUCG	75	TGG
1852	154436091	6	66	GAGUGGAGCCCGGAGGCCAU	70	GGG
1853	154434607	4	38.8	UAGAAAGAGCUGUCUCCCUC	50	CGG
1854	154436012	6	60.4	CACGUGCCUCAGGCCGCUCC	75	AGG
1855	154436024	6	61.3	CUGGAGCGGCCUGAGGCACG	75	TGG
1856	154434563	4	35.7	GGAGCCGUGCCAGUAUUCCC	65	AGG
1857	154434590	4	37.6	CUCCGGGACUGCUAACUGGC	65	AGG
1858	154434589	4	38.2	CUCCUGCCAGUUAGCAGUCC	60	CGG
1859	154435048	5	49.6	GCCAGGUGACACUGAGCCAG	65	CGG
1860	154435075	5	51.5	AAGAUGAGUUCCAGGAGUGG	50	GGG
1861	154435118	5	54.6	UACGGUUUGAGCUCAGAUAU	40	CGG
1862	154436065	6	64.2	AGGAGUUCGGGCAAGGCGAG	65	TGG
1863	154434594	4	37.9	CUCCCUCCGGGACUGCUAAC	65	TGG
1864	154435014	5	47.2	CACGGCAGUGACUGUGAUGU	55	TGG
1865	154436081	6	65.3	CGAGUGGAGCGAGUGGAGCC	70	CGG
1866	154436101	6	66.7	CGGAGGCCAUGGGCACGCCU	75	TGG
1867	154434651	4	41.9	AUGUGCGUCGCCAGUAGUGU	55	CGG
1868	154435043	5	49.3	CCGUGGCCAGAAACCCCCGC	75	TGG
1869	154435078	5	51.6	AAAGAUGAGUUCCAGGAGUG	45	GGG
1870	154435152	5	57	AAAGACAUUCACAACAUGGA	35	TGG
1871	154436053	6	63.3	UUCGUGCCCAGGAGGAGUUC	60	GGG
1872	154435026	5	48	CAACAUCACAGUCACUGCCG	55	TGG
1873	154436022	6	61.1	GAAGCUGCACCACGUGCCUC	65	AGG
1874	154436089	6	65.9	CAAGGCGUGCCCAUGGCCUC	70	CGG
1875	154435148	5	56.7	GGUCAAAGACAUUCACAACA	40	TGG
1876	154436048	6	63	GCCUUGCCCGAACUCCUCCU	65	GGG
1877	154436058	6	63.7	GCCCAGGAGGAGUUCGGGCA	70	AGG
1878	154436106	6	67.1	GCCAUGGGCACGCCUUGGAC	70	AGG
1879	154435032	5	48.5	CCAGCGGGGGUUUCUGGCCA	70	CGG
1880	154436052	6	63.3	CUUCGUGCCCAGGAGGAGUU	60	CGG
1881	154434690	4	44.7	ACUCAAACCUUUCAGGGUUG	45	TGG
1882	154435010	5	46.9	GCAGUGACUGUGAUGUUGGC	55	AGG
1883	154435083	5	52.1	UCUGUAGAAAGAUGAGUUCC	40	AGG
1884	154435986	6	58.6	CGUGGAUGACACAGUGAUGC	55	TGG
1885	154436088	6	65.8	AAGGCGUGCCCAUGGCCUCC	70	GGG
1886	154434549	4	34.7	GGGAAUACUGGCACGGCUCC	65	TGG
1887	154435038	5	48.9	ACUGAGCCAGCGGGGGUUUC	65	TGG
1888	154436042	6	62.5	CGUGGUGCAGCUUCGUGCCC	70	AGG
1889	154436074	6	64.8	GGCAAGGCGAGUGGAGCGAG	70	TGG
1890	154434650	4	41.9	GAACUUGCUCCCGACACUAC	55	TGG
1891	154435047	5	49.5	CCAGGUGACACUGAGCCAGC	65	GGG
1892	154435983	6	58.4	GGAUGACACAGUGAUGCUGG	55	AGG
1893	154434606	4	38.7	AGAAAGAGCUGUCUCCCUCC	55	GGG
1894	154435058	5	50.3	CCCGCUGGCUCAGUGUCACC	70	TGG
1895	154436090	6	66	CGAGUGGAGCCCGGAGGCCA	75	TGG

FIG. 36C

SEQ ID NO:	Genomic cut coordinate	Exon	CDS cut position %	crRNA	GC content	PAM
1896	154434569	4	36.1	GGAGAACUUCUGGGACUCCU	55	GGG
1897	154434684	4	44.3	AGCAAAACUCAAACCUUUCA	35	GGG
1898	154434683	4	44.2	CAGCAAAACUCAAACCUUUC	40	AGG
1899	154435001	5	46.3	GUGAUGUUGGCAGGCGGAUC	60	AGG
1900	154435065	5	50.8	CCAGGAGUGGGGGUCUUGCC	70	AGG
1901	154435077	5	51.7	GAAAGAUGAGUUCCAGGAGU	45	GGG
1902	154434579	4	36.8	CUAACUGGCAGGAGAACUUC	50	TGG
1903	154435078	5	51.7	AGAAAGAUGAGUUCCAGGAG	45	TGG
1904	154434561	4	35.5	UCUGGGACUCCUGGGAAUAC	55	TGG
1905	154434570	4	36.2	AGGAGAACUUCUGGGACUCC	55	TGG
1906	154435076	5	51.6	CCUGGCAAGACCCCCACUCC	70	TGG
1907	154436049	6	63	CGCCUUGCCCGAACUCCUCC	70	TGG
1908	154448149	7	69.2	GAGUCCUCCAGCUGAGAACG	60	AGG
1909	154454532	9	78.9	CCACAUUCCUGGUUGCUGGA	55	GGG
1910	154448142	7	68.7	GACACCUCGUUCUCAGCUGG	60	AGG
1911	154448145	7	68.9	GUGGACACCUCGUUCUCAGC	60	TGG
1912	154454520	9	78	CCUCCAGCAACCAGGAAUGU	55	GGG
1913	154454521	9	78.1	CCCUCCAGCAACCAGGAAUG	60	TGG
1914	154454514	9	77.6	GCAACCAGGAAUGUGGGCAG	60	TGG
1915	154454521	9	78.1	AGUACCACUGCCCACAUUCC	55	TGG
1916	154454528	9	78.6	CCAGGCUCCCUCCAGCAACC	70	AGG
1917	154454528	9	78.6	CUGCCCACAUUCCUGGUUGC	60	TGG
1918	154454531	9	78.8	CCCACAUUCCUGGUUGCUGG	60	AGG
1919	154448134	7	68.1	GUUCUCAGCUGGAGGACUCC	60	TGG
1920	154449976	8	75.4	GCAAAUGCGACAAGCCUCCC	60	AGG
1921	154465195	10	86.8	AGCUGCCCCAAAGAGUACGG	60	CGG
1922	154465287	10	93.3	UCGAGGUAUUGUCAGACCCC	55	AGG
1923	154454551	9	80.2	AAUGCAGAGGAGCGUUCCGA	55	AGG
1924	154465304	10	94.5	AUCUGGUCGGUUGUGGCUCG	60	AGG
1925	154465336	10	96.8	CUGAUGUCAUAAGGGCUCCG	55	TGG
1926	154465201	10	87.2	UGCAUCCGCCGUACUCUUUG	55	GGG
1927	154454564	9	81.2	UCAGAACAAUGGCAAUGCAG	45	AGG
1928	154465167	10	84.8	AAGCUGCGGGCUCUGAAGGA	60	AGG
1929	154465335	10	96.7	UGAUGUCAUAAGGGCUCCGU	50	GGG
1930	154454546	9	79.9	AGAGGAGCGUUCCGAAGGCC	65	AGG
1931	154465255	10	91	GACACCGGUGGGGAGAUGAG	65	AGG
1932	154465322	10	95.8	CCACAACCGACCAGAUGCCA	60	GGG
1933	154454577	9	82.1	UCUGCAUUGCCAUUGUUCUG	45	AGG
1934	154465198	10	87	ACCAGCUGCCCCAAAGAGUA	55	CGG
1935	154465265	10	91.8	GCUGCUGGGGGACACCGGUG	75	GGG
1936	154465311	10	95	CCCUGGCAUCUGGUCGGUUG	65	TGG
1937	154465317	10	95.5	GUGGGUCCCUGGCAUCUGGU	65	CGG
1938	154465328	10	96.2	AUAAGGGCUCCGUGGGUCCC	65	TGG
1939	154465199	10	87.1	CAUGCAUCCGCCGUACUCUU	55	TGG
1940	154465222	10	88.7	GGGGUGGGGUCGAGGCCUCUC	75	CGG
1941	154465262	10	91.5	UGUUCCUCUCAUCUCCCCAC	55	CGG
1942	154465266	10	91.8	GGCUGCUGGGGGACACCGGU	75	GGG
1943	154465282	10	93	CGGUGUCCCCCAGCAGCCUG	75	GGG
1944	154465321	10	95.7	CUCCGUGGGUCCCUGGCAUC	70	TGG
1945	154465321	10	95.7	GCCACAACCGACCAGAUGCC	65	AGG

FIG. 36D

SEQ ID NO:	Genomic cut coordinate	Exon	CDS cut position %	crRNA	GC content	PAM
1946	154465344	10	97.4	CUGUAUUGCUGAUGUCAUAA	35	GGG
1947	154465219	10	88.5	UGGGGCAGCUGGUCCCGGAG	75	AGG
1948	154465267	10	91.9	AGGCUGCUGGGGGACACCGG	75	TGG
1949	154465330	10	96.4	GACCAGAUGCCAGGGACCCA	65	CGG
1950	154465163	10	84.5	GUGGAAGCUGCGGGCUCUGA	65	AGG
1951	154465270	10	92.1	CCCAGGCUGCUGGGGGACAC	75	CGG
1952	154454546	9	79.9	GCUGGAGGGAGCCUGGCCUU	70	CGG
1953	154465200	10	87.1	AUGCAUCCGCCGUACUCUUU	50	GGG
1954	154465221	10	88.6	GGGUGGGUCGAGGCCUCUCC	75	GGG
1955	154465231	10	89.3	ACAAGCACUGGGGUGGGUCG	65	AGG
1956	154465237	10	89.8	AGAGGAACAAGCACUGGGGU	55	GGG
1957	154465208	10	87.7	GCCGUACUCUUUGGGGCAGC	65	TGG
1958	154465214	10	88.1	CUCUUUGGGGCAGCUGGUCC	65	CGG
1959	154465238	10	89.8	GAGAGGAACAAGCACUGGGG	60	TGG
1960	154465279	10	92.8	UUGUCAGACCCCAGGCUGCU	60	GGG
1961	154465277	10	92.6	GUCAGACCCCAGGCUGCUGG	70	GGG
1962	154465243	10	90.2	GAGAUGAGAGGAACAAGCAC	50	TGG
1963	154465345	10	97.4	UCUGUAUUGCUGAUGUCAUA	35	AGG
1964	154454539	9	79.4	CCUGGUUGCUGGAGGGAGCC	70	TGG
1965	154465280	10	92.8	ACCGGUGUCCCCCAGCAGCC	75	TGG
1966	154465280	10	92.8	AUUGUCAGACCCCAGGCUGC	60	TGG
1967	154465281	10	92.9	CCGGUGUCCCCCAGCAGCCU	75	GGG
1968	154465278	10	92.7	UGUCAGACCCCAGGCUGCUG	65	GGG

FIG. 36E

SEQ ID NO:	MIT	CFD	Elevation	CFF	Offtarget #	Azimuth	DeepSpCas9	CrisprScan	CFF	Lindel	inDelphi	Frameshift	Precision	Graf Motifs	Bioscore	CFF	CFF_75	Outofframe	Predictions
1746	72	86	36	65	166	48	54	62	55	90	91	91	59	OK	41	60	78	70	Knockout
1747	70	85	46	67	149	51	34	68	51	91	90	91	63	GGC	59	59	79	70	Knockout
1748	81	92	48	74	93	55	64	51	57	85	86	86	45	OK	62	65	80	72	Knockout
1749	86	91	53	77	79	75	69	81	75	85	84	85	45	OK	62	76	81	79	Knockout
1750	70	87	53	70	248	71	82	52	66	91	97	94	71	OK	68	69	82	77	Knockout
1751	91	96	42	77	49	50	51	57	53	82	91	87	60	OK	62	65	82	72	Knockout
1752	67	83	60	70	144	64	51	35	50	82	87	85	51	OK	62	60	77	68	Knockout
1753	53	77	53	61	264	71	70	64	66	83	90	87	65	OK	58	65	74	72	Knockout
1754	74	81	34	63	217	62	61	67	63	87	88	88	60	OK	62	63	75	71	Knockout
1755	81	89	47	72	178	66	60	57	61	71	85	78	57	OK	59	67	75	70	Knockout
1756	56	76	47	60	273	54	58	67	60	85	89	87	54	OK	48	60	73	69	Knockout
1757	79	90	42	70	175	49	25	57	44	90	93	92	61	TT	55	57	81	68	Knockout
1758	95	96	50	80	32	55	36	48	46	75	79	77	58	OK	55	63	79	68	Knockout
1759	73	90	42	68	133	40	31	75	49	86	87	86	54	OK	59	58	77	68	Knockout
1760	72	84	61	72	184	57	32	46	45	88	88	88	64	OK	65	59	80	68	Knockout
1761	66	82	60	69	329	62	38	43	48	82	86	84	64	OK	63	59	77	67	Knockout
1762	58	75	35	56	347	38	64	81	61	80	85	83	67	OK	52	58	69	67	Knockout
1763	61	78	59	66	238	71	63	26	53	90	73	82	62	OK	56	60	74	67	Knockout
1764	85	90	38	71	120	47	54	66	56	77	65	71	45	OK	50	63	71	66	Knockout
1765	75	89	49	71	134	46	44	43	44	83	85	84	47	OK	57	58	78	66	Knockout
1766	34	62	41	46	600	53	53	83	63	84	92	88	57	OK	65	54	67	66	Knockout
1767	56	75	66	66	262	56	17	53	42	89	89	89	61	OK	69	54	77	66	Knockout
1768	81	91	52	75	118	42	28	69	46	77	76	77	46	OK	62	61	76	66	Knockout
1769	75	88	49	71	116	50	24	53	42	85	88	86	56	TT	44	56	78	66	Knockout
1770	54	75	38	56	235	34	36	71	47	89	94	92	63	OK	45	51	74	65	Knockout
1771	78	94	37	70	171	32	21	73	42	84	85	85	53	TT	55	56	77	65	Knockout
1772	76	92	40	69	95	48	43	30	40	82	90	86	66	GGC	57	55	78	65	Knockout
1773	80	86	40	69	105	47	28	50	42	80	86	83	46	OK	61	55	76	65	Knockout
1774	68	78	53	66	255	60	36	31	42	80	92	86	56	OK	69	54	76	65	Knockout
1775	71	85	52	69	216	39	42	54	45	82	80	81	51	OK	44	57	75	65	Knockout
1776	59	80	48	62	280	45	48	65	53	83	79	81	54	OK	49	57	71	65	Knockout
1777	70	87	40	66	139	44	41	67	51	71	86	78	54	OK	54	58	72	65	Knockout
1778	72	82	64	73	190	53	22	39	38	82	84	83	54	OK	65	55	78	65	Knockout
1779	56	79	40	58	323	47	50	60	52	78	86	82	53	OK	51	55	70	64	Knockout
1780	51	54	48	51	384	60	43	66	56	87	84	86	53	OK	52	54	68	64	Knockout
1781	55	76	37	56	315	39	41	87	59	74	82	78	59	OK	54	58	67	64	Knockout
1782	83	90	53	75	118	59	31	51	47	68	70	69	49	OK	55	61	72	64	Knockout
1783	76	91	37	68	133	27	37	48	37	87	79	83	52	OK	59	53	76	63	Knockout
1784	71	85	36	64	153	35	31	79	48	81	70	75	55	OK	49	56	70	63	Knockout
1785	67	85	37	63	311	30	27	70	42	80	88	84	66	OK	31	53	73	63	Knockout
1786	65	84	49	66	172	48	29	36	38	85	86	85	61	OK	57	52	76	63	Knockout
1787	50	73	42	55	310	46	53	61	53	74	85	80	53	OK	42	54	67	63	Knockout
1788	56	83	53	64	263	56	66	65	62	68	60	64	46	OK	57	63	64	63	Knockout
1789	56	77	40	58	260	57	23	65	48	80	86	83	60	TT	65	53	70	63	Knockout
1790	78	84	37	66	130	49	45	46	47	75	78	77	42	OK	60	56	71	63	Knockout
1791	57	80	43	60	224	42	35	44	40	84	89	87	54	OK	58	50	73	62	Knockout
1792	75	81	49	68	129	52	47	51	50	67	70	68	57	OK	62	59	68	62	Knockout
1793	38	74	37	50	302	51	62	47	53	76	85	80	63	OK	55	51	65	61	Knockout
1794	74	85	36	65	177	47	51	46	48	67	65	66	52	OK	48	56	65	60	Knockout
1795	56	73	40	56	377	36	60	40	45	84	75	79	63	OK	55	51	68	60	Knockout

FIG. 36F

SEQ ID NO:	MIT	CFD	Elevation	CCT	Offtarget #	Azimuth	DeepSpCas9	CrispScan	DNI	Lindel	inDelphi	Frameshift	Precision	Graf Motifs	Bioscore	CCT_DNI	CFD_DNI	CrispScan	Interpretation predictions
1796	43	61	46	50	543	50	62	62	58	69	77	73	43	OK	51	54	62	60	Knockout
1797	70	82	60	71	230	47	34	17	33	74	79	76	49	OK	48	52	74	60	Knockout
1798	63	81	48	64	194	33	40	19	31	82	88	85	47	OK	57	47	75	60	Knockout
1799	67	82	38	62	275	44	50	74	56	72	46	59	48	OK	42	59	61	59	Knockout
1800	64	80	46	63	203	44	43	33	40	72	75	73	43	OK	59	52	68	59	Knockout
1801	56	69	43	56	317	42	50	23	38	84	82	83	45	OK	52	47	69	59	Knockout
1802	79	89	60	76	166	49	17	38	35	64	68	66	43	OK	63	55	71	59	Knockout
1803	33	75	32	47	297	60	57	46	54	77	77	77	38	OK	57	51	62	59	Knockout
1804	61	77	40	59	335	18	36	64	38	68	84	76	60	OK	32	49	68	58	Knockout
1805	79	91	37	69	165	34	46	64	48	66	51	58	48	OK	41	59	64	58	Knockout
1806	64	78	32	58	244	33	38	32	34	80	82	81	42	OK	41	46	69	58	Knockout
1807	49	71	34	51	369	44	28	45	39	81	87	84	52	OK	51	45	68	58	Knockout
1808	52	72	31	52	655	34	24	75	44	71	84	78	59	GGC	53	48	65	58	Knockout
1809	77	85	36	66	107	24	16	40	27	77	86	81	51	OK	58	46	74	58	Knockout
1810	54	71	31	52	366	38	51	54	48	78	72	75	54	OK	51	50	63	58	Knockout
1811	66	76	61	68	227	59	35	36	43	65	63	64	45	OK	53	56	66	58	Knockout
1812	67	88	51	69	140	48	39	31	39	68	66	67	46	TT	68	54	68	58	Knockout
1813	65	84	37	62	206	40	44	66	50	67	51	59	49	OK	44	56	61	57	Knockout
1814	26	64	24	35	649	48	37	68	51	79	85	82	57	OK	41	45	60	57	Knockout
1815	30	61	22	38	585	55	58	83	65	63	72	67	53	OK	60	52	53	57	Knockout
1816	65	84	64	71	203	65	58	8	44	55	60	57	48	OK	55	57	64	57	Knockout
1817	61	74	46	60	336	40	26	59	42	64	71	68	64	OK	59	51	64	56	Knockout
1818	39	76	32	49	258	62	57	62	60	66	54	60	48	OK	58	55	54	56	Knockout
1819	65	77	33	58	289	25	18	29	24	79	84	81	46	GGC	56	41	70	55	Knockout
1820	62	74	42	59	448	27	30	33	30	66	83	74	66	TT	59	45	67	55	Knockout
1821	65	85	62	71	193	57	20	24	34	65	58	61	50	OK	55	52	66	55	Knockout
1822	22	42	35	33	973	43	42	58	48	79	83	81	45	OK	42	40	57	54	Knockout
1823	53	83	34	57	266	55	61	49	55	52	47	50	59	OK	55	56	53	54	Knockout
1824	39	62	31	44	528	38	20	61	40	75	82	79	67	TT	48	42	61	54	Knockout
1825	73	86	53	71	146	27	17	48	31	49	67	58	44	TT	48	51	64	53	Knockout
1826	31	69	21	40	460	39	43	52	45	62	70	67	54	OK	49	42	53	51	Knockout
1827	81	85	48	71	198	45	23	38	35	38	53	45	63	OK	55	53	58	51	Knockout
1828	48	68	39	52	325	27	43	11	27	72	72	72	45	OK	49	39	62	50	Knockout
1829	31	69	31	44	470	35	37	31	34	68	77	72	44	TT	52	39	58	50	Knockout
1830	47	66	38	50	427	18	11	51	27	68	73	71	52	OK	49	39	60	49	Knockout
1831	46	71	32	50	323	27	19	44	30	60	53	57	60	OK	57	40	53	45	Knockout
1832	38	64	21	41	528	32	32	72	45	43	56	50	57	OK	52	43	45	45	Knockout
1833	28	52	31	37	842	51	60	74	62	37	33	35	57	OK	58	49	36	44	Knockout
1834	33	62	29	41	786	29	25	40	31	59	52	55	45	OK	42	36	48	43	Knockout
1835	86	92	44	74	85	64	53	74	64	81	78	79	44	OK	56	69	77	72	Knockout or soluble decoy receptor
1836	89	84	51	75	111	65	54	46	55	80	83	81	51	OK	57	65	78	70	Knockout or soluble decoy receptor
1837	97	96	41	79	32	53	60	45	53	82	86	84	52	OK	66	66	81	72	Knockout or soluble decoy receptor
1838	97	96	37	77	26	51	66	57	58	83	80	82	63	OK	55	68	80	72	Knockout or soluble decoy receptor
1839	75	86	61	74	164	56	54	34	48	90	90	90	65	OK	58	61	82	71	Knockout or soluble decoy receptor
1840	68	82	37	62	207	62	63	66	64	87	84	86	55	OK	60	63	74	70	Knockout or soluble decoy receptor
1841	75	86	60	74	158	51	40	46	46	95	93	89	64	OK	58	60	82	70	Knockout or soluble decoy receptor
1842	75	90	61	75	93	44	29	62	45	95	92	89	66	OK	60	60	82	70	Knockout or soluble decoy receptor
1843	88	91	47	75	89	60	57	38	52	85	76	81	62	OK	53	63	78	69	Knockout or soluble decoy receptor
1844	83	94	47	75	65	65	53	50	56	87	87	87	60	OK	66	65	81	72	Knockout or soluble decoy receptor
1845	83	93	37	71	79	53	60	83	65	83	79	81	50	OK	59	68	76	72	Knockout or soluble decoy receptor

FIG. 36G

SEQ ID NO:	MIT	CFD	Elevation	CFD	Offtarget #	Azimuth	DeepSpCas9	CrispScan	ES	Lindel	inDelphi	Frameshift	Precision	Graf Motifs	Bioscore	CFD_ESP	CFD_HF	avgMMEJ	Interference predictions
1846	68	74	37	60	225	71	60	86	75	84	90	87	56	OK	48	67	73	74	Knockout or soluble decoy recepto
1847	88	92	47	76	96	50	56	44	50	80	79	80	45	OK	43	63	76	69	Knockout or soluble decoy recepto
1848	49	71	48	56	352	67	56	77	67	86	93	90	60	OK	48	61	73	71	Knockout or soluble decoy recepto
1849	69	86	49	68	155	64	62	78	66	66	83	75	50	OK	53	68	72	70	Knockout or soluble decoy recepto
1850	73	84	47	68	240	63	62	76	67	74	72	73	50	OK	60	67	70	69	Knockout or soluble decoy recepto
1851	88	93	40	74	86	59	65	69	64	72	68	70	51	OK	58	69	72	69	Knockout or soluble decoy recepto
1852	68	85	48	67	182	50	82	81	64	76	77	76	50	OK	40	66	72	69	Knockout or soluble decoy recepto
1853	51	83	59	64	194	55	50	47	51	84	92	88	69	OK	60	58	76	68	Knockout or soluble decoy recepto
1854	82	92	38	71	119	42	48	56	49	81	86	84	57	OK	65	60	77	68	Knockout or soluble decoy recepto
1855	65	82	38	62	254	55	68	70	64	79	79	79	48	OK	64	63	70	68	Knockout or soluble decoy recepto
1856	86	91	57	78	67	57	65	45	56	71	66	69	63	OK	50	67	73	67	Knockout or soluble decoy recepto
1857	81	90	46	72	85	53	53	32	46	82	85	83	64	OK	61	59	78	67	Knockout or soluble decoy recepto
1858	76	85	52	71	161	51	55	52	53	75	78	76	42	OK	55	62	74	67	Knockout or soluble decoy recepto
1859	49	70	42	54	357	55	57	74	62	84	84	84	54	OK	57	58	69	67	Knockout or soluble decoy recepto
1860	51	70	59	60	382	64	59	67	63	76	78	77	51	OK	56	62	69	67	Knockout or soluble decoy recepto
1861	82	91	61	78	161	46	18	53	39	76	90	83	55	OK	60	58	81	67	Knockout or soluble decoy recepto
1862	76	89	50	72	133	48	36	73	52	74	79	77	49	OK	44	62	74	67	Knockout or soluble decoy recepto
1863	86	93	44	74	81	32	24	36	31	91	95	93	68	OK	64	53	84	66	Knockout or soluble decoy recepto
1864	67	83	49	66	165	53	56	58	56	72	79	75	58	OK	54	61	71	66	Knockout or soluble decoy recepto
1865	63	84	34	60	166	43	56	60	53	84	84	84	56	GGC	44	57	72	66	Knockout or soluble decoy recepto
1866	82	92	48	74	148	46	39	52	46	81	75	78	41	GGC	55	60	76	66	Knockout or soluble decoy recepto
1867	86	97	41	78	22	49	49	57	52	82	71	66	51	OK	55	65	72	65	Knockout or soluble decoy recepto
1868	84	92	46	74	96	60	46	43	50	70	75	72	41	OK	61	62	73	65	Knockout or soluble decoy recepto
1869	52	70	52	58	330	60	56	59	58	81	78	79	57	OK	57	58	69	65	Knockout or soluble decoy recepto
1870	53	74	48	58	324	61	61	32	51	81	89	85	63	OK	61	55	72	65	Knockout or soluble decoy recepto
1871	71	90	34	65	144	39	53	61	51	77	84	80	44	TT	53	58	73	65	Knockout or soluble decoy recepto
1872	82	89	49	73	121	68	52	32	51	70	67	69	42	OK	40	62	71	64	Knockout or soluble decoy recepto
1873	82	91	38	70	131	48	39	44	44	79	75	77	41	OK	59	57	74	64	Knockout or soluble decoy recepto
1874	69	84	37	63	186	34	41	69	48	79	81	80	47	OK	44	56	71	64	Knockout or soluble decoy recepto
1875	73	83	66	74	193	68	59	21	49	73	61	67	65	OK	50	62	70	63	Knockout or soluble decoy recepto
1876	69	87	50	69	139	51	62	64	59	53	71	62	71	TT	57	64	65	63	Knockout or soluble decoy recepto
1877	70	88	49	69	248	53	43	58	51	72	68	70	43	OK	46	60	69	63	Knockout or soluble decoy recepto
1878	80	93	44	72	118	48	42	52	47	72	69	71	42	OK	64	60	71	63	Knockout or soluble decoy recepto
1879	70	80	34	61	159	45	44	75	55	70	71	70	43	OK	48	58	66	62	Knockout or soluble decoy recepto
1880	66	86	31	61	161	37	25	54	39	87	88	87	55	OK	53	50	74	62	Knockout or soluble decoy recepto
1881	69	82	52	68	171	41	36	40	39	76	79	77	49	OK	48	53	72	61	Knockout or soluble decoy recepto
1882	58	74	35	56	258	58	53	31	47	79	82	80	61	OK	39	52	68	61	Knockout or soluble decoy recepto
1883	53	81	59	64	218	34	50	45	43	75	75	75	61	TT	46	54	70	61	Knockout or soluble decoy recepto
1884	72	88	51	70	141	49	53	27	43	63	76	70	57	OK	50	57	70	61	Knockout or soluble decoy recepto
1885	70	85	38	64	139	46	37	49	44	79	74	76	50	OK	44	54	70	61	Knockout or soluble decoy recepto
1886	88	93	47	76	95	34	42	39	38	66	65	65	47	OK	52	57	71	60	Knockout or soluble decoy recepto
1887	81	90	48	73	132	21	10	37	23	78	91	85	57	TT	47	48	79	60	Knockout or soluble decoy recepto
1888	88	90	37	72	95	43	37	39	40	69	72	70	41	OK	48	56	71	60	Knockout or soluble decoy recepto
1889	58	80	48	62	452	55	54	70	60	76	41	55	81	OK	48	61	60	60	Knockout or soluble decoy recepto
1890	96	97	43	78	36	50	35	21	35	69	59	64	49	OK	55	57	71	59	Knockout or soluble decoy recepto
1891	39	68	35	47	536	50	31	52	44	84	86	85	58	OK	58	46	66	59	Knockout or soluble decoy recepto
1892	48	74	47	56	321	75	60	50	62	63	58	60	47	OK	46	59	58	59	Knockout or soluble decoy recepto
1893	45	79	35	53	260	56	55	40	50	68	75	71	56	OK	61	52	62	58	Knockout or soluble decoy recepto
1894	61	77	43	60	226	46	47	31	41	74	71	73	50	OK	54	51	67	58	Knockout or soluble decoy recepto
1895	55	75	37	56	210	41	48	46	45	71	73	72	45	OK	38	50	64	58	Knockout or soluble decoy recepto

FIG. 36H

SEQ ID NO:	MIT	CFD	Elevation	CRISTA	Offtarget #	Azimuth	DeepSpCas9	CrisprScan	TSI	Lindel	inDelphi	Frameshift	Precision	Gratt Motifs	Bioscore	CRISTA	CFD	TSI	Interference predictions
1896	58	76	53	62	223	56	43	50	50	57	62	59	76	TT	42	56	61	57	Knockout or soluble decoy receptor
1897	62	77	64	68	285	35	11	19	22	79	87	83	61	TT	53	45	75	57	Knockout or soluble decoy receptor
1898	71	86	53	70	211	14	2	29	15	79	87	83	64	TT	52	43	76	56	Knockout or soluble decoy receptor
1899	90	96	48	78	91	46	40	56	47	54	53	43	63	OK	48	63	61	56	Knockout or soluble decoy receptor
1900	44	45	36	42	796	42	27	59	43	84	86	85	61	GGC	50	42	63	56	Knockout or soluble decoy receptor
1901	49	67	45	54	356	56	47	66	56	57	60	59	47	OK	48	55	56	56	Knockout or soluble decoy receptor
1902	76	87	53	72	147	26	19	26	24	63	62	62	45	TT	53	48	67	53	Knockout or soluble decoy receptor
1903	45	64	54	54	457	61	40	35	45	59	49	54	52	OK	47	50	54	51	Knockout or soluble decoy receptor
1904	34	71	45	50	546	45	39	35	40	51	67	59	60	OK	55	45	55	50	Knockout or soluble decoy receptor
1905	61	76	52	63	297	36	38	39	38	52	36	44	67	OK	42	50	53	48	Knockout or soluble decoy receptor
1906	25	74	20	40	432	48	32	32	37	65	71	68	47	OK	46	38	54	46	Knockout or soluble decoy receptor
1907	76	87	47	70	103	28	23	16	12	68	51	60	58	OK	57	41	65	47	Knockout or soluble decoy receptor
1908	73	86	42	67	131	64	72	69	68	75	74	74	57	OK	39	68	71	70	Soluble decoy receptor
1909	66	73	58	66	282	55	59	37	50	91	85	88	65	OK	50	58	77	68	Soluble decoy receptor
1910	72	87	50	70	108	60	52	47	53	74	77	75	43	OK	33	61	73	66	Soluble decoy receptor
1911	83	93	48	75	80	38	38	33	36	83	89	86	47	OK	27	56	80	66	Soluble decoy receptor
1912	45	75	60	60	386	55	65	45	55	76	88	82	58	OK	56	57	71	66	Soluble decoy receptor
1913	54	66	62	61	477	48	64	31	48	87	87	87	54	OK	55	54	74	65	Soluble decoy receptor
1914	51	74	49	58	352	55	52	61	56	72	79	76	57	OK	49	57	67	63	Soluble decoy receptor
1915	69	89	49	69	180	29	50	30	36	79	90	85	61	TT	54	53	77	63	Soluble decoy receptor
1916	53	71	44	56	454	50	51	31	44	90	91	90	64	OK	54	50	73	63	Soluble decoy receptor
1917	67	80	53	67	268	28	41	24	31	89	93	91	63	TT	55	49	79	63	Soluble decoy receptor
1918	57	72	62	64	399	52	40	33	42	78	71	74	50	OK	50	53	69	60	Soluble decoy receptor
1919	41	82	35	53	209	42	38	16	32	87	91	89	54	OK	30	42	71	58	Soluble decoy receptor
1920	82	95	46	74	74	53	56	34	48	72	82	77	65	OK	48	61	55	53	Soluble decoy receptor
1921	93	94	43	77	55	77	71	56	68	79	87	83	57	OK	50	72	80	76	Wildtype-like
1922	84	95	55	78	48	58	66	67	64	80	83	81	51	OK	35	71	80	74	Wildtype-like
1923	96	95	44	78	51	60	64	52	59	80	79	80	45	OK	57	69	79	72	Wildtype-like
1924	90	93	40	74	43	51	56	59	55	82	85	84	45	OK	38	65	79	71	Wildtype-like
1925	89	93	49	77	57	61	64	38	54	83	80	82	62	OK	37	66	79	71	Wildtype-like
1926	91	95	44	77	29	56	56	40	51	77	87	82	62	TT	56	64	80	70	Wildtype-like
1927	59	77	60	65	260	68	64	45	59	82	80	81	48	OK	64	62	73	69	Wildtype-like
1928	48	75	59	61	289	55	62	72	63	77	87	82	58	OK	49	62	71	69	Wildtype-like
1929	93	95	44	77	47	60	55	62	59	75	64	70	46	OK	38	68	74	69	Wildtype-like
1930	86	91	41	73	96	46	49	57	51	78	82	80	46	GGC	50	62	76	68	Wildtype-like
1931	63	78	38	60	213	52	68	57	59	84	90	87	66	OK	51	59	73	68	Wildtype-like
1932	68	86	44	66	154	62	58	40	53	82	88	85	56	OK	26	60	75	68	Wildtype-like
1933	59	80	58	66	240	57	51	34	47	85	90	88	57	OK	65	56	77	67	Wildtype-like
1934	75	86	52	71	145	44	54	58	52	79	80	80	54	OK	57	61	75	67	Wildtype-like
1935	80	82	38	67	244	44	42	92	59	76	69	72	56	OK	42	63	69	66	Wildtype-like
1936	71	92	41	68	303	41	51	47	46	81	85	83	48	OK	33	57	75	66	Wildtype-like
1937	47	62	38	49	355	56	66	70	64	80	91	86	65	OK	38	56	67	66	Wildtype-like
1938	71	85	38	65	138	44	53	48	48	82	89	85	59	OK	36	57	75	66	Wildtype-like
1939	97	97	43	79	23	26	20	31	26	90	88	89	65	TT	48	52	84	65	Wildtype-like
1940	65	82	44	64	232	35	19	77	44	86	90	88	63	TT	46	54	76	65	Wildtype-like
1941	51	73	49	58	341	57	62	76	65	72	75	73	47	OK	46	61	65	65	Wildtype-like
1942	76	85	53	71	231	43	43	58	48	76	79	77	63	OK	42	60	74	65	Wildtype-like
1943	44	75	36	52	299	59	57	77	64	81	78	79	41	OK	46	58	66	65	Wildtype-like
1944	67	85	58	70	178	41	27	52	40	80	90	85	60	OK	38	55	78	65	Wildtype-like
1945	63	86	40	63	149	40	55	31	42	88	91	90	67	GGC	26	52	76	65	Wildtype-like

FIG. 36I

SEQ ID NO:	MIT	CFD	Elevation	G2T	Offtarget #	Azimuth	DeepSpCas9	CrisprScan	G2T	Lindel	inDelphi	Frameshift	Precision	Graf Motifs	Bioscore	G2T - G2T	G2T - G2	G2T - G2T	Interference predictions
1946	75	88	82	75	154	47	18	33	33	84	86	85	56	OK	54	54	80	64	Wildtype-like
1947	68	76	32	59	305	56	39	76	58	76	72	74	43	OK	46	58	66	63	Wildtype-like
1948	75	79	34	63	277	33	45	67	55	76	66	71	53	OK	44	69	67	63	Wildtype-like
1949	45	78	44	56	294	55	63	44	54	77	84	80	48	OK	40	55	68	63	Wildtype-like
1950	62	77	49	63	246	46	45	67	53	69	75	72	44	OK	53	58	67	62	Wildtype-like
1951	34	67	23	41	857	52	57	61	63	79	84	82	63	OK	42	52	61	62	Wildtype-like
1952	35	70	27	44	522	42	40	86	56	79	80	79	44	TT	51	50	62	60	Wildtype-like
1953	97	98	43	79	20	23	16	46	26	75	76	76	42	TT	48	53	77	60	Wildtype-like
1954	59	77	38	58	291	37	24	55	39	85	84	84	48	OK	46	48	71	60	Wildtype-like
1955	67	80	32	60	244	43	44	57	48	72	74	73	43	OK	45	54	66	60	Wildtype-like
1956	42	56	28	42	587	64	45	48	52	77	84	80	55	OK	49	47	61	58	Wildtype-like
1957	83	92	47	74	73	38	26	39	34	60	68	64	53	OK	53	54	69	57	Wildtype-like
1958	65	82	49	65	221	42	20	56	39	68	65	67	42	OK	50	52	66	57	Wildtype-like
1959	25	64	22	37	479	55	49	60	55	80	80	80	43	OK	49	46	59	57	Wildtype-like
1960	62	76	43	60	217	40	34	39	38	79	68	74	70	OK	45	49	67	57	Wildtype-like
1961	38	64	25	42	382	56	56	54	55	75	68	72	47	OK	43	49	57	56	Wildtype-like
1962	37	75	45	52	413	42	59	35	45	67	70	68	43	OK	58	49	60	55	Wildtype-like
1963	43	85	52	60	177	38	14	23	25	78	82	80	47	OK	54	43	70	55	Wildtype-like
1964	43	59	42	48	467	33	15	41	30	82	85	83	57	GGC	57	39	66	54	Wildtype-like
1965	50	72	31	51	244	30	27	37	31	73	72	73	57	GGC	43	41	62	52	Wildtype-like
1966	55	76	33	55	226	32	47	22	34	72	64	68	49	OK	43	44	61	52	Wildtype-like
1967	29	72	28	40	315	37	34	54	42	75	75	75	41	GGC	43	41	58	52	Wildtype-like
1968	41	70	36	49	326	49	52	38	46	39	50	44	57	OK	43	48	47	47	Wildtype-like

FIG. 36J

SEQ ID NO:	Genomic cut coordinate	Exon	CDS cut position	CDS cut position %	Strand	Start coordinate	End coordinate	crRNA	GC content	PAM
1969	55976241	3	37	1.3	+	55976224	55976243	AGUGGUGAGGAAAAUAAACA	35	AGG
1970	55969839	4	80	2.9	-	55969836	55969855	GGUGAACUUCUAGAUCCAUG	45	TGG
1971	55969835	4	84	3	+	55969818	55969837	UCAGGACUGAUAUAACCACA	40	TGG
1972	55969704	4	215	7.8	+	55969687	55969706	GCUCCUUAGGAAUAGUAAAA	35	TGG
1973	55969654	4	265	9.6	+	55969637	55969656	UAUAUCUGUAAAGGUGACAC	35	TGG
1974	55969759	4	160	5.8	-	55969756	55969775	UGUGCUAAAGGAAAAAUGUA	30	TGG
1975	55969724	4	195	7.1	-	55969721	55969740	UAAAUGCUAAUUACAUUGUC	25	TGG
1976	55969599	4	320	11.6	-	55969596	55969615	ACUUGCAACAUUCUUACAUU	30	CGG
1977	55969645	4	274	9.9	+	55969628	55969647	UAAUGAAGCUAUAUCUGUAA	25	AGG
1978	55969817	4	102	3.7	+	55969800	55969819	AGUUGUACAACUGGAGAUUC	40	AGG
1979	55969691	4	228	8.3	+	55969674	55969693	AUGAUAGUAUAUUGCUCCUU	30	AGG
1980	55969771	4	148	5.4	-	55969768	55969787	CACUGCAGUUUGUGUGCUAA	45	AGG
1981	55969575	4	344	12.5	-	55969572	55969591	CAGCUUGAACAGAAUGUUUA	35	TGG
1982	55969808	4	111	4	+	55969791	55969810	UUAGAAUGAAGUUGUACAAC	30	TGG
1983	55969696	4	223	8.1	-	55969693	55969712	AAACCAUUUUACUAUUCCUA	25	AGG
1984	55968356	5	410	14.9	-	55968353	55968372	UUGAGUUGCAUUGUGAACGA	40	GGG
1985	55968355	5	411	14.9	-	55968352	55968371	UGAGUUGCAUUGUGAACGAG	45	GGG
1986	55963467	7	697	25.3	-	55963464	55963483	UUUAUCAGUGAUCAACUCAG	35	AGG
1987	55963363	7	801	29.1	-	55963360	55963379	GGACCAAAGAUGCCUCAACU	50	TGG
1988	55963356	7	808	29.3	-	55963353	55963372	AGAUGCCUCAACUUGGAGCC	55	AGG
1989	55960552	8	822	29.8	+	55960535	55960554	GUGGAUGCUGUGUCUUCAGG	55	AGG
1990	55960470	8	904	32.8	-	55960467	55960486	GUUUAGGAUUCGCUGUAUGA	40	AGG
1991	55960423	8	951	34.5	-	55960420	55960439	ACUGGAGUGAAGAAGCAAGU	45	GGG
1992	55960533	8	841	30.5	+	55960516	55960535	GACAGUGAAUGAAGAUCGGG	50	TGG
1993	55964265	6	538	19.5	+	55964248	55964267	AUCAACAGUGCAUGAGGUGG	50	GGG
1994	55964264	6	539	19.6	+	55964247	55964266	AAUCAACAGUGCAUGAGGUG	45	GGG
1995	55964262	6	541	19.6	+	55964245	55964264	AUAAUCAACAGUGCAUGAGG	40	TGG
1996	55964259	6	544	19.7	+	55964242	55964261	AGAAUAAUCAACAGUGCAUG	35	AGG
1997	55964190	6	613	22.2	+	55964173	55964192	AUCUGAUGUAACCUUCCCAA	40	GGG
1998	55963425	7	739	26.8	+	55963408	55963427	AACACUCUUAAUACUUGGGU	35	TGG
1999	55960530	8	844	30.6	+	55960513	55960532	UUGGACAGUGAAUGAAGAUC	40	GGG
2000	55960424	8	950	34.5	-	55960421	55960440	GACUGGAGUGAAGAAGCAAG	50	TGG
2001	55968357	5	409	14.8	-	55968354	55968373	UUUGAGUUGCAUUGUGAACG	40	AGG
2002	55968326	5	440	16	-	55968323	55968342	AUGAGGUGUGAGUGGGAUGG	55	TGG
2003	55964263	6	540	19.6	+	55964246	55964265	UAAUCAACAGUGCAUGAGGU	40	GGG
2004	55963421	7	743	26.9	+	55963404	55963423	UUAUAACACUCUUAAUACUU	20	GGG
2005	55960457	8	917	33.3	-	55960454	55960473	UGUAUGAAGGAAGAUGGUAA	35	GGG
2006	55960450	8	924	33.5	-	55960447	55960466	AGGAAGAUGGUAAGGGAUAC	45	TGG
2007	55968309	5	457	16.6	-	55968306	55968325	UGGUGGAAGGGAAACACACU	50	TGG
2008	55963489	7	675	24.5	+	55963472	55963491	AUCACUGAUAAAUUAUGUGG	30	CGG
2009	55960463	8	911	33	-	55960460	55960479	AUUCGCUGUAUGAAGGAAGA	40	TGG
2010	55960441	8	933	33.8	-	55960438	55960457	GUAAGGGAUACUGGAGUGAC	50	TGG
2011	55968333	5	433	15.7	-	55968330	55968349	GAAGAAAAUGAGGUGUGAGU	40	GGG
2012	55964189	6	614	22.3	+	55964172	55964191	GAUCUGAUGUAACCUUCCCA	45	AGG
2013	55968343	5	423	15.3	-	55968340	55968359	UGAACGAGGGGAAGAAAAUG	45	AGG
2014	55964194	6	609	22.1	-	55964191	55964210	UAGAAGCAGAGAAUGCCCUU	45	GGG
2015	55963371	7	793	28.8	+	55963354	55963373	GCUCCAAGUUGAGGCAUCUU	50	TGG
2016	55960529	8	845	30.6	+	55960512	55960531	CUUGGACAGUGAAUGAAGAU	40	CGG
2017	55960458	8	916	33.2	-	55960455	55960474	CUGUAUGAAGGAAGAUGGUA	40	AGG
2018	55964150	6	653	23.7	-	55964147	55964166	AAUUUUGAUCCUGUAUAUAA	20	AGG

FIG. 37A

SEQ ID NO:	Genomic cut coordinate	Exon	CDS cut position	CDS cut position %	Strand	Start coordinate	End coordinate	crRNA	GC content	PAM
2019	55963486	7	678	24.6	+	55963469	55963488	UUGAUCACUGAUAAAUUAUG	25	TGG
2020	55968334	5	432	15.7	-	55968331	55968350	GGAAGAAAAUGAGGUGUGAG	45	TGG
2021	55960511	8	863	31.3	+	55960494	55960513	CUGUAAAAGGUUUAAGGUCU	35	TGG
2022	55968321	5	445	16.1	-	55968318	55968337	GUGUGAGUGGGAUGGUGGAA	55	GGG
2023	55964195	6	608	22.1	-	55964192	55964211	GUAGAAGCAGAGAAUGCCCU	50	TGG
2024	55960549	8	825	29.9	+	55960532	55960551	CGGGUGGAUGCUGUGUCUUC	60	AGG
2025	55964190	6	613	22.2	-	55964187	55964206	AGCAGAGAAUGCCCUUGGGA	55	AGG
2026	55963494	7	670	24.3	+	55963477	55963496	UGAUAAAUUAUGUGGCGGAU	35	TGG
2027	55968329	5	437	15.9	-	55968326	55968345	AAAAUGAGGUGUGAGUGGGA	45	TGG
2028	55968322	5	444	16.1	-	55968319	55968338	GGUGUGAGUGGGAUGGUGGA	60	AGG
2029	55963438	7	726	26.3	-	55963435	55963454	CUAGUAUCUUAAAAUUGACA	25	TGG
2030	55963420	7	744	27	+	55963403	55963422	AUUAUAACACUCUUAAUACU	20	TGG
2031	55969557	4	362	13.1	-	55969554	55969573	UAUGGAAUCACAAUAAUUUC	25	AGG
2032	55963495	7	669	24.3	+	55963478	55963497	GAUAAAUUAUGUGGCGGAUU	35	GGG
2033	55960505	8	869	31.5	+	55960488	55960507	CAUAUUCUGUAAAAGGUUUA	25	AGG
2034	55960498	8	876	31.8	+	55960481	55960500	CUAAACACAUAUUCUGUAAA	25	AGG
2035	55964217	6	586	21.3	-	55964214	55964233	UUUUGUCAACAUUGAAGUCU	30	GGG
2036	55964218	6	585	21.2	-	55964215	55964234	AUUUUGUCAACAUUGAAGUC	30	TGG
2037	55968376	5	390	14.1	+	55968359	55968378	ACAAUGCAACUCAAAUUUUU	25	AGG
2038	55942696	16	1992	72.3	-	55942693	55942712	CAAAGAGUCAUAUUGCCCAG	45	TGG
2039	55942681	16	2007	72.8	+	55942664	55942683	CUUACCCUUGGAGGAGUGUG	55	AGG
2040	55941562	17	2276	82.6	+	55941545	55941564	UGUGUACCACGGUAGAAUAC	45	TGG
2041	55941557	17	2281	82.7	-	55941554	55941573	CACUGUCCAGUAUUCUACCG	50	TGG
2042	55941551	17	2287	83	+	55941534	55941553	UCUGUAGCCACUGUGUACCA	50	CGG
2043	55941547	17	2291	83.1	-	55941544	55941563	UAUUCUACCGUGGUACACAG	45	TGG
2044	55941526	17	2312	83.9	+	55941509	55941528	AGACUUGGACUGACGGAACU	50	TGG
2045	55941161	17	2677	97.1	-	55941158	55941177	AUUUGAAACAGUUGGCAUGG	40	AGG
2046	55941114	17	2724	98.8	+	55941097	55941116	CCGCCUUGCCGUACAGUCUG	65	TGG
2047	55941111	17	2727	98.9	-	55941108	55941127	GUUACUUACCACAGACUGUA	40	CGG
2048	55941106	17	2732	99.1	-	55941103	55941122	UUACCACAGACUGUACGGCA	50	AGG
2049	55941103	17	2735	99.2	-	55941100	55941119	CCACAGACUGUACGGCAAGG	60	CGG
2050	55942674	16	2014	73.1	-	55942671	55942690	GUCACCUCACACUCCUCCAA	55	GGG
2051	55941654	17	2184	79.2	-	55941651	55941670	GACACAGCAGUGGUAUUGGG	55	GGG
2052	55941430	17	2408	87.3	-	55941427	55941446	UUAGUAGAUCAUGUAGAUGG	35	CGG
2053	55941145	17	2693	97.7	-	55941142	55941161	AUGGAGGCUGCGACUGAUGA	55	AGG
2054	55942692	16	1996	72.4	+	55942675	55942694	AGGAGUGUGAGGUGACCACU	55	GGG
2055	55941480	17	2358	85.5	+	55941463	55941482	CGCUCCUCUGAAUCUAACAA	45	GGG
2056	55941511	17	2327	84.4	+	55941494	55941513	ACUCGGAUCUUGAGAAGACU	45	TGG
2057	55941317	17	2521	91.4	-	55941314	55941333	GCAAGUUUCAUCAGUCAAUG	40	AGG
2058	55941405	17	2433	88.2	+	55941388	55941407	UGUUUGAAGUACUGUUGCCU	40	GGG
2059	55942711	16	1977	71.7	+	55942694	55942713	UGGGCAAUAUGACUCUUUGA	40	AGG
2060	55941411	17	2427	88	-	55941408	55941427	GCGGUGAUGGUAUUUUGCCC	55	AGG
2061	55941164	17	2674	97	-	55941161	55941180	AAGAUUUGAAACAGUUGGCA	35	TGG
2062	55941129	17	2709	98.3	+	55941112	55941131	GUCUGUGGUAAGUAACUUUU	35	AGG
2063	55942675	16	2013	73	-	55942672	55942691	GGUCACCUCACACUCCUCCA	60	AGG
2064	55941479	17	2359	85.6	+	55941462	55941481	CCGCUCCUCUGAAUCUAACA	50	AGG
2065	55941198	17	2640	95.8	+	55941181	55941200	UCUACUUGUCCCUCAGUACC	50	TGG
2066	55942691	16	1997	72.4	+	55942674	55942693	GAGGAGUGUGAGGUGACCAC	60	TGG
2067	55941657	17	2181	79.1	-	55941654	55941673	AAGGACACAGCAGUGGUAUU	45	GGG
2068	55941494	17	2344	85	+	55941477	55941496	UAACAAGGGCUGGGUAGACU	50	CGG

FIG. 37B

SEQ ID NO:	Genomic cut coordinate	Exon	CDS cut position	CDS cut position %	Strand	Start coordinate	End coordinate	crRNA	GC content	PAM
2069	55941485	17	2353	85.3	+	55941468	55941487	CUCUGAAUCUAACAAGGGCU	45	GGG
2070	55941196	17	2642	95.8	-	55941193	55941212	GCUUUUGGUCCAGGUACUGA	50	GGG
2071	55941761	17	2077	75.3	-	55941758	55941777	UUUCACUGAUGUAAGUGUUG	35	TGG
2072	55941695	17	2143	77.7	-	55941692	55941711	AUCAUUGGACCUGUUCAAAA	35	AGG
2073	55941473	17	2365	85.8	-	55941470	55941489	CCAGCCCUUGUUAGAUUCAG	50	AGG
2074	55941404	17	2434	88.3	+	55941387	55941406	CUGUUUGAAGUACUGUUGCC	45	TGG
2075	55941262	17	2576	93.4	-	55941259	55941278	GAUCAUAUUUCACAAUCCUG	35	TGG
2076	55941655	17	2183	79.2	-	55941652	55941671	GGACACAGCAGUGGUAUUGG	55	GGG
2077	55941618	17	2220	80.5	+	55941601	55941620	UCAUCACUGCUAGAAAUGCU	40	TGG
2078	55941255	17	2583	93.7	-	55941252	55941271	UUUCACAAUCCUGUGGAUCU	40	GGG
2079	55942726	16	1962	71.2	+	55942709	55942728	UUUGAAGGAUCUGGAACAUU	35	AGG
2080	55941710	17	2128	77.2	-	55941707	55941726	UCCAGAAGAUCUGAAAUCAU	35	TGG
2081	55941433	17	2405	87.2	-	55941430	55941449	CAAUUAGUAGAUCAUGUAGA	30	TGG
2082	55941169	17	2669	96.8	-	55941166	55941185	GUAGAAAGAUUUGAAACAGU	30	TGG
2083	55941787	17	2051	74.4	-	55941784	55941803	AAAGAUCAAAUGUAUUCAGA	25	TGG
2084	55941362	17	2476	89.8	+	55941345	55941364	AAAAUGUGAAAUAUCUGGAC	30	TGG
2085	55941205	17	2633	95.5	-	55941202	55941221	GCAGCAGAUGCUUUUGGUCC	55	AGG
2086	55941664	17	2174	78.9	-	55941661	55941680	AAUACUGAAGGACACAGCAG	45	TGG
2087	55941658	17	2180	79.1	-	55941655	55941674	GAAGGACACAGCAGUGGUAU	50	TGG
2088	55941468	17	2370	86	-	55941465	55941484	CCUUGUUAGAUUCAGAGGAG	45	CGG
2089	55941236	17	2602	94.4	-	55941233	55941252	UGGGCAAAUGAAAAUGUUUC	35	AGG
2090	55941197	17	2641	95.8	-	55941194	55941213	UGCUUUUGGUCCAGGUACUG	50	AGG
2091	55947528	15	1901	69	-	55947525	55947544	UUCCUAUUGACAACUCUUCU	35	GGG
2092	55942717	16	1971	71.5	+	55942700	55942719	AUAUGACUCUUUGAAGGAUC	35	TGG
2093	55941484	17	2354	85.4	+	55941467	55941486	CCUCUGAAUCUAACAAGGGC	50	TGG
2094	55941726	17	2112	76.6	+	55941709	55941728	GAUUUCAGAUCUUCUGGAAA	35	AGG
2095	55941720	17	2118	76.8	+	55941703	55941722	UCCAAUGAUUUCAGAUCUUC	35	TGG
2096	55941424	17	2414	87.6	-	55941421	55941440	GAUCAUGUAGAUGGCGGUGA	50	TGG
2097	55947529	15	1900	68.9	-	55947526	55947545	AUUCCUAUUGACAACUCUUC	35	TGG
2098	55941456	17	2382	86.4	+	55941439	55941458	UCUACUAAUUGUAGAUCUUC	30	TGG
2099	55941257	17	2581	93.6	+	55941240	55941259	UUUCAUUUGCCCAGAUCCAC	45	AGG
2100	55941256	17	2582	93.7	-	55941253	55941272	AUUUCACAAUCCUGUGGAUC	40	TGG
2101	55941211	17	2627	95.3	-	55941208	55941227	GUUUCUGCAGCAGAUGCUUU	45	TGG
2102	55941630	17	2208	80.1	-	55941627	55941646	CUUCAUGCAUGUCAUCUUCU	40	AGG
2103	55957247	9	1017	36.9	+	55957230	55957249	CUGUAGCCUUGAGUAUGGGA	50	TGG
2104	55957243	9	1021	37	+	55957226	55957245	AGUUCUGUAGCCUUGAGUAU	40	GGG
2105	55957217	9	1047	38	-	55957214	55957233	ACAGAACUGUACAACUCGUG	45	TGG
2106	55957213	9	1051	38.1	-	55957210	55957229	AACUGUACAACUCGUGUGGA	45	AGG
2107	55956178	10	1113	40.4	-	55956175	55956194	AUGAAGUGACUCUCACAAGA	40	TGG
2108	55954979	11	1280	46.4	+	55954962	55954981	AUGCUUUAAGAUCCAUUACA	30	GGG
2109	55954924	11	1335	48.4	-	55954921	55954940	GGGUGGAAUGGACUACUCCA	55	AGG
2110	55954923	11	1336	48.5	-	55954920	55954939	GGUGGAAUGGACUACUCCAA	50	GGG
2111	55954861	11	1398	50.7	+	55954844	55954863	UGUUGCCAGUCUGUGAUACA	45	GGG
2112	55954855	11	1404	50.9	-	55954852	55954871	AAGCACCCUGUAUCACAGAC	50	TGG
2113	55954827	11	1432	51.9	+	55954810	55954829	UCUUAAAUAGGUGCGAUGCA	40	CGG
2114	55954814	11	1445	52.4	-	55954811	55954830	GUGCAUCGCACCUAUUUAAG	45	AGG
2115	55952273	12	1528	55.4	-	55952270	55952289	AGGAAGCCCUGAAUCCAUAA	45	AGG
2116	55952067	13	1560	56.6	+	55952050	55952069	CGAACAGUAGGUCCUUUGGA	50	AGG
2117	55952055	13	1572	57	-	55952052	55952071	CUUCCAAAGGACCUACUGUU	45	CGG
2118	55951580	14	1723	62.5	+	55951563	55951582	GGACAAUGUAUAUUCUGUGU	35	GGG

FIG. 37C

SEQ ID NO:	Genomic cut coordinate	Exon	CDS cut position	CDS cut position %	Strand	Start coordinate	End coordinate	crRNA	GC content	PAM
2119	55951579	14	1724	62.5	+	55951562	55951581	AGGACAAUGUAUAUUCUGUG	35	TGG
2120	55951559	14	1744	63.3	+	55951542	55951561	CAAUGUGUCACUAGUCAAAG	40	AGG
2121	55951541	14	1762	63.9	-	55951538	55951557	GACUAGUGACACAUUGUACA	40	TGG
2122	55947565	15	1864	67.6	+	55947548	55947567	UAAGCAAACAGGCACGACUA	45	TGG
2123	55952041	13	1586	57.5	-	55952038	55952057	ACUGUUCGGACAAAAAAAGU	35	AGG
2124	55951509	14	1794	65.1	-	55951506	55951525	CAGCAUACACAGAUGAAGGU	45	GGG
2125	55947554	15	1875	68	+	55947537	55947556	AAUAGGAAUGCUAAGCAAAC	35	AGG
2126	55957242	9	1022	37.1	+	55957225	55957244	CAGUUCUGUAGCCUUGAGUA	45	TGG
2127	55956223	10	1068	38.7	+	55956206	55956225	UUUCCAUUGGCUUCAAAAGG	40	AGG
2128	55954941	11	1318	47.8	-	55954938	55954957	CAAAGAUAACAUGCUUUGGG	40	TGG
2129	55952040	13	1587	57.6	-	55952037	55952056	CUGUUCGGACAAAAAAAGUA	35	GGG
2130	55952015	13	1612	58.5	-	55952012	55952031	AAACGAAGCUGUCUUAGAGU	40	GGG
2131	55951532	14	1771	64.2	-	55951529	55951548	CACAUUGUACAUGGUACGAA	40	TGG
2132	55951513	14	1790	64.9	-	55951510	55951529	AUGGCAGCAUACACAGAUGA	45	AGG
2133	55951488	14	1815	65.8	+	55951471	55951490	GGGGUAGUAAAAGUGAAUUC	40	TGG
2134	55956215	10	1076	39	-	55956212	55956231	UUGCCUCCUUUUGAAGCCAA	45	TGG
2135	55952304	12	1497	54.3	+	55952287	55952306	CCUGGUCCAUCAGCAUAUAC	50	TGG
2136	55952278	12	1523	55.2	+	55952261	55952280	GGUAUGCCUUUAUGGAUUCA	40	GGG
2137	55952016	13	1611	58.4	-	55952013	55952032	AAAACGAAGCUGUCUUAGAG	40	TGG
2138	55954860	11	1399	50.7	+	55954843	55954862	UUGUUGCCAGUCUGUGAUAC	45	AGG
2139	55952002	13	1625	58.9	+	55951985	55952004	UCUGAACAUCAACAGGAAGU	40	TGG
2140	55951987	13	1640	59.5	-	55951984	55952003	CUUCCUGUUGAUGUUCAGAA	40	TGG
2141	55951510	14	1793	65	-	55951507	55951526	GCAGCAUACACAGAUGAAGG	50	TGG
2142	55951468	14	1835	66.6	-	55951465	55951484	ACUUUUACUACCCCAAAGUU	35	TGG
2143	55954978	11	1281	46.5	+	55954961	55954980	AAUGCUUUAAGAUCCAUUAC	30	AGG
2144	55954894	11	1365	49.5	-	55954891	55954910	UAAAGAAAUAUAUACUUGAG	20	TGG
2145	55952293	12	1508	54.7	-	55952290	55952309	CCAGUAUAUGCUGAUGGACC	50	AGG
2146	55956135	10	1156	41.9	+	55956118	55956137	GAGAUUUACUGUCAGUUUUG	35	TGG
2147	55954955	11	1304	47.3	+	55954938	55954957	CCCAAAGCAUGUUAUCUUUG	40	GGG
2148	55954945	11	1314	47.7	-	55954942	55954961	UCCCCAAAGAUAACAUGCUU	40	TGG
2149	55952277	12	1524	55.3	+	55952260	55952279	AGGUAUGCCUUUAUGGAUUC	40	AGG
2150	55957271	9	993	36	+	55957254	55957273	UCUAUUUUAUACCAGAAACU	25	TGG
2151	55952063	13	1564	56.7	+	55952046	55952065	UGUCCGAACAGUAGGUCCUU	50	TGG
2152	55957283	9	981	35.6	+	55957266	55957285	CAGAAACUUGGUGCUUUAGA	40	TGG
2153	55957271	9	993	36	-	55957268	55957287	CAUCUAAAGCACCAAGUUUC	40	TGG
2154	55956204	10	1087	39.4	-	55956201	55956220	UGAAGCCAAUGGAAAAAUCU	35	TGG
2155	55956077	10	1214	44	-	55956074	55956093	CUAACAGUAAGAAAUCUUGU	30	TGG
2156	55954953	11	1306	47.4	+	55954936	55954955	CACCCAAAGCAUGUUAUCUU	40	TGG
2157	55954944	11	1315	47.7	-	55954941	55954960	CCCCAAAGAUAACAUGCUUU	40	GGG
2158	55954918	11	1341	48.6	+	55954901	55954920	UAUUUCUUUACAGAUUCCCU	30	TGG
2159	55952270	12	1531	55.5	+	55952253	55952272	UUGUUUAAGGUAUGCCUUUA	30	TGG
2160	55952055	13	1572	57	+	55952038	55952057	ACUUUUUUUGUCCGAACAGU	35	AGG
2161	55951943	13	1684	61.1	+	55951926	55951945	ACCAGUUUCAUUUCCAAUGA	35	TGG
2162	55951505	14	1798	65.2	-	55951502	55951521	AUACACAGAUGAAGGUGGGA	45	AGG
2163	55956029	10	1262	45.8	-	55956026	55956045	AUCCCUGCCUGUGACUUUCA	50	AGG
2164	55952286	12	1515	55	+	55952269	55952288	UUUAUGGAUUCAGGGCUUCC	45	TGG
2165	55954936	11	1323	48	-	55954933	55954952	AUAACAUGCUUUGGGUGGAA	40	TGG
2166	55947537	15	1892	68.6	+	55947520	55947539	CUCCCAGAAGAGUUGUCAAU	45	AGG
2167	55956089	10	1202	43.6	+	55956072	55956091	CAACAAGAUUUCUUACUGUU	30	AGG
2168	55954841	11	1418	51.4	-	55954838	55954857	ACAGACUGGCAACAAGAAGA	45	TGG

FIG. 37D

SEQ ID NO:	Genomic cut coordinate	Exon	CDS cut position	CDS cut position %	Strand	Start coordinate	End coordinate	crRNA	GC content	PAM
2169	55952299	12	1502	54.5	-	55952296	55952315	GUUACUCCAGUAUAUGCUGA	40	TGG
2170	55957242	9	1022	37.1	-	55957239	55957258	AUAGAUCCAUCCCAUACUCA	40	AGG
2171	55954954	11	1305	47.3	+	55954937	55954956	ACCCAAAGCAUGUUAUCUUU	35	GGG
2172	55956220	10	1071	38.8	+	55956203	55956222	AUUUUUCCAUUGGCUUCAAA	30	AGG
2173	55956090	10	1201	43.6	+	55956073	55956092	AACAAGAUUUCUUACUGUUA	25	GGG
2174	55951945	13	1682	61	-	55951942	55951961	AUAUUUUAUAGAACCAUCAU	20	TGG
2175	55951933	13	1694	61.4	-	55951930	55951949	ACCAUCAUUGGAAAUGAAAC	35	TGG
2176	55951995	13	1632	59.2	+	55951978	55951997	AAUCCAUUCUGAACAUCAAC	35	AGG
2177	55941084	17	2754	99.9	+	55941067	55941086	GAACUACUAGUCCUUCACUG	45	AGG
2178	55941084	17	2754	99.9	-	55941081	55941100	GCGGCUACAUGCCUCAGUGA	60	AGG

FIG. 37E

SEQ ID NO:	MIT	CFD	Elevation	CFD	Offtarget #	Azimuth	DeepSpCas9	CrisprScan	CFD	Lindel	inDelphi	Frameshift	Precision	Graf Motifs	Bioscore	On-target	Off-target	Overall	Interpretation Predictions
1969	36	67	68	57	660	64	54	36	51	83	88	85	55	OK	63	54	71	65	Knockout
1970	44	85	54	61	135	71	51	34	52	83	82	83	52	OK	62	56	72	65	Knockout
1971	44	84	52	60	138	68	69	36	58	74	72	73	53	OK	69	59	67	64	Knockout
1972	71	82	62	72	157	28	22	27	26	85	87	86	53	OK	56	49	79	61	Knockout
1973	50	83	32	55	182	56	63	35	51	72	84	78	59	OK	63	53	66	61	Knockout
1974	29	71	45	48	424	53	49	25	42	85	89	87	63	OK	65	45	68	59	Knockout
1975	47	73	45	55	302	36	25	35	32	85	88	87	60	OK	65	44	71	58	Knockout
1976	39	83	51	58	208	44	14	32	30	82	92	87	56	TT	64	44	72	58	Knockout
1977	52	78	64	64	282	48	12	39	33	84	84	74	48	OK	64	49	69	57	Knockout
1978	40	86	61	62	175	44	23	42	36	58	80	69	58	TT	59	49	66	58	Knockout
1979	67	86	63	72	176	31	24	50	35	61	58	60	48	TT	54	53	66	56	Knockout
1980	41	84	52	59	171	46	3	36	28	81	77	79	44	OK	64	44	69	55	Knockout
1981	38	81	47	55	213	25	10	37	24	82	83	82	59	TT	60	40	69	54	Knockout
1982	42	84	52	59	196	40	35	8	28	66	70	68	52	OK	57	44	64	52	Knockout
1983	41	36	62	46	1195	44	24	18	29	42	51	46	51	OK	51	37	46	40	Knockout
1984	73	87	49	70	117	63	44	73	60	83	83	83	59	OK	62	65	76	71	Knockout or soluble decoy receptor
1985	72	89	55	72	114	66	51	67	61	75	75	75	52	OK	58	67	73	69	Knockout or soluble decoy receptor
1986	40	74	51	55	255	69	55	52	59	89	90	90	64	OK	53	57	72	66	Knockout or soluble decoy receptor
1987	84	93	57	78	103	58	44	16	39	85	86	86	56	OK	53	59	82	68	Knockout or soluble decoy receptor
1988	77	88	52	72	150	50	38	39	42	84	87	86	54	GGC	55	57	79	67	Knockout or soluble decoy receptor
1989	62	70	57	63	298	63	56	63	61	82	90	86	47	OK	53	62	74	70	Knockout or soluble decoy receptor
1990	89	93	49	77	51	43	62	32	46	82	90	86	55	OK	63	61	82	70	Knockout or soluble decoy receptor
1991	60	78	67	68	281	67	66	54	63	79	82	81	56	OK	58	66	74	71	Knockout or soluble decoy receptor
1992	71	86	59	72	187	62	54	56	57	72	72	72	47	OK	51	65	72	67	Knockout or soluble decoy receptor
1993	66	80	52	66	186	50	46	77	56	80	68	74	48	OK	57	62	70	66	Knockout or soluble decoy receptor
1994	65	85	63	71	411	61	41	63	55	77	66	72	46	OK	58	63	71	66	Knockout or soluble decoy receptor
1995	72	84	60	72	175	63	50	40	51	77	66	71	44	OK	53	62	72	65	Knockout or soluble decoy receptor
1996	69	83	60	71	193	62	40	34	45	78	77	78	52	OK	62	58	74	65	Knockout or soluble decoy receptor
1997	43	81	42	55	192	68	64	52	61	82	72	77	44	OK	58	58	66	65	Knockout or soluble decoy receptor
1998	79	88	59	75	105	47	38	27	37	80	85	82	53	OK	52	56	79	65	Knockout or soluble decoy receptor
1999	69	85	59	71	202	53	50	68	56	67	66	66	46	OK	56	64	69	65	Knockout or soluble decoy receptor
2000	48	68	65	60	416	66	53	45	55	77	83	80	56	OK	44	58	70	65	Knockout or soluble decoy receptor
2001	67	89	53	70	133	60	38	18	39	84	84	84	53	OK	62	54	77	64	Knockout or soluble decoy receptor
2002	34	52	30	36	610	52	58	83	66	85	91	86	59	OK	66	53	63	64	Knockout or soluble decoy receptor
2003	69	86	60	72	368	55	48	40	46	73	75	74	56	OK	57	60	73	64	Knockout or soluble decoy receptor
2004	68	77	61	69	241	41	37	35	38	82	87	85	62	TT	48	53	77	64	Knockout or soluble decoy receptor
2005	53	74	65	64	330	65	41	50	52	75	79	77	49	OK	55	58	71	64	Knockout or soluble decoy receptor
2006	64	75	61	67	341	46	34	34	38	80	93	87	57	OK	63	52	77	64	Knockout or soluble decoy receptor
2007	37	80	45	54	390	52	48	38	46	90	88	89	55	OK	67	50	71	63	Knockout or soluble decoy receptor
2008	38	78	47	54	212	59	58	48	54	82	78	80	52	OK	51	54	67	63	Knockout or soluble decoy receptor
2009	67	78	49	65	154	53	46	37	45	77	79	78	55	OK	61	55	71	63	Knockout or soluble decoy receptor
2010	71	82	52	68	148	48	55	63	55	77	55	66	60	OK	62	62	67	63	Knockout or soluble decoy receptor
2011	44	58	60	54	635	62	52	56	57	77	72	75	49	OK	59	55	64	62	Knockout or soluble decoy receptor
2012	49	79	42	57	216	66	56	25	49	82	78	80	47	OK	58	53	68	62	Knockout or soluble decoy receptor
2013	36	55	65	52	531	59	59	39	52	76	81	78	53	OK	65	52	65	61	Knockout or soluble decoy receptor
2014	35	79	42	52	270	60	63	56	60	77	68	72	46	TT	57	56	62	61	Knockout or soluble decoy receptor
2015	77	91	53	74	121	31	19	37	29	76	83	80	59	TT	52	51	77	61	Knockout or soluble decoy receptor
2016	60	86	49	65	209	52	40	48	47	71	70	70	55	OK	56	56	68	61	Knockout or soluble decoy receptor
2017	62	79	57	66	226	41	46	38	42	78	75	77	45	OK	55	54	71	61	Knockout or soluble decoy receptor
2018	54	71	63	63	320	35	13	33	27	88	91	89	58	OK	57	45	76	60	Knockout or soluble decoy receptor

FIG. 37F

SEQ ID NO:	MIT	CFD	Elevation	CFD	Offtarget #	Azimuth	DeepSpCas9	CrisprScan	CFD	Lindel	inDelphi	Frameshift	Precision	Graf Motifs	Bioscore	On-target	Off-target	Overall	Intervention Annotations
2019	37	71	47	52	285	61	36	49	49	73	84	79	61	OK	60	50	65	60	Knockout or soluble decoy receptor
2020	28	52	61	47	1658	55	50	31	45	87	86	86	65	OK	59	46	67	59	Knockout or soluble decoy receptor
2021	70	81	63	71	189	38	19	40	32	72	76	74	47	OK	56	52	73	59	Knockout or soluble decoy receptor
2022	28	44	52	41	846	53	44	74	57	77	73	75	46	OK	64	49	58	58	Knockout or soluble decoy receptor
2023	36	77	41	52	297	51	58	40	50	75	68	71	45	OK	57	51	62	58	Knockout or soluble decoy receptor
2024	68	86	53	69	147	32	15	64	37	67	68	67	45	TT	53	53	68	58	Knockout or soluble decoy receptor
2025	36	69	34	46	318	62	55	37	51	69	75	72	44	OK	58	49	59	57	Knockout or soluble decoy receptor
2026	86	94	57	79	75	44	1	34	26	64	66	65	51	OK	39	53	72	57	Knockout or soluble decoy receptor
2027	39	51	34	41	584	59	44	43	49	76	79	78	44	OK	66	45	59	56	Knockout or soluble decoy receptor
2028	24	55	23	34	920	48	53	60	54	79	79	79	61	OK	64	44	57	56	Knockout or soluble decoy receptor
2029	53	72	64	63	308	59	25	7	30	72	75	73	44	OK	61	47	68	56	Knockout or soluble decoy receptor
2030	66	81	60	69	244	39	14	11	21	75	81	78	62	OK	48	45	74	56	Knockout or soluble decoy receptor
2031	38	82	48	56	232	36	9	35	23	82	91	86	61	TT	56	40	71	55	Knockout or soluble decoy receptor
2032	80	94	47	74	86	35	18	41	31	58	64	61	50	OK	38	52	67	55	Knockout or soluble decoy receptor
2033	47	73	65	62	312	20	5	19	15	87	93	90	64	TT	57	38	76	55	Knockout or soluble decoy receptor
2034	45	64	70	60	414	29	8	10	16	88	88	88	59	OK	63	36	74	54	Knockout or soluble decoy receptor
2035	39	78	47	55	280	49	22	43	38	82	72	67	50	OK	70	46	61	53	Knockout or soluble decoy receptor
2036	41	80	46	56	245	40	14	27	27	75	73	74	53	OK	71	41	65	52	Knockout or soluble decoy receptor
2037	35	70	48	51	310	14	3	23	11	72	87	79	62	TT	62	31	65	47	Knockout or soluble decoy receptor
2038	42	77	54	58	155	74	51	60	62	83	83	83	45	OK	56	60	70	66	Membrane-bound decoy receptor
2039	69	81	53	68	160	53	60	79	61	81	71	76	66	OK	54	64	72	66	Membrane-bound decoy receptor
2040	91	96	47	78	44	51	50	24	42	77	90	84	57	OK	58	60	61	66	Membrane-bound decoy receptor
2041	93	96	50	80	53	72	64	49	62	83	91	87	58	OK	62	71	83	76	Membrane-bound decoy receptor
2042	80	85	40	62	167	62	79	54	65	85	95	90	63	OK	56	63	76	72	Membrane-bound decoy receptor
2043	87	91	47	75	84	78	77	40	64	93	86	94	67	OK	55	70	85	78	Membrane-bound decoy receptor
2044	92	94	53	80	64	51	47	46	48	85	74	79	58	OK	47	64	80	69	Membrane-bound decoy receptor
2045	58	71	57	62	266	65	55	38	53	89	93	91	61	OK	44	57	76	68	Membrane-bound decoy receptor
2046	46	91	54	64	58	58	54	65	59	86	88	87	59	OK	54	61	75	70	Membrane-bound decoy receptor
2047	79	86	61	76	113	51	56	42	50	93	86	91	66	OK	57	63	83	72	Membrane-bound decoy receptor
2048	46	92	50	63	75	67	64	54	62	85	79	82	45	OK	54	63	73	69	Membrane-bound decoy receptor
2049	47	90	45	61	95	78	79	60	69	93	86	90	67	OK	51	65	78	75	Membrane-bound decoy receptor
2050	67	83	60	70	175	64	53	54	57	73	77	75	47	OK	54	64	72	67	Membrane-bound decoy receptor
2051	50	80	29	53	180	69	67	59	65	81	87	84	62	OK	47	59	68	67	Membrane-bound decoy receptor
2052	61	70	40	57	202	70	75	66	70	68	78	73	55	OK	43	64	65	67	Membrane-bound decoy receptor
2053	82	89	52	74	156	55	62	65	61	59	72	65	61	OK	32	68	70	67	Membrane-bound decoy receptor
2054	36	76	42	51	349	68	61	81	70	76	77	77	53	OK	59	61	64	66	Membrane-bound decoy receptor
2055	46	83	50	63	71	61	61	53	58	71	84	78	59	OK	56	61	70	68	Membrane-bound decoy receptor
2056	79	94	49	74	73	50	35	27	37	79	82	80	46	OK	48	56	77	64	Membrane-bound decoy receptor
2057	43	86	54	61	114	68	31	29	43	87	88	87	54	OK	30	52	74	64	Membrane-bound decoy receptor
2058	51	80	46	59	222	53	42	40	45	81	88	84	53	GGC	45	52	72	63	Membrane-bound decoy receptor
2059	42	87	46	58	156	38	42	37	39	83	93	88	60	OK	52	49	73	62	Membrane-bound decoy receptor
2060	38	82	58	59	406	52	46	42	47	81	79	80	46	OK	42	53	70	62	Membrane-bound decoy receptor
2061	53	71	64	63	414	54	41	35	43	79	82	80	46	OK	35	53	72	62	Membrane-bound decoy receptor
2062	74	83	60	72	151	27	9	48	28	83	89	86	61	TT	49	50	79	62	Membrane-bound decoy receptor
2063	47	80	40	56	279	61	64	32	52	71	77	74	65	OK	54	54	65	61	Membrane-bound decoy receptor
2064	47	93	49	63	88	44	34	27	35	84	86	85	52	OK	50	49	74	61	Membrane-bound decoy receptor
2065	48	85	36	56	178	47	58	27	44	80	86	83	63	OK	31	50	70	61	Membrane-bound decoy receptor
2066	35	75	29	46	331	54	66	69	63	74	67	70	48	OK	58	55	58	60	Membrane-bound decoy receptor
2067	50	85	45	60	230	33	37	58	43	79	77	78	60	TT	59	51	69	60	Membrane-bound decoy receptor
2068	68	90	37	65	120	53	31	42	42	73	72	72	41	OK	50	53	69	60	Membrane-bound decoy receptor

FIG. 37G

SEQ ID NO:	MIT	CFD	Elevation	CFD	Offtarget #	Azimuth	DeepSpCas9	CrisprScan	CFD	Lindel	inDelphi	Frameshift	Precision	Graf Motifs	Bioscore	CFD	DFF	Overall	Membrane-bound/soluble
2069	44	87	45	59	147	48	38	53	46	75	76	76	47	OK	57	52	67	60	Membrane-bound decoy receptor
2070	44	89	42	58	127	58	53	30	47	71	78	75	47	OK	35	53	66	60	Membrane-bound decoy receptor
2071	56	70	59	62	289	58	42	35	45	69	71	70	52	OK	53	54	68	59	Membrane-bound decoy receptor
2072	47	81	51	60	182	44	12	49	35	81	83	82	56	OK	42	47	71	59	Membrane-bound decoy receptor
2073	45	84	33	54	122	56	38	62	52	66	74	70	61	OK	47	53	62	59	Membrane-bound decoy receptor
2074	56	81	42	60	181	39	31	21	30	85	89	87	62	GGC	44	45	73	59	Membrane-bound decoy receptor
2075	41	84	60	62	172	65	49	33	49	71	64	67	47	OK	37	55	64	59	Membrane-bound decoy receptor
2076	39	76	47	54	352	57	61	45	54	51	81	66	63	OK	59	54	60	58	Membrane-bound decoy receptor
2077	40	83	44	56	177	52	58	26	45	80	67	74	62	OK	43	50	65	58	Membrane-bound decoy receptor
2078	41	85	45	57	183	48	37	34	40	73	79	76	59	OK	35	48	67	58	Membrane-bound decoy receptor
2079	53	81	54	63	283	42	19	55	39	65	76	70	49	TT	53	51	67	57	Membrane-bound decoy receptor
2080	47	72	65	61	362	41	28	45	38	63	78	71	60	OK	39	50	66	57	Membrane-bound decoy receptor
2081	58	84	52	65	144	50	37	33	40	68	66	67	61	OK	42	52	66	57	Membrane-bound decoy receptor
2082	40	71	48	53	306	53	38	45	45	72	73	73	51	OK	39	49	63	57	Membrane-bound decoy receptor
2083	32	60	51	48	544	54	39	31	41	77	80	78	48	OK	41	44	63	56	Membrane-bound decoy receptor
2084	33	58	46	46	684	46	26	32	35	81	87	84	53	OK	35	40	65	55	Membrane-bound decoy receptor
2085	60	78	49	62	293	39	29	40	36	69	67	68	47	OK	26	49	65	55	Membrane-bound decoy receptor
2086	44	76	38	53	304	66	62	42	57	53	50	51	61	OK	45	55	52	54	Membrane-bound decoy receptor
2087	41	81	43	56	210	46	33	45	41	63	69	66	51	OK	51	48	60	54	Membrane-bound decoy receptor
2088	39	75	45	53	198	68	49	60	58	56	46	51	59	OK	43	56	52	54	Membrane-bound decoy receptor
2089	29	71	54	51	447	33	10	33	25	81	89	85	56	TT	32	38	68	54	Membrane-bound decoy receptor
2090	33	68	35	46	468	51	37	30	39	71	86	79	60	OK	35	42	62	54	Membrane-bound decoy receptor
2091	64	84	62	70	178	39	14	14	22	60	72	66	69	TT	60	46	68	53	Membrane-bound decoy receptor
2092	41	82	46	56	178	33	29	41	34	72	67	69	44	OK	50	45	63	53	Membrane-bound decoy receptor
2093	44	90	32	55	98	40	24	9	20	80	81	81	46	OK	57	38	68	52	Membrane-bound decoy receptor
2094	43	69	64	59	362	42	15	16	24	70	68	69	48	OK	34	41	64	51	Membrane-bound decoy receptor
2095	65	82	65	71	216	21	5	9	12	66	67	66	46	TT	44	41	69	50	Membrane-bound decoy receptor
2096	35	80	30	48	364	59	53	57	56	49	40	45	57	OK	35	52	47	50	Membrane-bound decoy receptor
2097	55	84	52	64	172	21	7	15	14	69	69	69	49	TT	60	39	66	48	Membrane-bound decoy receptor
2098	56	85	55	66	153	33	14	11	19	60	59	59	46	TT	52	43	63	48	Membrane-bound decoy receptor
2099	33	72	17	37	608	54	18	40	37	65	66	65	49	OK	27	37	51	47	Membrane-bound decoy receptor
2100	42	86	51	60	181	32	14	16	21	61	60	61	52	OK	27	40	60	47	Membrane-bound decoy receptor
2101	49	58	57	55	542	39	16	24	26	58	63	61	44	TT	31	41	58	47	Membrane-bound decoy receptor
2102	37	72	64	58	318	35	6	9	17	56	67	62	67	TT	46	37	60	46	Membrane-bound decoy receptor
2103	74	82	81	72	171	63	60	48	57	80	85	83	50	OK	48	65	77	71	Soluble decoy receptor
2104	73	87	58	73	146	64	51	57	57	76	78	77	49	OK	48	65	75	69	Soluble decoy receptor
2105	91	84	47	77	69	63	56	65	61	76	80	78	50	OK	58	69	78	72	Soluble decoy receptor
2106	82	95	52	80	82	58	50	47	52	87	87	87	64	OK	65	66	83	73	Soluble decoy receptor
2107	73	78	60	70	208	60	44	42	49	90	86	88	55	OK	58	60	79	69	Soluble decoy receptor
2108	68	80	60	69	208	61	48	55	55	85	88	86	61	OK	51	62	78	70	Soluble decoy receptor
2109	76	73	61	70	220	57	66	46	57	83	81	82	60	OK	43	64	76	70	Soluble decoy receptor
2110	83	86	61	77	69	70	59	72	67	78	66	72	44	OK	43	72	75	72	Soluble decoy receptor
2111	69	87	60	72	179	58	64	49	57	88	88	88	64	OK	57	65	80	72	Soluble decoy receptor
2112	80	69	45	71	109	60	45	55	53	90	86	89	55	OK	53	62	80	71	Soluble decoy receptor
2113	92	93	50	78	86	68	64	41	58	92	86	89	61	OK	59	68	84	75	Soluble decoy receptor
2114	97	97	50	81	21	56	36	42	45	84	92	88	60	OK	59	63	85	71	Soluble decoy receptor
2115	76	84	62	74	204	52	39	41	44	82	90	86	56	OK	58	59	80	68	Soluble decoy receptor
2116	80	69	53	74	73	65	67	33	55	74	81	78	63	OK	55	64	76	69	Soluble decoy receptor
2117	64	89	53	75	101	55	46	55	52	86	88	87	65	TT	60	64	81	71	Soluble decoy receptor
2118	50	79	63	64	213	62	61	42	55	84	86	86	52	OK	66	60	75	68	Soluble decoy receptor

FIG. 37H

SEQ ID NO:	MIT	CFD	Elevation	CCTop	Offtarget #	Azimuth	DeepSpCas9	CrispScan	CRISTA	Lindel	inDelphi	Frameshift	Precision	Graf Motifs	Bioscore	DNA_CCTop	DNA_FD	cynoDNA	Interference predictions
2119	56	70	63	63	332	61	61	44	55	89	88	89	64	OK	66	59	76	69	Soluble decoy receptor
2120	81	88	61	77	127	63	41	39	48	81	79	80	55	OK	58	62	78	68	Soluble decoy receptor
2121	85	92	60	79	83	61	67	31	53	85	85	85	62	OK	79	66	82	72	Soluble decoy receptor
2122	83	96	53	81	62	52	65	48	55	81	85	83	60	OK	60	68	82	73	Soluble decoy receptor
2123	74	88	60	74	119	57	49	32	46	79	82	80	54	OK	55	60	77	67	Soluble decoy receptor
2124	71	84	59	71	194	63	68	49	60	66	76	71	55	OK	45	66	71	67	Soluble decoy receptor
2125	64	74	58	65	268	49	41	50	47	86	94	90	57	OK	66	56	78	67	Soluble decoy receptor
2126	72	85	58	72	172	39	48	45	44	82	83	83	56	OK	49	58	77	66	Soluble decoy receptor
2127	65	77	61	68	226	54	40	39	44	83	88	85	56	OK	50	56	77	66	Soluble decoy receptor
2128	60	58	58	59	400	61	59	47	56	83	87	85	61	OK	59	57	72	66	Soluble decoy receptor
2129	72	84	60	72	135	50	37	49	45	80	82	81	57	OK	57	59	76	66	Soluble decoy receptor
2130	77	88	49	71	121	58	46	32	45	77	87	82	50	OK	56	58	77	66	Soluble decoy receptor
2131	93	95	57	82	58	59	48	46	51	61	71	66	57	OK	70	66	74	66	Soluble decoy receptor
2132	54	74	59	62	299	56	66	60	61	72	76	74	56	OK	60	62	68	66	Soluble decoy receptor
2133	70	87	54	70	161	44	41	29	38	86	93	89	57	TT	55	54	80	66	Soluble decoy receptor
2134	63	78	53	65	236	43	24	81	49	83	79	81	46	OK	40	57	73	65	Soluble decoy receptor
2135	84	94	47	75	83	41	19	40	33	84	88	86	57	OK	56	54	80	65	Soluble decoy receptor
2136	78	89	60	76	123	40	25	31	32	84	93	88	61	TT	46	54	82	65	Soluble decoy receptor
2137	79	85	47	70	148	54	39	31	41	78	86	82	53	OK	56	56	76	65	Soluble decoy receptor
2138	77	88	60	75	130	38	14	52	35	77	86	81	55	OK	49	55	78	64	Soluble decoy receptor
2139	49	68	54	57	383	61	53	36	50	82	87	85	56	OK	56	53	71	64	Soluble decoy receptor
2140	61	76	61	66	237	52	29	40	40	90	80	85	56	OK	58	53	75	64	Soluble decoy receptor
2141	62	79	59	67	228	62	63	40	55	67	72	70	53	OK	55	61	68	64	Soluble decoy receptor
2142	73	83	60	72	167	38	33	41	37	80	83	81	56	OK	48	55	77	64	Soluble decoy receptor
2143	74	89	60	74	154	43	27	28	33	78	88	83	61	TT	51	54	79	63	Soluble decoy receptor
2144	44	54	63	54	687	63	37	45	48	85	91	88	60	OK	68	51	71	63	Soluble decoy receptor
2145	76	89	44	70	121	54	57	45	52	72	61	67	44	OK	38	61	68	63	Soluble decoy receptor
2146	57	74	65	65	260	44	20	46	37	79	87	83	61	TT	49	51	74	62	Soluble decoy receptor
2147	73	79	65	72	187	55	26	21	34	78	84	81	62	TT	43	53	77	62	Soluble decoy receptor
2148	71	86	62	73	179	36	38	28	34	79	77	78	45	TT	58	54	76	62	Soluble decoy receptor
2149	77	90	61	76	123	25	6	39	23	84	92	88	55	TT	47	50	82	62	Soluble decoy receptor
2150	49	72	66	63	440	49	38	14	34	81	90	85	55	OK	57	48	74	61	Soluble decoy receptor
2151	92	96	41	76	36	42	30	41	38	73	65	69	44	TT	49	57	73	61	Soluble decoy receptor
2152	72	77	60	70	209	37	24	54	38	67	79	73	61	OK	50	54	71	60	Soluble decoy receptor
2153	66	85	61	71	193	27	9	28	21	84	92	88	57	TT	51	46	79	60	Soluble decoy receptor
2154	56	73	64	64	357	41	16	29	29	81	92	86	59	OK	67	47	75	60	Soluble decoy receptor
2155	61	79	61	67	180	51	43	3	32	75	88	81	63	TT	56	50	74	60	Soluble decoy receptor
2156	81	93	62	79	114	26	10	24	20	80	85	83	59	TT	44	49	81	60	Soluble decoy receptor
2157	70	86	65	74	176	38	21	28	29	78	78	78	47	TT	58	51	76	60	Soluble decoy receptor
2158	53	67	63	61	402	54	41	19	38	83	81	82	44	OK	49	50	71	60	Soluble decoy receptor
2159	65	80	65	70	266	22	1	44	22	83	94	88	65	TT	49	46	79	60	Soluble decoy receptor
2160	71	76	60	69	212	52	9	32	31	77	83	80	52	OK	61	50	74	60	Soluble decoy receptor
2161	63	79	65	69	222	34	24	25	28	82	86	83	57	OK	68	48	76	60	Soluble decoy receptor
2162	44	56	51	50	414	64	51	22	46	81	86	83	58	OK	50	48	67	60	Soluble decoy receptor
2163	61	74	65	67	263	24	16	35	25	84	89	87	57	TT	51	46	77	59	Soluble decoy receptor
2164	68	85	57	70	171	30	21	20	24	76	89	82	63	TT	33	47	76	59	Soluble decoy receptor
2165	56	63	59	59	332	46	25	44	38	76	74	75	48	OK	60	49	67	58	Soluble decoy receptor
2166	45	86	46	59	163	47	19	36	34	75	84	80	46	OK	56	47	69	58	Soluble decoy receptor
2167	51	80	53	61	222	35	17	32	28	86	77	81	66	TT	59	45	71	57	Soluble decoy receptor
2168	57	73	64	65	327	57	65	39	54	41	64	52	62	OK	53	59	59	57	Soluble decoy receptor

FIG. 37I

SEQ ID NO:	MIT	CFD	Elevation	CFF	Offtarget #	Azimuth	DeepSpCas9	CrispiScan	Ott	Lindel	inDelphi	Frameshift	Precision	Graf Motifs	Bioscore	OT_OFF	OFF_53	OTSA41	Interference predictions
2169	78	87	53	73	112	61	56	18	45	60	50	55	52	OK	41	59	64	57	Soluble decoy receptor
2170	36	70	39	49	309	59	57	14	43	74	76	75	45	OK	48	46	62	56	Soluble decoy receptor
2171	69	83	65	72	191	25	9	28	21	76	75	76	44	TT	43	47	74	56	Soluble decoy receptor
2172	37	48	61	49	618	39	5	34	26	84	89	86	51	OK	49	37	68	54	Soluble decoy receptor
2173	58	72	63	64	339	32	19	47	33	55	68	61	49	OK	61	48	63	53	Soluble decoy receptor
2174	68	80	64	71	307	44	15	24	28	46	73	59	70	OK	68	49	65	53	Soluble decoy receptor
2175	48	68	66	60	316	45	24	19	29	62	75	68	54	OK	56	45	64	53	Soluble decoy receptor
2176	44	88	51	61	131	44	33	8	28	54	56	55	57	OK	68	45	58	48	Soluble decoy receptor
2177	82	89	47	73	61	79	76	47	67	66	93	90	61	OK	0	70	81	76	Wildtype-like
2178	77	92	59	76	81	61	65	45	57	84	90	87	50	OK	0	67	82	73	Wildtype-like

FIG. 37J

SEQ ID NO:	Genomic cut coordinate	Exon	CDS cut position	CDS cut position %	Strand	Start coordinate	End coordinate	crRNA	GC content	PAM
2179	6334212	2	71	5.2	-	6334209	6334228	UUGGUGGGAAUAUACCCCUC	50	AGG
2180	6334211	2	72	5.3	-	6334208	6334227	UGGUGGGAAUAUACCCCUCA	50	GGG
2181	6334210	2	73	5.3	-	6334207	6334226	GGUGGGAAUAUACCCCUCAG	55	GGG
2182	6334209	2	74	5.4	+	6334192	6334211	CCAGUCCAAUAACCCCUGAG	55	GGG
2183	6334207	2	76	5.6	+	6334190	6334209	GACCAGUCCAAUAACCCCUG	55	AGG
2184	6334183	2	100	7.3	-	6334180	6334199	UGGACUGGUCCCUCACCUAG	60	GGG
2185	6334095	2	188	13.7	-	6334092	6334111	UGCUGUACCAAGUGCCACAA	50	AGG
2186	6333856	3	202	14.8	+	6333839	6333858	UGGACAGUCAUUGUACAAGU	40	AGG
2187	6333836	3	222	16.2	-	6333833	6333852	ACAAUGACUGUCCAGGCCCG	60	GGG
2188	6333817	3	241	17.6	-	6333814	6333833	GGGGCAGGAUACGGACUGCA	65	GGG
2189	6333742	3	316	23.1	-	6333739	6333758	CAGCUGCUCCAAAUGCCGAA	55	AGG
2190	6333486	4	352	25.7	-	6333483	6333502	GGAGAUCUCUUCUUGCACAG	50	TGG
2191	6333467	4	371	27.1	-	6333464	6333483	GUGGACCGGGACACCGUGUG	70	TGG
2192	6333386	4	452	33	+	6333369	6333388	AGAGGUGCACGGUCCCAUUG	60	AGG
2193	6333473	4	365	26.7	+	6333456	6333475	UGCAGCCACACACGGUGUCC	65	CGG
2194	6334208	2	75	5.5	+	6334191	6334210	ACCAGUCCAAUAACCCCUGA	50	GGG
2195	6333843	3	215	15.7	-	6333840	6333859	UACUUGUACAAUGACUGUCC	40	AGG
2196	6333465	4	373	27.3	+	6333448	6333467	GUUCUUCCUGCAGCCACACA	55	CGG
2197	6333741	3	317	23.2	-	6333738	6333757	AGCUGCUCCAAAUGCCGAAA	50	GGG
2198	6334185	2	98	7.2	+	6334168	6334187	UCUCCCUGUCCCCUAGGUGA	60	GGG
2199	6333831	3	227	16.6	+	6333814	6333833	UGCAGUCCGUAUCCUGCCCC	65	GGG
2200	6334185	2	98	7.2	-	6334182	6334201	AUUGGACUGGUCCCUCACCU	55	AGG
2201	6334149	2	134	9.8	-	6334146	6334165	AGAGAUAGUGUGUGUCCCCA	50	AGG
2202	6333790	3	268	19.6	+	6333773	6333792	GUGGUUUUCUGAAGCGGUGA	50	AGG
2203	6334227	2	56	4.1	-	6334224	6334243	GUGCUCCUGGAGCUGUUGGU	60	GGG
2204	6334184	2	99	7.2	-	6334181	6334200	UUGGACUGGUCCCUCACCUA	55	GGG
2205	6333804	3	254	18.6	-	6333801	6333820	GACUGCAGGGAGUGUGAGAG	60	CGG
2206	6334178	2	105	7.7	-	6334175	6334194	UGGUCCCUCACCUAGGGGAC	65	AGG
2207	6333830	3	228	16.7	+	6333813	6333832	CUGCAGUCCGUAUCCUGCCC	65	CGG
2208	6334124	2	159	11.6	+	6334107	6334126	CAGCAAAUCGAAUUAUUUUG	30	AGG
2209	6341803	1	11	0.8	+	6341786	6341805	GCAGGUCAGGCACGGUGGAG	70	AGG
2210	6333818	3	240	17.5	-	6333815	6333834	CGGGGCAGGAUACGGACUGC	70	AGG
2211	6333481	4	357	26.1	-	6333478	6333497	UCUCUUCUUGCACAGUGGAC	50	CGG
2212	6333838	3	220	16.1	-	6333835	6333854	GUACAAUGACUGUCCAGGCC	55	CGG
2213	6334184	2	99	7.2	+	6334167	6334186	UUCUCCCUGUCCCCUAGGUG	60	AGG
2214	6334145	2	138	10.1	+	6334128	6334147	GGGUGGAUAUAUUUUCCUUG	40	GGG
2215	6333410	4	428	31.3	+	6333393	6333412	AGAGGCUGCAAUUGAAGCAC	50	TGG
2216	6333437	4	401	29.3	+	6333420	6333439	GGUUUUCACUCCAAUAAUGC	40	CGG
2217	6334198	2	85	6.2	-	6334195	6334214	CCCCUCAGGGGUUAUUGGAC	60	TGG
2218	6333837	3	221	16.2	-	6333834	6333853	UACAAUGACUGUCCAGGCCC	55	GGG
2219	6334203	2	80	5.8	-	6334200	6334219	AUAUACCCCUCAGGGGUUAU	45	TGG
2220	6333445	4	393	28.7	-	6333442	6333461	GCUGCAGGAAGAACCAGUAC	55	CGG
2221	6333771	3	287	21	+	6333754	6333773	AGCUGAGGCAGUGUCUGAGG	60	TGG
2222	6334128	2	155	11.3	+	6334111	6334130	AAAUCGAAUUAUUUUGAGGG	30	TGG
2223	6334144	2	139	10.2	+	6334127	6334146	AGGGUGGAUAUAUUUUCCUU	35	GGG
2224	6334143	2	140	10.2	+	6334126	6334145	GAGGGUGGAUAUAUUUUCCU	40	TGG
2225	6333836	3	222	16.2	+	6333819	6333838	UCCGUAUCCUGCCCCGGGCC	75	TGG
2226	6334177	2	106	7.7	-	6334174	6334193	GGUCCCUCACCUAGGGGACA	65	GGG
2227	6333826	3	232	17	-	6333823	6333842	UCCAGGCCCGGGGCAGGAUA	70	CGG
2228	6333140	5	479	35	+	6333123	6333142	ACACGGUGUUCUGUUUCUCC	50	TGG

FIG. 38A

SEQ ID NO:	Genomic cut coordinate	Exon	CDS cut position	CDS cut position %	Strand	Start coordinate	End coordinate	crRNA	GC content	PAM
2229	6333832	3	226	16.5	-	6333829	6333848	UGACUGUCCAGGCCCGGGGC	75	AGG
2230	6341795	1	19	1.4	+	6341778	6341797	UGGCAGCAGCAGGUCAGGCA	65	CGG
2231	6333480	4	358	26.2	-	6333477	6333496	CUCUUCUUGCACAGUGGACC	55	GGG
2232	6333436	4	402	29.4	-	6333433	6333452	AGAACCAGUACCGGCAUUAU	45	TGG
2233	6333392	4	446	32.6	+	6333375	6333394	GCACGGUCCCAUUGAGGCAG	65	AGG
2234	6333443	4	395	28.9	+	6333426	6333445	CACUCCAAUAAUGCCGGUAC	50	TGG
2235	6334125	2	158	11.5	+	6334108	6334127	AGCAAAUCGAAUUAUUUUGA	25	GGG
2236	6333460	4	378	27.6	-	6333457	6333476	GGGACACCGUGUGUGGCUGC	70	AGG
2237	6333756	3	302	22.1	+	6333739	6333758	UUCGGCAUUUGGAGCAGCUG	55	AGG
2238	6333768	3	290	21.2	+	6333751	6333770	AGCAGCUGAGGCAGUGUCUG	60	AGG
2239	6334179	2	104	7.6	+	6334162	6334181	CUCUCUUCUCCCUGUCCCCU	60	AGG
2240	6341798	1	16	1.2	+	6341781	6341800	CAGCAGCAGGUCAGGCACGG	70	TGG
2241	6333416	4	422	30.8	+	6333399	6333418	UGCAAUUGAAGCACUGGAAA	40	AGG
2242	6334233	2	50	3.7	+	6334216	6334235	AUAUUCCCACCAACAGCUCC	50	AGG
2243	6333113	5	506	37	-	6333110	6333129	ACCGUGUGCACCUGCCAUGC	65	AGG
2244	6333114	5	505	36.9	+	6333097	6333116	UAGAAAGAAACCUGCAUGGC	45	AGG
2245	6333110	5	509	37.2	+	6333093	6333112	CUCUUAGAAAGAAACCUGCA	40	TGG
2246	6333123	5	496	36.3	+	6333106	6333125	ACCUGCAUGGCAGGUGCACA	60	CGG
2247	6330908	6	569	41.6	+	6330891	6330910	GGCACAACUUCGUGCACUCC	60	AGG
2248	6330628	7	708	51.8	-	6330625	6330644	GUUUAAUGUAUCGCUACCAA	35	CGG
2249	6330625	7	711	52	-	6330622	6330641	UAAUGUAUCGCUACCAACGG	45	TGG
2250	6330623	7	713	52.1	+	6330606	6330625	AGAGCUUGGACUUCCACCGU	55	TGG
2251	6330038	9	796	58.2	-	6330035	6330054	AGGAACUACUACUAAGCCCC	50	TGG
2252	6329930	9	904	66.1	+	6329913	6329932	AAAGUUGGGACAGUCACCGG	55	GGG
2253	6329929	9	905	66.2	+	6329912	6329931	CAAAGUUGGGACAGUCACCG	55	GGG
2254	6329916	9	918	67.1	+	6329899	6329918	CUGCGGGGAGCCGCAAAGUU	65	GGG
2255	6329915	9	919	67.2	-	6329912	6329931	CGGUGACUGUCCCAACUUUG	55	CGG
2256	6329901	9	933	68.2	+	6329884	6329903	GGUGGUGCCACCUCUCUGCG	70	GGG
2257	6329900	9	934	68.3	-	6329897	6329916	CUUUGCGGCUCCCCCGCAGAG	70	AGG
2258	6329883	9	951	69.5	+	6329866	6329885	GGGUCAGCCCCCUGAUAGGG	70	TGG
2259	6329880	9	954	69.7	-	6329877	6329896	AGGUGGCACCACCCUAUCAG	60	GGG
2260	6329879	9	955	69.8	-	6329876	6329895	GGUGGCACCACCCUAUCAGG	65	GGG
2261	6329609	10	1070	78.2	+	6329592	6329611	CCACGGCGUACAGCGUCGCG	75	GGG
2262	6329595	10	1084	79.2	-	6329592	6329611	CGCGACGCUGUACGCCGUGG	75	TGG
2263	6329592	10	1087	79.5	+	6329575	6329594	CGGGGGCACGUUCUCCACCA	70	CGG
2264	6329575	10	1104	80.7	+	6329558	6329577	AAUUCCUUCCAGCGCAACGG	55	GGG
2265	6329574	10	1105	80.8	+	6329557	6329576	GAAUUCCUUCCAGCGCAACG	55	GGG
2266	6329572	10	1107	80.9	+	6329555	6329574	ACGAAUUCCUUCCAGCGCAA	50	CGG
2267	6329568	10	1111	81.2	-	6329565	6329584	CGUGCCCCCGUUGCGCUGGA	75	AGG
2268	6329557	10	1122	82	-	6329554	6329573	UGCGCUGGAAGGAAUUCGUG	55	CGG
2269	6329524	10	1155	84.4	-	6329521	6329540	UGAGCGACCACGAGAUCGAU	55	CGG
2270	6329464	10	1215	88.8	-	6329461	6329480	AAUACAGCAUGCUGGCGACC	55	TGG
2271	6329461	10	1218	89	-	6329458	6329477	ACAGCAUGCUGGCGACCUGG	65	AGG
2272	6329440	10	1239	90.6	+	6329423	6329442	UCCAGCGUGGCCUCGCGCCG	80	CGG
2273	6329984	9	850	62.1	+	6329967	6329986	GGGCACGGGACUGAAGCCCA	70	GGG
2274	6329899	9	935	68.3	+	6329882	6329901	AGGGUGGUGCCACCUCUCUG	65	CGG
2275	6329863	9	971	71	+	6329846	6329865	CGAGGGCUGUCGCAAGGAUG	65	GGG
2276	6329881	9	953	69.7	-	6329878	6329897	GAGGUGGCACCACCCUAUCA	60	GGG
2277	6330602	7	734	53.7	-	6330599	6330618	AAGUCCAAGCUCUACUCCAU	45	TGG
2278	6330271	8	763	55.8	-	6330268	6330287	GAAAUCGACACCUGAAAAAG	40	AGG

FIG. 38B

SEQ ID NO:	Genomic cut coordinate	Exon	CDS cut position	CDS cut position %	Strand	Start coordinate	End coordinate	crRNA	GC content	PAM
2279	6329472	10	1207	88.2	-	6329469	6329488	CGAGGCGCAAUACAGCAUGC	60	TGG
2280	6329608	10	1071	78.3	+	6329591	6329610	ACCACGGCGUACAGCGUCGC	70	GGG
2281	6329607	10	1072	78.4	+	6329590	6329609	CACCACGGCGUACAGCGUCG	70	CGG
2282	6329490	10	1189	86.9	-	6329487	6329506	GAACGGGCGCUGCCUGCGCG	80	AGG
2283	6329862	9	972	71.1	+	6329845	6329864	GCGAGGGCUGUCGCAAGGAU	65	GGG
2284	6330609	7	727	53.1	+	6330592	6330611	CUCACCAAUGGAGUAGAGCU	50	TGG
2285	6329939	9	895	65.4	+	6329922	6329941	ACAGUCACCGGGGGUAUAGG	60	TGG
2286	6329821	9	1013	74	+	6329804	6329823	UGUCCUCCCACUUCUGAAGG	55	GGG
2287	6329935	9	899	65.7	-	6329932	6329951	UCCAGCUCCACCUAUACCCC	60	CGG
2288	6329813	9	1021	74.6	-	6329810	6329829	CAACCCCCUUCAGAAGUGGG	60	AGG
2289	6329548	10	1131	82.7	-	6329545	6329564	AGGAAUUCGUGCGGCGCCUA	60	GGG
2290	6329489	10	1190	87	+	6329472	6329491	UGCUGUAUUGCGCCUCGCGC	65	AGG
2291	6329390	10	1289	94.2	-	6329387	6329406	CUCCGCGACAUGGACCUGCU	65	GGG
2292	6329915	9	919	67.2	+	6329898	6329917	UCUGCGGGGAGCCGCAAAGU	65	TGG
2293	6329861	9	973	71.1	+	6329844	6329863	GGCGAGGGCUGUCGCAAGGA	70	TGG
2294	6329598	10	1081	79	-	6329595	6329614	CCCCGCGACGCUGUACGCCG	80	TGG
2295	6329572	10	1107	80.9	-	6329569	6329588	AGAACGUGCCCCCGUUGCGC	70	TGG
2296	6329795	9	1039	76	+	6329778	6329797	GUCUAGGCUCUGUGGCUUGU	55	GGG
2297	6329439	10	1240	90.6	-	6329436	6329455	GCGGCGCACGCCGCGGCGCG	95	AGG
2298	6329857	9	977	71.4	+	6329840	6329859	CGGAGGCGAGGGCUGUCGCA	75	AGG
2299	6329507	10	1172	85.7	-	6329504	6329523	GAUCGGCUGGAGCUGCAGAA	60	CGG
2300	6330033	9	801	58.6	+	6330016	6330035	AAGCUUGGGUUUGGGGCCAG	60	GGG
2301	6329543	10	1136	83	+	6329526	6329545	UCUCGUGGUCGCUCAGCCCU	65	AGG
2302	6329819	9	1015	74.2	+	6329802	6329821	GCUGUCCUCCCACUUCUGAA	55	GGG
2303	6329427	10	1252	91.5	+	6329410	6329429	GCGUCCCAGCAGCUCCAGCG	75	TGG
2304	6329506	10	1173	85.7	-	6329503	6329522	AUCGGCUGGAGCUGCAGAAC	60	GGG
2305	6329927	9	907	66.3	+	6329910	6329929	CGCAAAGUUGGGACAGUCAC	55	CGG
2306	6329794	9	1040	76	+	6329777	6329796	UGUCUAGGCUCUGUGGCUUG	55	TGG
2307	6329680	9	954	69.7	+	6329863	6329882	AUGGGGUCAGCCCCCUGAUA	60	GGG
2308	6329399	10	1280	93.6	+	6329382	6329401	AGCCCAGCAGGUCCAUGUCG	65	CGG
2309	6329528	10	1151	84.1	+	6329511	6329530	GCUCCAGCCGAUCGAUCUCG	65	TGG
2310	6329520	10	1159	84.7	-	6329517	6329536	CGACCACGAGAUCGAUCGGC	65	TGG
2311	6329936	9	898	65.6	+	6329919	6329938	GGGACAGUCACCGGGGGUAU	65	AGG
2312	6329370	10	1309	95.7	-	6329367	6329386	GGGCUGCCUGGAGGACAUCG	70	AGG
2313	6330019	9	815	59.6	+	6330002	6330021	CUGGAGUGGGACUGAAGCUU	55	GGG
2314	6329430	10	1249	91.3	-	6329427	6329446	GCCGCGGCGCGAGGCCACGC	90	TGG
2315	6329400	10	1279	93.5	-	6329397	6329416	GGGACGCGUGCUCCGCGACA	75	TGG
2316	6330654	7	682	49.9	+	6330637	6330656	CAUUAAACCAAUGAAGAGGA	35	GGG
2317	6329879	9	955	69.8	+	6329862	6329881	GAUGGGGUCAGCCCCCUGAU	65	AGG
2318	6329970	9	864	63.2	+	6329953	6329972	GUGAAGGUGGAACUGGGCAC	60	GGG
2319	6329820	9	1014	74.1	+	6329803	6329822	CUGUCCUCCCACUUCUGAAG	55	GGG
2320	6330650	7	686	50.1	+	6330633	6330652	GAUACAUUAAACCAAUGAAG	30	AGG
2321	6330653	7	683	49.9	+	6330636	6330655	ACAUUAAACCAAUGAAGAGG	35	AGG
2322	6329573	10	1106	80.8	+	6329556	6329575	CGAAUUCCUUCCAGCGCAAC	55	GGG
2323	6329988	9	846	61.8	+	6329971	6329990	ACGGGACUGAAGCCCAGGGU	65	GGG
2324	6329900	9	934	68.3	+	6329883	6329902	GGGUGGUGCCACCUCUCUGC	70	GGG
2325	6330026	9	808	59.1	+	6330009	6330028	GGGACUGAAGCUUGGGUUUG	55	GGG
2326	6329928	9	906	66.2	+	6329911	6329930	GCAAAGUUGGGACAGUCACC	55	GGG
2327	6330018	9	816	59.6	+	6330001	6330020	CCUGGAGUGGGACUGAAGCU	60	TGG
2328	6330006	9	828	60.5	+	6329989	6330008	GUGGGGGUGAAGCCUGGAGU	65	GGG

FIG. 38C

SEQ ID NO:	Genomic cut coordinate	Exon	CDS cut position	CDS cut position %	Strand	Start coordinate	End coordinate	crRNA	GC content	PAM
2329	6329379	10	1300	95	-	6329376	6329395	GGACCUGCUGGGCUGCCUGG	75	AGG
2330	6329420	10	1259	92	-	6329417	6329436	GAGGCCACGCUGGAGCUGCU	70	GGG
2331	6329446	10	1233	90.1	-	6329443	6329462	CCUGGAGGCGGCGCACGCCG	85	CGG
2332	6329987	9	847	61.9	+	6329970	6329989	CACGGGACUGAAGCCCAGGG	70	TGG
2333	6329983	9	851	62.2	+	6329966	6329985	UGGGCACGGGACUGAAGCCC	70	AGG
2334	6329897	9	937	68.5	-	6329894	6329913	UGCGGCUCCCCGCAGAGAGG	75	TGG
2335	6330024	9	810	59.2	+	6330007	6330026	GUGGGACUGAAGCUUGGGUU	55	TGG
2336	6329827	9	1007	73.6	+	6329810	6329829	CCCACUUCUGAAGGGGGUUG	60	GGG
2337	6329458	10	1221	89.3	-	6329455	6329474	GCAUGCUGGCGACCUGGAGG	70	CGG
2338	6329367	10	1312	95.9	-	6329364	6329383	CUGCCUGGAGGACAUCGAGG	65	AGG
2339	6329826	9	1008	73.7	+	6329809	6329828	UCCCACUUCUGAAGGGGGUU	55	GGG
2340	6329816	9	1018	74.4	-	6329813	6329832	CCCCAACCCCCUUCAGAAGU	60	GGG
2341	6329846	9	988	72.2	+	6329829	6329848	GGGGAUGGGGUCGGAGGCGA	75	GGG
2342	6329682	9	952	69.6	-	6329879	6329898	AGAGGUGGCACCACCCUAUC	60	AGG
2343	6329549	10	1130	82.6	-	6329546	6329565	AAGGAAUUCGUGCGGCGCCU	60	AGG
2344	6329825	9	1009	73.8	+	6329808	6329827	CUCCCACUUCUGAAGGGGGU	60	TGG
2345	6329818	9	1016	74.3	+	6329801	6329820	CGCUGUCCUCCCACUUCUGA	60	AGG
2346	6329989	9	845	61.8	+	6329972	6329991	CGGGACUGAAGCCCAGGGUG	70	GGG
2347	6330650	7	686	50.1	-	6330647	6330666	CUUUUAUCCCUCCUCUUCAU	40	TGG
2348	6329969	9	865	63.2	+	6329952	6329971	GGUGAAGGUGGAACUGGGCA	60	CGG
2349	6330025	9	809	59.1	+	6330008	6330027	UGGGACUGAAGCUUGGGUUU	50	GGG
2350	6330007	9	827	60.5	-	6330004	6330023	CCAAGCUUCAGUCCCACUCC	60	AGG
2351	6330662	7	674	49.3	+	6330645	6330664	CAAUGAAGAGGAGGGAUAAA	40	AGG
2352	6329387	10	1292	94.4	+	6329370	6329389	UGUCCUCCAGGCAGCCCAGC	70	AGG
2353	6329382	10	1297	94.8	-	6329379	6329398	CAUGGACCUGCUGGGCUGCC	70	TGG
2354	6329817	9	1017	74.3	-	6329814	6329833	UCCCCAACCCCCUUCAGAAG	60	TGG
2355	6329457	10	1222	89.3	+	6329440	6329459	CCGCGGCGUGCGCCGCCUCC	90	AGG
2356	6329945	9	889	65	+	6329928	6329947	ACCGGGGGUAUAGGUGGAGC	65	TGG
2357	6330000	9	834	61	+	6329983	6330002	CCCAGGGUGGGGGUGAAGCC	75	TGG
2358	6329990	9	844	61.7	-	6329987	6330006	UCCAGGCUUCACCCCCACCC	70	TGG
2359	6329391	10	1288	94.2	-	6329388	6329407	GCUCCGCGACAUGGACCUGC	70	TGG
2360	6330032	9	802	58.6	+	6330015	6330034	GAAGCUUGGGGUUUGGGGCCA	60	GGG
2361	6329989	9	845	61.8	-	6329986	6330005	CCAGGCUUCACCCCCACCCU	70	GGG
2362	6329375	10	1304	95.3	+	6329358	6329377	GCGCCUCCUCGAUGUCCUCC	70	AGG
2363	6329832	9	1002	73.2	+	6329815	6329834	UUCUGAAGGGGGUUGGGGAU	55	GGG
2364	6330031	9	803	58.7	+	6330014	6330033	UGAAGCUUGGGUUUGGGGCC	60	AGG
2365	6329845	9	989	72.3	+	6329828	6329847	UGGGGAUGGGGUCGGAGGCG	75	AGG
2366	6329840	9	994	72.7	+	6329823	6329842	GGGGUUGGGGAUGGGGUCGG	75	AGG
2367	6329831	9	1003	73.3	+	6329814	6329833	CUUCUGAAGGGGGUUGGGGA	60	TGG
2368	6329421	10	1258	92	-	6329418	6329437	CGAGGCCACGCUGGAGCUGC	75	TGG
2369	6329948	9	886	64.8	+	6329931	6329950	GGGGGUAUAGGUGGAGCUGG	65	AGG
2370	6330702	7	634	46.3	+	6330685	6330704	GACCAGGGGCAACAGCACUG	65	TGG
2371	6330864	6	613	44.8	-	6330861	6330880	UGAGAAUGUUAAGGGCACUG	45	AGG
2372	6330883	6	594	43.4	+	6330866	6330885	CCCUUAACAUUCUCAAUCUG	40	GGG
2373	6330857	6	620	45.3	-	6330854	6330873	GUUAAGGGCACUGAGGACUC	55	AGG
2374	6330687	7	649	47.4	+	6330670	6330689	AAGACCAAAGAAAAUGACCA	35	GGG
2375	6330872	6	605	44.2	-	6330869	6330888	CCCCAGAUUGAGAAUGUUAA	40	GGG
2376	6330688	7	648	47.4	+	6330671	6330690	AGACCAAAGAAAAUGACCAG	40	GGG
2377	6330887	6	590	43.1	+	6330870	6330889	UAACAUUCUCAAUCUGGGGU	40	AGG
2378	6330680	7	656	48	-	6330677	6330696	UUGCCCCUGGUCAUUUUCUU	45	TGG

FIG. 38D

SEQ ID NO:	Genomic cut coordinate	Exon	CDS cut position	CDS cut position %	Strand	Start coordinate	End coordinate	crRNA	GC content	PAM
2379	6330882	6	595	43.5	+	6330865	6330884	GCCCUUAACAUUCUCAAUCU	40	GGG
2380	6330873	6	604	44.2	-	6330870	6330889	ACCCCAGAUUGAGAAUGUUA	40	AGG
2381	6330693	7	643	47	-	6330690	6330709	CACCACAGUGCUGUUGCCCC	65	TGG
2382	6330686	7	650	47.5	+	6330669	6330688	AAAGACCAAAGAAAAUGACC	35	AGG
2383	6330881	6	596	43.6	+	6330864	6330883	UGCCCUUAACAUUCUCAAUC	40	TGG
2384	6329357	10	1322	96.6	-	6329354	6329373	GACAUCGAGGAGGCGCUUUG	60	CGG
2385	6329332	10	1347	98.5	+	6329315	6329334	CUGAGAAGACUGGGCGCGGG	70	CGG
2386	6329329	10	1350	98.7	+	6329312	6329331	CAUCUGAGAAGACUGGGCGC	60	GGG
2387	6329328	10	1351	98.8	+	6329311	6329330	UCAUCUGAGAAGACUGGGCG	55	CGG
2388	6329337	10	1342	98.1	+	6329320	6329339	AAGACUGGGCGCGGGCGGGA	75	GGG
2389	6329323	10	1356	99.1	+	6329306	6329325	CAGCCUCAUCUGAGAAGACU	50	GGG
2390	6329336	10	1343	98.2	+	6329319	6329338	GAAGACUGGGCGCGGGCGGG	80	AGG
2391	6329333	10	1346	98.4	+	6329316	6329335	UGAGAAGACUGGGCGCGGGC	70	GGG
2392	6329322	10	1357	99.2	+	6329305	6329324	GCAGCCUCAUCUGAGAAGAC	55	TGG
2393	6329345	10	1334	97.5	+	6329328	6329347	GCGCGGGCGGGAGGGCGGCG	95	GGG
2394	6329343	10	1336	97.7	+	6329326	6329345	GGGCGCGGGCGGGAGGGCGG	95	CGG
2395	6329344	10	1335	97.6	+	6329327	6329346	GGCGCGGGCGGGAGGGCGGC	95	GGG

FIG. 38E

SEQ ID NO:	MIT	CFD	Elevation	CCTF	Offtarget #	Azimuth	DeepSpCas9	CrisprScan	CCT	Lindel	inDelphi	Frameshift	Precision	Graf Motifs	Bioscore	CCT_CCTF	CCT_MIT	CCTFMIT	Interference predictions
2179	89	94	52	78	73	51	52	90	84	71	74	73	43	OK	47	71	75	72	Knockout
2180	82	91	81	78	117	53	54	55	54	74	80	77	43	OK	57	66	78	70	Knockout
2181	81	89	61	77	112	73	67	71	73	78	89	83	59	OK	57	74	80	77	Knockout
2182	76	91	52	74	102	74	73	56	66	86	91	86	63	OK	57	71	81	77	Knockout
2183	87	92	54	78	71	69	55	56	60	76	81	78	44	OK	49	69	78	72	Knockout
2184	86	90	51	76	105	69	52	54	58	79	78	78	45	OK	48	67	77	71	Knockout
2185	70	85	53	69	191	62	52	62	59	83	85	84	65	OK	74	64	77	71	Knockout
2186	86	91	80	79	100	64	64	55	61	73	70	71	58	OK	61	70	75	70	Knockout
2187	78	87	35	67	100	69	69	73	73	76	81	78	52	OK	47	68	72	72	Knockout
2188	80	88	40	69	128	62	71	79	71	85	87	86	67	OK	60	70	76	75	Knockout
2189	89	91	58	78	112	58	36	49	48	88	83	85	54	OK	61	64	82	71	Knockout
2190	72	86	60	73	132	72	62	45	60	85	92	88	66	OK	58	66	81	74	Knockout
2191	92	97	37	75	51	67	54	78	66	88	93	90	63	OK	62	71	83	77	Knockout
2192	88	94	47	76	70	62	57	65	61	78	88	83	56	OK	67	69	80	74	Knockout
2193	82	89	44	72	129	54	45	46	48	85	87	86	54	OK	63	60	79	69	Knockout
2194	86	91	54	77	88	57	42	44	48	77	80	81	44	OK	57	62	79	69	Knockout
2195	82	91	80	78	92	59	47	29	45	80	86	83	46	OK	56	61	80	69	Knockout
2196	51	79	42	57	412	61	57	55	58	92	94	93	60	OK	69	58	75	69	Knockout
2197	86	87	56	77	155	53	29	53	45	84	82	83	43	OK	61	61	80	68	Knockout
2198	77	80	49	69	239	53	68	45	55	79	80	79	51	OK	53	62	74	66	Knockout
2199	79	81	47	72	97	44	54	64	54	77	76	76	48	OK	43	63	74	68	Knockout
2200	83	92	48	74	73	52	49	37	46	75	89	82	65	OK	54	60	78	67	Knockout
2201	47	78	53	59	233	59	52	49	53	91	87	89	60	OK	61	56	74	67	Knockout
2202	84	89	53	75	142	56	46	46	49	72	83	78	55	OK	60	62	76	67	Knockout
2203	61	81	48	63	259	57	61	69	62	69	79	74	82	OK	57	63	69	67	Knockout
2204	80	94	51	75	86	46	58	86	57	68	73	70	45	OK	48	66	73	67	Knockout
2205	47	69	45	54	529	64	51	49	55	83	89	86	59	OK	54	54	70	65	Knockout
2206	85	88	47	68	135	47	35	54	45	79	85	82	56	OK	48	56	74	64	Knockout
2207	76	86	46	69	260	44	46	47	46	80	77	79	49	OK	45	57	74	64	Knockout
2208	67	80	62	70	153	46	8	44	33	85	91	88	61	TT	54	51	79	64	Knockout
2209	70	80	49	66	299	50	42	58	50	75	78	77	43	OK	51	58	71	64	Knockout
2210	89	95	38	74	66	46	42	43	44	66	78	72	49	OK	60	59	73	63	Knockout
2211	72	81	58	70	174	50	29	43	41	81	77	79	44	OK	63	56	75	63	Knockout
2212	66	82	49	66	156	54	42	39	45	77	77	77	49	GGC	50	55	71	63	Knockout
2213	72	84	49	68	235	49	44	42	45	74	76	75	46	OK	53	57	72	63	Knockout
2214	57	77	70	68	245	61	38	31	43	77	77	77	46	TT	61	56	72	63	Knockout
2215	70	79	58	69	211	53	62	37	51	66	67	66	43	OK	61	60	68	62	Knockout
2216	78	91	81	77	143	59	46	10	38	66	79	72	56	OK	66	57	75	62	Knockout
2217	87	91	54	77	68	46	31	14	30	77	78	77	45	OK	53	54	77	62	Knockout
2218	66	82	49	66	205	45	50	36	44	76	79	77	50	OK	50	55	72	62	Knockout
2219	90	93	50	78	62	32	21	27	27	80	87	83	56	TT	56	52	80	62	Knockout
2220	74	90	82	75	191	60	64	61	62	46	50	49	52	OK	65	68	62	62	Knockout
2221	45	60	46	50	581	61	56	66	62	72	70	71	44	OK	67	56	61	61	Knockout
2222	59	76	61	65	212	59	11	31	34	78	81	80	55	OK	53	50	72	60	Knockout
2223	48	71	66	61	270	37	30	62	43	75	74	74	48	TT	59	52	68	60	Knockout
2224	57	80	62	66	199	32	20	51	34	77	85	81	59	TT	58	50	74	60	Knockout
2225	78	86	37	68	129	37	13	44	31	79	83	81	52	GGC	44	49	74	60	Knockout
2226	67	71	42	60	402	65	41	35	47	77	72	74	58	OK	48	53	67	60	Knockout
2227	63	75	32	57	275	40	39	70	50	74	72	73	48	OK	52	53	65	60	Knockout
2228	60	82	59	67	160	47	38	15	33	82	75	79	50	OK	55	50	73	60	Knockout

FIG. 38F

SEQ ID NO:	MIT	CFD	Elevation	CFF	Offtarget #	Azimuth	DeepSpCas9	CrispRScan	CFF	Lindel	inDelphi	Frameshift	Precision	Graf Motifs	Bioscore	CFF_KO	CFF_KI	CFF_HDR	Edit for mature protein form
2229	67	84	38	63	243	48	25	44	39	76	82	79	54	OK	43	51	71	60	Knockout
2230	40	69	15	41	639	60	82	74	85	76	70	73	48	OK	55	53	57	60	Knockout
2231	73	85	60	73	252	50	28	25	34	72	75	74	46	OK	63	54	73	60	Knockout
2232	92	96	51	80	52	27	21	42	30	58	78	68	62	TT	62	55	74	59	Knockout
2233	72	87	42	67	108	48	56	58	54	70	48	58	60	OK	71	60	62	59	Knockout
2234	97	98	51	82	35	40	21	39	33	56	68	62	47	OK	68	58	72	59	Knockout
2235	57	73	65	65	251	37	11	25	24	79	88	83	58	OK	53	45	74	58	Knockout
2236	48	84	33	55	208	48	59	53	53	65	65	65	50	OK	65	54	60	58	Knockout
2237	54	79	49	61	232	59	51	60	57	58	54	56	52	OK	59	59	58	58	Knockout
2238	37	64	44	48	536	57	55	56	56	67	66	66	64	OK	65	52	57	57	Knockout
2239	36	51	39	43	774	50	30	34	38	86	87	86	55	OK	44	40	65	56	Knockout
2240	12	24	5	14	1521	63	60	74	66	85	94	89	62	OK	47	40	52	56	Knockout
2241	62	75	65	67	246	41	9	37	29	68	69	69	44	OK	65	48	68	55	Knockout
2242	60	80	53	64	260	54	53	16	41	54	48	50	50	OK	56	53	57	52	Knockout
2243	69	87	49	68	117	51	37	42	43	89	86	92	62	OK	61	56	80	68	Knockout or soluble decoy receptor
2244	52	77	61	63	372	50	57	45	51	89	95	92	67	OK	61	57	78	69	Knockout or soluble decoy receptor
2245	62	76	65	68	266	55	59	32	49	91	87	88	63	OK	60	58	76	68	Knockout or soluble decoy receptor
2246	62	81	48	64	242	58	44	53	52	78	67	72	57	OK	67	58	68	62	Knockout or soluble decoy receptor
2247	88	96	41	75	62	48	42	24	38	72	77	74	44	OK	43	56	75	62	Knockout or soluble decoy receptor
2248	91	95	48	76	54	68	51	54	58	80	73	76	48	OK	60	68	77	71	Membrane-bound receptor
2249	97	98	47	81	16	70	57	60	62	79	86	82	59	OK	53	71	82	75	Membrane-bound receptor
2250	91	94	54	80	79	61	61	50	57	76	80	78	45	OK	53	69	79	72	Membrane-bound receptor
2251	89	94	46	76	66	61	66	38	55	78	80	79	44	OK	41	66	78	70	Membrane-bound receptor
2252	86	91	46	75	97	73	72	69	78	71	70	70	45	OK	39	76	73	74	Membrane-bound receptor
2253	79	89	48	72	153	69	60	52	60	75	85	80	61	OK	39	66	76	71	Membrane-bound receptor
2254	90	97	41	76	110	37	39	65	54	76	82	79	55	OK	38	65	77	70	Membrane-bound receptor
2255	85	93	53	77	72	55	33	57	48	80	89	84	62	TT	32	63	81	70	Membrane-bound receptor
2256	74	87	49	70	143	65	65	51	60	87	86	87	63	OK	41	65	78	72	Membrane-bound receptor
2257	85	88	45	72	155	64	56	58	59	85	87	86	55	OK	40	66	79	72	Membrane-bound receptor
2258	85	89	49	74	133	53	61	58	57	79	86	82	53	OK	42	68	78	71	Membrane-bound receptor
2259	88	95	60	81	86	62	68	48	59	81	85	83	58	OK	44	70	82	74	Membrane-bound receptor
2260	90	93	53	78	79	67	66	62	66	73	80	76	46	OK	44	72	77	74	Membrane-bound receptor
2261	97	98	37	78	18	66	66	58	63	92	89	91	58	OK	46	70	84	77	Membrane-bound receptor
2262	89	58	40	79	13	58	54	79	64	72	70	71	41	OK	63	71	75	71	Membrane-bound receptor
2263	84	89	48	74	64	69	56	82	72	61	68	65	66	OK	60	73	69	70	Membrane-bound receptor
2264	97	97	40	78	37	67	72	49	63	69	84	76	61	OK	58	70	77	72	Membrane-bound receptor
2265	97	97	43	79	44	68	71	34	58	86	79	82	57	OK	65	69	81	73	Membrane-bound receptor
2266	89	95	58	81	43	56	31	52	46	82	83	83	44	OK	65	63	82	70	Membrane-bound receptor
2267	92	96	39	76	40	52	40	53	48	89	81	85	63	OK	63	62	80	70	Membrane-bound receptor
2268	88	91	57	79	90	67	66	66	66	75	77	76	46	OK	69	73	77	74	Membrane-bound receptor
2269	96	98	37	78	11	59	49	56	55	70	89	80	65	OK	63	66	79	71	Membrane-bound receptor
2270	90	94	57	80	69	52	54	29	45	80	90	85	54	OK	64	63	83	70	Membrane-bound receptor
2271	82	88	48	73	136	62	62	55	60	85	87	86	52	OK	69	66	80	73	Membrane-bound receptor
2272	90	94	41	75	76	48	57	62	56	82	85	84	58	OK	52	65	79	71	Membrane-bound receptor
2273	64	81	48	64	244	60	72	67	73	76	67	72	42	OK	38	69	68	70	Membrane-bound receptor
2274	61	78	49	63	259	60	58	61	60	84	94	89	65	OK	40	61	76	70	Membrane-bound receptor
2275	80	91	48	73	82	55	59	68	61	72	75	73	45	OK	53	67	73	69	Membrane-bound receptor
2276	86	95	45	75	89	52	45	44	47	81	88	84	55	OK	48	61	80	69	Membrane-bound receptor
2277	81	93	61	78	105	54	49	59	54	77	74	76	43	OK	58	66	77	69	Membrane-bound receptor
2278	74	82	62	73	181	57	58	42	52	82	81	82	57	OK	42	62	77	69	Membrane-bound receptor

FIG. 38G

SEQ ID NO:	MIT	CFD	Elevation	OOF	Offtarget #	Azimuth	DeepSpCas9	CrisprScan	DL	Lindel	inDelphi	Frameshift	Precision	Grat Motifs	Bioscore	OOF_577	OOF_43	2108411	Interference predictions
2279	94	86	45	76	26	55	56	18	43	85	89	87	58	OK	74	80	83	68	Membrane-bound receptor
2280	96	93	41	79	16	42	54	52	49	76	84	80	64	OK	47	84	79	68	Membrane-bound receptor
2281	97	87	38	77	24	62	53	54	56	70	74	72	54	OK	51	87	75	68	Membrane-bound receptor
2282	84	94	41	73	75	45	55	53	51	81	87	84	60	OK	66	82	79	68	Membrane-bound receptor
2283	92	86	47	76	42	40	48	60	56	73	75	74	41	OK	50	87	76	68	Membrane-bound receptor
2284	80	91	61	77	118	51	52	36	46	84	76	80	56	OK	62	82	79	66	Membrane-bound receptor
2285	92	95	47	78	53	52	56	51	53	69	79	74	65	OK	40	88	76	68	Membrane-bound receptor
2286	53	78	66	65	270	59	55	55	56	82	84	83	54	OK	38	80	74	68	Membrane-bound receptor
2287	70	84	61	72	297	62	68	42	57	74	75	76	43	OK	33	84	73	68	Membrane-bound receptor
2288	58	72	52	61	249	67	67	52	62	78	84	81	64	OK	46	81	71	68	Membrane-bound receptor
2289	97	86	40	78	25	55	31	62	56	70	62	66	46	OK	66	87	72	67	Membrane-bound receptor
2290	97	96	37	77	22	37	41	42	40	79	90	85	53	OK	67	59	81	67	Membrane-bound receptor
2291	89	95	36	73	49	52	35	59	49	82	74	78	66	OK	52	61	76	67	Membrane-bound receptor
2292	93	97	40	77	44	43	33	62	46	71	65	78	54	OK	32	81	77	67	Membrane-bound receptor
2293	85	94	45	75	120	39	51	58	49	74	80	77	53	OK	42	82	76	67	Membrane-bound receptor
2294	97	96	39	76	37	61	61	49	57	70	57	64	46	OK	56	87	71	66	Membrane-bound receptor
2295	96	97	37	77	28	44	52	20	39	80	83	82	45	OK	54	58	79	66	Membrane-bound receptor
2296	62	80	57	66	172	37	44	36	39	87	95	91	69	TT	34	53	79	66	Membrane-bound receptor
2297	54	83	42	60	288	45	29	69	48	88	92	90	60	OK	49	54	75	66	Membrane-bound receptor
2298	82	90	42	71	92	53	47	73	58	66	70	68	47	OK	35	85	70	66	Membrane-bound receptor
2299	53	80	42	58	211	60	58	45	54	87	83	85	55	OK	55	56	72	66	Membrane-bound receptor
2300	46	69	35	50	338	48	40	100	65	78	88	83	66	OK	38	58	66	66	Membrane-bound receptor
2301	82	92	36	70	84	48	49	60	52	80	70	75	44	OK	58	81	73	66	Membrane-bound receptor
2302	57	81	48	62	204	49	63	34	49	86	88	86	66	OK	41	55	75	66	Membrane-bound receptor
2303	35	84	47	55	240	69	68	54	64	85	72	79	55	OK	64	59	67	66	Membrane-bound receptor
2304	86	86	49	67	195	44	52	63	53	76	79	77	45	OK	54	80	72	66	Membrane-bound receptor
2305	84	93	53	77	80	41	18	56	38	74	84	79	59	OK	36	58	78	65	Membrane-bound receptor
2306	47	77	48	57	265	47	52	48	49	87	93	90	60	TT	35	53	74	65	Membrane-bound receptor
2307	88	92	51	77	87	42	33	64	46	70	75	72	40	OK	50	82	75	65	Membrane-bound receptor
2308	86	86	35	70	176	60	64	50	56	61	70	65	47	OK	56	64	68	65	Membrane-bound receptor
2309	96	93	37	76	17	63	60	36	53	81	65	63	54	OK	57	86	70	65	Membrane-bound receptor
2310	97	96	41	78	10	52	44	29	42	71	74	72	46	OK	61	80	75	64	Membrane-bound receptor
2311	91	95	47	78	66	42	31	67	47	82	74	68	47	OK	33	82	73	64	Membrane-bound receptor
2312	70	81	47	66	293	60	73	66	66	68	52	60	64	OK	59	66	63	64	Membrane-bound receptor
2313	47	77	38	54	319	44	65	69	59	79	76	78	43	TT	39	57	66	64	Membrane-bound receptor
2314	71	91	43	68	168	34	38	48	40	78	87	82	62	OK	55	54	75	64	Membrane-bound receptor
2315	93	95	39	76	40	47	56	51	51	69	62	66	39	OK	57	84	71	64	Membrane-bound receptor
2316	54	70	65	63	329	62	52	48	54	76	75	76	55	OK	57	59	69	64	Membrane-bound receptor
2317	50	87	48	62	537	46	32	66	48	78	86	82	63	OK	44	55	72	64	Membrane-bound receptor
2318	56	78	53	62	324	54	57	77	63	73	57	65	52	OK	37	62	64	63	Membrane-bound receptor
2319	61	78	52	64	250	52	50	46	49	74	75	75	43	OK	39	56	69	62	Membrane-bound receptor
2320	56	77	65	66	232	62	59	20	47	75	74	74	41	OK	52	57	70	62	Membrane-bound receptor
2321	53	64	58	58	521	55	60	41	52	75	75	75	47	OK	57	55	67	62	Membrane-bound receptor
2322	93	96	51	81	31	35	10	45	30	72	81	77	50	OK	66	56	79	62	Membrane-bound receptor
2323	54	77	48	60	217	50	43	90	61	67	59	63	47	OK	45	60	61	61	Membrane-bound receptor
2324	63	80	48	64	229	40	51	37	43	73	82	77	43	OK	40	53	70	61	Membrane-bound receptor
2325	53	77	61	64	309	46	43	42	44	79	72	76	64	TT	31	54	70	61	Membrane-bound receptor
2326	74	84	53	70	176	52	48	32	44	81	76	69	48	OK	39	57	70	61	Membrane-bound receptor
2327	56	80	41	59	317	46	49	36	44	79	81	80	54	OK	39	51	69	61	Membrane-bound receptor
2328	43	68	48	53	483	50	58	75	61	64	69	66	47	OK	36	57	60	60	Membrane-bound receptor

FIG. 38H

SEQ ID NO:	MIT	CFD	Elevation	GSF	Offtarget #	Azimuth	DeepSpCas9	CrisprScan	CSS	Lindel	InDelphi	Frameshift	Precision	Graf Motifs	Bioscore	GSF_CSS	Graf_Lin	Combined	Interference predictions
2329	39	59	49	49	540	63	63	54	60	73	71	72	48	OK	56	55	60	60	Membrane-bound receptor
2330	54	78	32	55	272	44	57	58	53	82	60	71	72	OK	57	54	63	60	Membrane-bound receptor
2331	79	87	39	68	198	43	56	70	57	67	42	58	64	OK	53	63	61	60	Membrane-bound receptor
2332	53	67	47	56	295	49	44	79	57	65	68	66	56	OK	47	57	61	60	Membrane-bound receptor
2333	52	73	38	54	336	36	57	65	53	77	71	74	40	OK	37	54	64	60	Membrane-bound receptor
2334	34	45	33	37	401	56	58	59	58	82	86	84	49	OK	44	47	61	60	Membrane-bound receptor
2335	65	83	51	68	224	23	46	68	46	77	61	69	52	OK	31	56	67	60	Membrane-bound receptor
2336	60	75	44	60	244	38	46	71	52	69	69	69	56	OK	40	56	64	60	Membrane-bound receptor
2337	58	80	38	59	222	46	57	53	52	68	71	69	49	OK	57	55	64	60	Membrane-bound receptor
2338	69	82	38	63	251	63	63	65	64	62	39	50	55	OK	53	63	57	59	Membrane-bound receptor
2339	73	84	53	70	173	24	28	31	28	77	80	78	55	OK	39	49	74	59	Membrane-bound receptor
2340	46	82	51	60	215	52	42	45	46	63	77	70	59	OK	39	53	65	59	Membrane-bound receptor
2341	42	49	34	42	1059	41	50	82	61	67	80	73	55	OK	29	51	57	59	Membrane-bound receptor
2342	46	89	37	57	122	28	9	71	36	77	90	84	63	OK	48	47	70	59	Membrane-bound receptor
2343	98	94	48	79	31	40	30	35	32	62	63	62	45	GGC	66	55	71	58	Membrane-bound receptor
2344	76	82	62	73	198	30	19	38	29	65	77	71	52	OK	32	51	72	58	Membrane-bound receptor
2345	71	84	61	72	158	31	23	24	26	78	76	77	46	OK	42	49	74	58	Membrane-bound receptor
2346	44	66	38	49	364	33	44	80	52	77	67	72	48	OK	45	51	61	58	Membrane-bound receptor
2347	58	73	64	65	271	33	10	39	27	71	84	78	56	OK	53	46	71	57	Membrane-bound receptor
2348	37	59	48	48	695	49	45	50	48	80	70	75	46	OK	32	48	61	57	Membrane-bound receptor
2349	54	77	55	62	297	24	45	59	43	79	54	66	60	TT	31	52	64	57	Membrane-bound receptor
2350	59	79	46	61	241	53	49	23	42	63	65	64	49	OK	30	52	63	56	Membrane-bound receptor
2351	44	60	66	56	522	28	36	43	36	73	82	78	63	OK	56	46	67	56	Membrane-bound receptor
2352	42	69	46	52	410	47	28	42	39	68	83	76	61	OK	65	46	64	56	Membrane-bound receptor
2353	49	68	37	51	375	34	40	63	46	74	67	70	65	GGC	56	48	61	56	Membrane-bound receptor
2354	67	82	42	64	243	52	52	32	45	59	58	59	49	OK	39	54	61	56	Membrane-bound receptor
2355	51	78	39	56	266	29	22	69	40	67	74	70	51	OK	57	48	63	55	Membrane-bound receptor
2356	74	84	60	73	103	42	56	48	49	51	37	44	49	OK	37	61	58	55	Membrane-bound receptor
2357	44	67	36	49	658	36	19	52	36	77	78	78	54	GGC	39	42	63	54	Membrane-bound receptor
2358	32	48	32	37	689	39	58	43	47	72	83	78	68	OK	45	42	57	54	Membrane-bound receptor
2359	81	91	42	71	86	32	37	19	29	66	57	61	46	OK	62	50	66	54	Membrane-bound receptor
2360	48	64	40	51	372	38	36	39	34	71	80	75	60	OK	24	42	63	53	Membrane-bound receptor
2361	36	60	34	44	682	47	42	43	44	68	63	66	48	OK	45	44	55	51	Membrane-bound receptor
2362	63	88	34	61	153	47	29	39	38	60	46	53	58	OK	59	50	57	51	Membrane-bound receptor
2363	44	65	43	51	422	33	8	63	35	71	59	65	52	OK	39	43	58	50	Membrane-bound receptor
2364	41	62	33	45	416	27	7	40	25	76	83	79	51	GGC	23	35	62	50	Membrane-bound receptor
2365	42	52	30	41	1168	28	9	65	34	68	75	71	46	OK	30	38	56	49	Membrane-bound receptor
2366	14	27	5	15	2736	40	21	96	52	73	66	80	57	OK	40	34	47	49	Membrane-bound receptor
2367	32	56	30	40	630	30	23	50	34	66	65	66	49	OK	29	37	53	47	Membrane-bound receptor
2368	49	69	38	52	302	25	34	34	31	64	43	54	60	OK	57	42	53	46	Membrane-bound receptor
2369	22	30	28	27	988	65	55	82	67	44	34	39	62	OK	37	47	38	44	Membrane-bound receptor
2370	58	78	43	60	273	75	77	44	65	86	94	81	60	OK	60	62	75	72	Soluble decoy receptor
2371	62	77	58	66	252	74	74	39	62	75	83	79	61	OK	39	64	72	69	Soluble decoy receptor
2372	57	81	55	64	188	61	50	51	54	81	84	82	60	OK	43	59	73	67	Soluble decoy receptor
2373	63	85	49	66	164	56	59	55	57	69	77	73	64	OK	42	61	69	65	Soluble decoy receptor
2374	28	62	59	50	770	67	63	29	53	72	87	79	57	OK	63	51	64	61	Soluble decoy receptor
2375	52	88	54	64	125	44	21	46	37	75	80	77	56	OK	44	51	71	60	Soluble decoy receptor
2376	28	69	35	44	733	71	57	51	60	73	74	74	40	OK	65	52	59	59	Soluble decoy receptor
2377	50	69	55	58	252	56	31	36	41	70	79	75	55	OK	47	50	66	58	Soluble decoy receptor
2378	57	76	57	63	233	28	5	45	26	76	89	83	60	TT	54	45	73	58	Soluble decoy receptor

FIG. 38I

SEQ ID NO:	MIT	CFD	Elevation	CRT	Offtarget #	Azimuth	DeepSpCas9	CrisprScan	CST	Lindel	inDelphi	Frameshift	Precision	Graf Motifs	Bioscore	CRT_CST	CRT_FS	CST_FS	Interference predictions
2379	69	80	53	71	120	42	34	23	33	56	79	69	80	OK	45	52	70	57	Soluble decoy receptor
2380	71	79	55	70	155	43	32	28	34	64	71	67	46	OK	44	52	69	57	Soluble decoy receptor
2381	40	85	35	53	233	45	61	36	47	72	57	64	45	OK	58	50	59	55	Soluble decoy receptor
2382	31	44	55	43	1013	55	58	12	42	76	78	77	40	OK	62	42	60	54	Soluble decoy receptor
2383	58	69	58	68	123	34	15	2	16	80	77	78	60	OK	44	42	73	54	Soluble decoy receptor
2384	90	95	43	76	44	56	30	44	43	69	96	85	66	TT	54	60	84	71	Wildtype-like
2385	78	90	38	69	208	50	46	91	62	72	94	63	69	OK	0	66	66	65	Wildtype-like
2386	94	90	49	74	122	56	54	39	50	75	66	70	49	OK	0	62	72	65	Wildtype-like
2387	66	80	40	62	199	53	43	43	46	86	75	81	43	OK	0	54	71	63	Wildtype-like
2388	50	74	29	51	214	50	36	60	55	77	85	81	57	OK	0	53	66	63	Wildtype-like
2389	67	85	46	66	188	47	46	48	47	74	69	71	44	OK	0	57	69	61	Wildtype-like
2390	50	79	32	54	297	39	32	78	49	75	85	80	60	OK	0	51	67	61	Wildtype-like
2391	78	83	37	66	170	46	44	49	46	75	64	68	58	OK	0	56	68	60	Wildtype-like
2392	47	82	41	57	578	45	46	28	40	79	73	76	58	OK	0	48	66	57	Wildtype-like
2393	14	35	19	23	1636	27	19	86	44	79	69	74	56	OK	34	33	46	47	Wildtype-like
2394	14	37	17	19	2762	10	23	69	41	76	82	79	56	OK	28	30	49	48	Wildtype-like
2395	16	41	12	23	1721	19	16	76	37	72	84	78	64	OK	35	30	50	46	Wildtype-like

FIG. 38J

SEQ ID NO:	Genomic cut coordinate	Exon	CDS cut position	CDS cut position %	Strand	Start coordinate	End coordinate	crRNA	GC content	PAM
2396	12167119	1	28	2	-	12167116	12167135	CUCCAGUCCGACGGCCAGCG	75	CGG
2397	12188813	2	96	6.9	-	12188810	12188829	CUCCCGGGCUCCGGGGCGUA	80	GGG
2398	12188814	2	97	7	+	12188797	12188816	GGCAUUUACACCCUACGCCC	60	CGG
2399	12188820	2	103	7.4	-	12188817	12188836	GCAUGUGCUCCCGGGCUCCG	75	GGG
2400	12188828	2	111	8	-	12188825	12188844	CUGAGCCGGCAUGUGCUCCC	70	GGG
2401	12188889	2	172	12.4	+	12188872	12188891	GUGCUGCAGCAAAUGCUCGC	60	CGG
2402	12190992	3	214	15.4	-	12190989	12191008	GGAGUCACACACGGUGUCCG	65	AGG
2403	12191001	3	223	16.1	-	12190998	12191017	GUCCUCACAGGAGUCACACA	55	CGG
2404	12191010	3	232	16.7	+	12190993	12191012	CACCGUGUGUGACUCCUGUG	60	AGG
2405	12191013	3	235	17	-	12191010	12191029	GGUGUAUGUGCUGUCCUCAC	55	AGG
2406	12191034	3	256	18.5	-	12191031	12191050	GGGAACCCAGUUCCAGAGCU	60	GGG
2407	12191797	4	331	23.9	+	12191780	12191799	GGAAACUCAAGCCUGCACUC	55	GGG
2408	12191797	4	331	23.9	-	12191794	12191813	GCGGUUCUGUUCCCGAGUGC	65	AGG
2409	12191854	4	388	28	+	12191837	12191856	GUACUGCGCGCUGAGCAAGC	65	AGG
2410	12191858	4	392	28.3	+	12191841	12191860	UGCGCGCUGAGCAAGCAGGA	65	GGG
2411	12191886	4	420	30.3	-	12191883	12191902	CCCGGGCGGCACUUGCGCAG	80	CGG
2412	12188834	2	117	8.4	+	12188817	12188836	CGGAGCCCGGGAGCACAUGC	75	CGG
2413	12190986	3	208	15	+	12190969	12190988	AGUCUUCUGUACCAAGACCU	45	CGG
2414	12188842	2	125	9	-	12188839	12188858	GGUCAUAGUAUUCUCUGAGC	45	CGG
2415	12188890	2	173	12.5	+	12188873	12188892	UGCUGCAGCAAAUGCUCGCC	60	GGG
2416	12190986	3	208	15	-	12190983	12191002	ACACACGGUGUCCGAGGUCU	60	TGG
2417	12167137	1	46	3.3	+	12167120	12167139	GGCCGUCGGACUGGAGCUCU	70	GGG
2418	12191055	3	277	20	-	12191052	12191071	GGAGCCACAGCUCAAGCACU	60	CGG
2419	12191857	4	391	28.2	+	12191840	12191859	CUGCGCGCUGAGCAAGCAGG	70	AGG
2420	12167143	1	52	3.8	+	12167126	12167145	CGGACUGGAGCUCUGGGCUG	70	CGG
2421	12191796	4	330	23.8	+	12191779	12191798	UGGAAACUCAAGCCUGCACU	50	CGG
2422	12191062	3	284	20.5	+	12191045	12191064	GUUCCCGAGUGCUUGAGCUG	60	TGG
2423	12188822	2	105	7.6	+	12188805	12188824	CACCCUACGCCCCGGAGCCC	80	GGG
2424	12191035	3	257	18.5	-	12191032	12191051	CGGGAACCCAGUUCCAGAGC	65	TGG
2425	12188863	2	146	10.5	-	12188860	12188879	UGCAGCACAUCUGAGCUGUC	55	TGG
2426	12191033	3	255	18.4	+	12191016	12191035	ACAGCACAUACACCCAGCUC	55	TGG
2427	12191835	4	369	26.6	-	12191832	12191851	CUCAGCGCGCAGUACCAGCC	70	GGG
2428	12188821	2	104	7.5	+	12188804	12188823	ACACCCUACGCCCCGGAGCC	75	CGG
2429	12167128	1	37	2.7	-	12167125	12167144	AGCCCAGAGCUCCAGUCCGA	65	CGG
2430	12188822	2	105	7.6	-	12188819	12188838	CGGCAUGUGCUCCCGGGCUC	75	CGG
2431	12191859	4	393	28.4	+	12191842	12191861	GCGCGCUGAGCAAGCAGGAG	70	GGG
2432	12191040	3	262	18.9	+	12191023	12191042	AUACACCCAGCUCUGGAACU	50	GGG
2433	12190963	3	185	13.3	-	12190960	12190979	UACAGAAGACUUUUGCAUGU	35	TGG
2434	12167164	1	73	5.3	+	12167147	12167166	GGCGCACGCCUUGCCCGCCC	85	AGG
2435	12188829	2	112	8.1	-	12188826	12188845	UCUGAGCCGGCAUGUGCUCC	65	CGG
2436	12191780	4	314	22.7	-	12191777	12191796	UGCAGGCUUGAGUUUCCACC	55	TGG
2437	12191836	4	370	26.7	-	12191833	12191852	GCUCAGCGCGCAGUACCAGC	70	CGG
2438	12191080	3	302	21.8	+	12191063	12191082	UGUGGCUCCCGCUGUAGCUC	65	TGG
2439	12167123	1	32	2.3	+	12167106	12167125	GUCUGGGCCGCGCUGGCCGU	80	CGG
2440	12167136	1	45	3.2	+	12167119	12167138	UGGCCGUCGGACUGGAGCUC	70	TGG
2441	12191832	4	366	26.4	+	12191815	12191834	UCUGCACCUGCAGGCCCGGC	75	TGG
2442	12188814	2	97	7	-	12188811	12188830	GCUCCCGGGCUCCGGGGCGU	85	AGG
2443	12188821	2	104	7.5	-	12188818	12188837	GGCAUGUGCUCCCGGGCUCC	75	GGG
2444	12167103	1	12	0.9	-	12167100	12167119	AGCGCGGCCCAGACGGCGAC	80	GGG
2445	12191873	4	407	29.4	-	12191870	12191889	UGCGCAGCGGCGCGCACAGC	80	CGG

FIG. 39A

SEQ ID NO:	Genomic cut coordinate	Exon	CDS cut position	CDS cut position %	Strand	Start coordinate	End coordinate	crRNA	GC content	PAM
2446	12167128	1	37	2.7	+	12167111	12167130	GGCCGCGCUGGCCGUCGGAC	85	TGG
2447	12167104	1	13	0.9	-	12167101	12167120	CAGCGCGGCCCAGACGGCGA	80	CGG
2448	12167110	1	19	1.4	-	12167107	12167126	GACGGCCAGCGCGGCCCAGA	80	CGG
2449	12191865	4	399	28.8	+	12191848	12191867	UGAGCAAGCAGGAGGGGUGC	65	CGG
2450	12191816	4	350	25.3	-	12191813	12191832	CGGGCCUGCAGGUGCAGAUG	70	CGG
2451	12191827	4	361	26	-	12191824	12191843	GCAGUACCAGCCGGGCCUGC	75	AGG
2452	12191823	4	357	25.8	+	12191806	12191825	AGAACCGCAUCUGCACCUGC	60	AGG
2453	12191828	4	362	26.1	+	12191811	12191830	CGCAUCUGCACCUGCAGGCC	70	CGG
2454	12167116	1	25	1.8	+	12167099	12167118	CGUCGCCGUCUGGGCCGCGC	85	TGG
2455	12191039	3	261	18.8	+	12191022	12191041	CAUACACCCAGCUCUGGAAC	55	TGG
2456	12191897	4	431	31.1	+	12191880	12191899	CCGCUGCGCAAGUGCCGCCC	80	GGG
2457	12191900	4	434	31.3	-	12191897	12191916	UGGCCACGCCGAAGCCCGGG	80	CGG
2458	12192445	5	472	34.1	+	12192428	12192447	AGGAACUGAAACAUCAGACG	45	TGG
2459	12192465	5	492	35.5	-	12192462	12192481	GAGAACGUCCCCGGGGCACA	70	GGG
2460	12192468	5	495	35.7	+	12192451	12192470	UGUGCAAGCCCUGUGCCCCG	70	GGG
2461	12192472	5	499	36	-	12192469	12192488	CGUGUUGGAGAACGUCCCCG	65	GGG
2462	12192474	5	501	36.1	-	12192471	12192490	GUCGUGUUGGAGAACGUCCC	60	CGG
2463	12192496	5	523	37.7	+	12192479	12192498	CUCCAACACGACUUCAUCCA	50	CGG
2464	12192502	5	529	38.2	-	12192499	12192518	GUGGGGCCUGCAAAUAUCCG	60	TGG
2465	12192881	6	570	41.1	+	12192864	12192883	GUAACGUGGUGGCCAUCCCU	60	GGG
2466	12192886	6	575	41.5	-	12192883	12192902	CAUCCAUGCUUGCAUUCCCA	50	GGG
2467	12192880	6	569	41.1	+	12192863	12192882	UGUAACGUGGUGGCCAUCCC	60	TGG
2468	12191918	4	452	32.6	+	12191901	12191920	GGCUUCGGCGUGGCCAGACC	75	AGG
2469	12192473	5	500	36.1	-	12192470	12192489	UCGUGUUGGAGAACGUCCCC	60	GGG
2470	12192894	6	583	42.1	+	12192877	12192896	CAUCCCUGGGAAUGCAAGCA	55	TGG
2471	12191903	4	437	31.5	-	12191900	12191919	GUCUGGCCACGCCGAAGCCC	75	GGG
2472	12191904	4	438	31.6	-	12191901	12191920	GGUCUGGCCACGCCGAAGCC	75	CGG
2473	12192466	5	493	35.6	-	12192463	12192482	GGAGAACGUCCCCGGGGCAC	75	AGG
2474	12192882	6	571	41.2	-	12192879	12192898	CAUGCUUGCAUUCCCAGGGA	55	TGG
2475	12192467	5	494	35.6	+	12192450	12192469	GUGUGCAAGCCCUGUGCCCC	70	GGG
2476	12192487	5	514	37.1	-	12192484	12192503	AUCCGUGGAUGAAGUCGUGU	50	TGG
2477	12192887	6	576	41.6	-	12192884	12192903	GCAUCCAUGCUUGCAUUCCC	55	AGG
2478	12191908	4	442	31.9	+	12191891	12191910	GUGCCGCCCGGGCUUCGGCG	85	TGG
2479	12192507	5	534	38.5	+	12192490	12192509	CUUCAUCCACGGAUAUUUGC	45	AGG
2480	12192466	5	493	35.6	+	12192449	12192468	GGUGUGCAAGCCCUGUGCCC	70	CGG
2481	12191903	4	437	31.5	+	12191886	12191905	CGCAAGUGCCGCCCGGGCUU	75	CGG
2482	12191896	4	430	31	+	12191879	12191898	GCCGCUGCGCAAGUGCCGCC	80	CGG
2483	12194020	7	853	61.5	+	12194003	12194022	GAACUGUGUCAUCAUGACCC	50	AGG
2484	12201989	9	923	66.6	+	12201972	12201991	UUGCCUGCCGAUAAGGCCCG	65	GGG
2485	12201997	9	931	67.2	+	12201980	12201999	CGAUAAGGCCCGGGGUACAC	65	AGG
2486	12201998	9	932	67.2	+	12201981	12202000	GAUAAGGCCCGGGGUACACA	60	GGG
2487	12202098	9	1032	74.5	-	12202095	12202114	GCCUGUGGCUGGUUCCGAGU	65	GGG
2488	12202099	9	1033	74.5	-	12202096	12202115	UGCCUGUGGCUGGUUCCGAG	65	TGG
2489	12206769	10	1135	81.9	-	12206766	12206785	GAUGCAGGUGACAUUGACCU	50	GGG
2490	12206784	10	1150	83	-	12206781	12206800	GCUACAGACGUUCACGAUGC	55	AGG
2491	12206844	10	1210	87.3	+	12206827	12206846	CUCCCAAGCCAGCUCCACAA	60	TGG
2492	12206872	10	1238	89.3	-	12206869	12206888	CGUCCUUCGGGGACUCCGAG	70	GGG
2493	12206883	10	1249	90.1	-	12206880	12206899	GGGGACCUGCUCGUCCUUCG	70	GGG
2494	12206907	10	1273	91.8	+	12206890	12206909	GCAGGUCCCCUUCUCCAAGG	65	AGG
2495	12202108	9	1042	75.2	+	12202091	12202110	GCCCACUCGGAACCAGCCAC	70	AGG

FIG. 39B

SEQ ID NO:	Genomic cut coordinate	Exon	CDS cut position	CDS cut position %	Strand	Start coordinate	End coordinate	crRNA	GC content	PAM
2496	12202095	9	1029	74.2	+	12202078	12202097	UGGACAGAAGGGCGCCCACU	65	CGG
2497	12201972	9	906	65.4	-	12201969	12201988	GCCUUAUCGGCAGGCAAGUG	60	AGG
2498	12206847	10	1213	87.5	-	12206844	12206863	GGAAUCUGUGUCUCCCAUUG	50	TGG
2499	12194594	8	876	63.2	-	12194591	12194610	GCUUCUCUCUGCAGGCACAA	55	GGG
2500	12202084	9	1018	73.4	+	12202067	12202086	GGCCAGUGCGUUGGACAGAA	60	GGG
2501	12206874	10	1240	89.5	-	12206871	12206890	CUCGUCCUUCGGGGACUCCG	70	AGG
2502	12201987	9	921	66.5	+	12201970	12201989	ACUUGCCUGCCGAUAAGGCC	60	CGG
2503	12202115	9	1049	75.7	+	12202098	12202117	CGGAACCAGCCACAGGCACC	70	AGG
2504	12202132	9	1066	76.9	+	12202115	12202134	ACCAGGCGUGGAGGCCAGUG	70	GGG
2505	12206873	10	1239	89.4	-	12206870	12206889	UCGUCCUUCGGGGACUCCGA	65	GGG
2506	12206761	10	1127	81.3	-	12206758	12206777	UGACAUUGACCUGGGUCCCA	55	TGG
2507	12202060	9	994	71.7	-	12202057	12202076	CGCACUGGCCGAGCUCUCCA	70	GGG
2508	12201981	9	915	66	-	12201978	12201997	GUACCCCGGGCCUUAUCGGC	70	AGG
2509	12194613	8	895	64.6	+	12194596	12194615	CCUGCAGAGAGAAGCCAAGG	60	TGG
2510	12194610	8	892	64.4	+	12194593	12194612	GUGCCUGCAGAGAGAAGCCA	60	AGG
2511	12201988	9	922	66.5	+	12201971	12201990	CUUGCCUGCCGAUAAGGCCC	65	GGG
2512	12206832	10	1198	86.4	-	12206829	12206848	CAUUGUGGAGCUGGCUUGGG	60	AGG
2513	12201994	9	928	67	-	12201991	12202010	CUCGGGGCCCUGUGUACCCC	75	GGG
2514	12202083	9	1017	73.4	+	12202066	12202085	CGGCCAGUGCGUUGGACAGA	65	AGG
2515	12202123	9	1057	76.3	+	12202106	12202125	GCCACAGGCACCAGGCGUGG	75	AGG
2516	12202075	9	1009	72.8	-	12202072	12202091	CGCCCUUCUGUCCAACGCAC	65	TGG
2517	12206880	10	1246	89.9	+	12206863	12206882	CAGCCCCUCGGAGUCCCCGA	75	AGG
2518	12202010	9	944	68.1	-	12202007	12202026	UCAGCAGGUGCUGCUGCUCG	65	GGG
2519	12201995	9	929	67	-	12201992	12202011	GCUCGGGGCCCUGUGUACCC	75	CGG
2520	12202075	9	1009	72.8	+	12202058	12202077	GGAGAGCUCGGCCAGUGCGU	70	TGG
2521	12202025	9	959	69.2	-	12202022	12202041	AGCUCGGCGCUGUGAUCAGC	65	AGG
2522	12193996	7	829	59.8	+	12193979	12193998	GGGUCUACUAAUAAUAGGAG	40	TGG
2523	12201985	9	919	66.3	-	12201982	12202001	CUGUGUACCCCGGGCCUUAU	60	CGG
2524	12206815	10	1181	85.2	-	12206812	12206831	GGGAGGAGCACUGUGAGCUG	65	TGG
2525	12206910	10	1276	92.1	-	12206907	12206926	CCGAAAGGCACAUUCCUCCU	55	TGG
2526	12206885	10	1251	90.3	-	12206882	12206901	AAGGGGACCUGCUCGUCCUU	60	CGG
2527	12206868	10	1234	89	+	12206851	12206870	AGACACAGAUUCCAGCCCCU	55	CGG
2528	12206904	10	1270	91.6	+	12206887	12206906	CGAGCAGGUCCCCUUCUCCA	65	AGG
2529	12206845	10	1211	87.4	+	12206828	12206847	UCCCAAGCCAGCUCCACAAU	55	GGG
2530	12206751	10	1117	80.6	-	12206748	12206767	CUGGGUCCCAUGGCCACCAG	70	GGG
2531	12201982	9	916	66.1	+	12201965	12201984	GCCUCACUUGCCUGCCGAUA	60	AGG
2532	12194595	8	877	63.3	-	12194592	12194611	GGCUUCUCUCUGCAGGCACA	60	AGG
2533	12202120	9	1054	76	+	12202103	12202122	CCAGCCACAGGCACCAGGCG	75	TGG
2534	12202158	9	1092	78.8	+	12202141	12202160	GGGAGGCCCGGGCCAGCACC	85	GGG
2535	12193991	7	824	59.5	+	12193974	12193993	GCCUUGGGUCUACUAAUAAU	40	AGG
2536	12206770	10	1136	82	-	12206767	12206786	CGAUGCAGGUGACAUUGACC	55	TGG
2537	12202113	9	1047	75.5	-	12202110	12202129	GCCUCCACGCCUGGUGCCUG	75	TGG
2538	12206903	10	1269	91.6	-	12206900	12206919	GCACAUUCCUCCUUGGAGAA	50	GGG
2539	12206889	10	1255	90.5	+	12206872	12206891	GGAGUCCCCGAAGGACGAGC	70	AGG
2540	12194602	8	884	63.8	-	12194599	12194618	CCACCUUGGCUUCUCUCUGC	60	AGG
2541	12206884	10	1250	90.2	-	12206881	12206900	AGGGGACCUGCUCGUCCUUC	65	GGG
2542	12206835	10	1201	86.7	-	12206832	12206851	UCCCAUUGUGGAGCUGGCUU	55	GGG
2543	12202153	9	1087	78.4	-	12202150	12202169	UGAGCUCCCGGUGCUGGCCC	75	GGG
2544	12202157	9	1091	78.7	+	12202140	12202159	GGGGAGGCCCGGGCCAGCAC	85	CGG
2545	12202061	9	995	71.8	-	12202058	12202077	ACGCACUGGCCGAGCUCUCC	70	AGG

FIG. 39C

SEQ ID NO:	Genomic cut coordinate	Exon	CDS cut position	CDS cut position %	Strand	Start coordinate	End coordinate	crRNA	GC content	PAM
2546	12202109	9	1043	75.3	-	12202106	12202125	CCACGCCUGGUGCCUGUGGC	75	TGG
2547	12206756	10	1122	81	+	12206739	12206758	AUUCUUCCCCUGGUGGCCAU	55	GGG
2548	12202166	9	1100	79.4	+	12202149	12202168	CGGGCCAGCACCGGGAGCUC	80	AGG
2549	12202154	9	1088	78.5	-	12202151	12202170	CUGAGCUCCCGGUGCUGGCC	75	CGG
2550	12202054	9	988	71.3	+	12202037	12202056	GAGCUCCAGCAGCAGCUCCC	70	TGG
2551	12202131	9	1065	76.8	+	12202114	12202133	CACCAGGCGUGGAGGCCAGU	70	GGG
2552	12206752	10	1118	80.7	-	12206749	12206768	CCUGGGUCCCAUGGCCACCA	70	GGG
2553	12202012	9	946	68.3	-	12202009	12202028	GAUCAGCAGGUGCUGCUGCU	60	CGG
2554	12206904	10	1270	91.6	-	12206901	12206920	GGCACAUUCCUCCUUGGAGA	55	AGG
2555	12206763	10	1129	81.5	+	12206746	12206765	CCCUGGUGGCCAUGGGACCC	75	AGG
2556	12202122	9	1056	76.2	-	12202119	12202138	GCCCCACUGGCCUCCACGCC	80	TGG
2557	12206836	10	1202	86.7	-	12206833	12206852	CUCCCAUUGUGGAGCUGGCU	60	TGG
2558	12206868	10	1234	89	-	12206865	12206884	CUUCGGGGACUCCGAGGGGC	75	TGG
2559	12202041	9	975	70.3	-	12202038	12202057	AGGGAGCUGCUGCUGGAGCU	65	CGG
2560	12206755	10	1121	80.9	+	12206738	12206757	GAUUCUUCCCCUGGUGGCCA	60	TGG
2561	12202063	9	997	71.9	+	12202046	12202065	CAGCAGCUCCCCUGGAGAGCU	65	CGG
2562	12206753	10	1119	80.7	-	12206750	12206769	ACCUGGGUCCCAUGGCCACC	70	AGG
2563	12206841	10	1207	87.1	-	12206838	12206857	UGUGUCUCCCAUUGUGGAGC	55	TGG
2564	12206902	10	1268	91.5	-	12206899	12206918	CACAUUCCUCCUUGGAGAAG	50	GGG
2565	12202144	9	1078	77.8	-	12202141	12202160	GGUGCUGGCCCGGGCCUCCC	85	CGG
2566	12202137	9	1071	77.3	+	12202120	12202139	GCGUGGAGGCCAGUGGGGCC	80	GGG
2567	12202138	9	1072	77.3	+	12202121	12202140	CGUGGAGGCCAGUGGGGCCG	80	GGG
2568	12202147	9	1081	78	+	12202130	12202149	CAGUGGGGCCGGGGAGGCCC	85	GGG
2569	12202011	9	945	68.2	-	12202008	12202027	AUCAGCAGGUGCUGCUGCUC	60	GGG
2570	12202146	9	1080	77.9	+	12202129	12202148	CCAGUGGGGCCGGGGAGGCC	85	CGG
2571	12202135	9	1069	77.1	-	12202132	12202151	CCGGGCCUCCCCCGGCCCCAC	90	TGG
2572	12202136	9	1070	77.2	+	12202119	12202138	GGCGUGGAGGCCAGUGGGGC	80	CGG
2573	12202141	9	1075	77.6	+	12202124	12202143	GGAGGCCAGUGGGGCCGGGG	85	AGG
2574	12202048	9	982	70.9	-	12202045	12202064	GCUCUCCAGGGAGCUGCUGC	70	TGG
2575	12192928	6	617	44.5	-	12192925	12192944	CUGGGGCCAUACUCCGGGUG	70	GGG
2576	12192929	6	618	44.6	-	12192926	12192945	CCUGGGGCCAUACUCCGGGU	70	GGG
2577	12192941	6	630	45.5	+	12192924	12192943	CCACCCGGAGUAUGGCCCCA	70	GGG
2578	12192942	6	631	45.5	+	12192925	12192944	CACCCGGAGUAUGGCCCCAG	70	GGG
2579	12192971	6	660	47.6	-	12192968	12192987	UGUUGGGAUCGUGUGGACAC	55	TGG
2580	12192978	6	667	48.1	-	12192975	12192994	CUGCGUGUGUUGGGAUCGUG	60	TGG
2581	12192987	6	676	48.8	-	12192984	12193003	UGGAGUUGGCUGCGUGUGUU	55	GGG
2582	12193060	6	749	54	-	12193057	12193076	CAGUGCUCCCUUCAGCUGGG	65	GGG
2583	12193976	7	809	58.4	+	12193959	12193978	AUUGUGGGUGUGACAGCCUU	50	GGG
2584	12192965	6	654	47.2	-	12192962	12192981	GAUCGUGUGGACACUGGCUG	60	GGG
2585	12192927	6	616	44.4	-	12192924	12192943	UGGGGCCAUACUCCGGGUGG	70	GGG
2586	12193032	6	721	52	-	12193029	12193048	GCCCAUUGGGAGCAGGAAGG	65	AGG
2587	12192930	6	619	44.7	-	12192927	12192946	CCCUGGGGCCAUACUCCGGG	75	TGG
2588	12192933	6	622	44.9	+	12192916	12192935	CACGUCCCCCACCCGGAGUA	70	TGG
2589	12192934	6	623	44.9	-	12192931	12192950	CUGCCCCUGGGGCCAUACUC	70	CGG
2590	12192946	6	635	45.8	-	12192943	12192962	GGGGUAAGUGUACUGCCCCU	60	GGG
2591	12192966	6	655	47.3	-	12192963	12192982	GGAUCGUGUGGACACUGGCU	60	GGG
2592	12192988	6	677	48.8	-	12192985	12193004	CUGGAGUUGGCUGCGUGUGU	60	TGG
2593	12192926	6	615	44.4	+	12192909	12192928	GCACGUCCACGUCCCCCACC	75	CGG
2594	12192945	6	634	45.7	-	12192942	12192961	GGGUAAGUGUACUGCCCCUG	60	GGG
2595	12192940	6	629	45.4	+	12192923	12192942	CCCACCCGGAGUAUGGCCCC	75	AGG

FIG. 39D

SEQ ID NO:	Genomic cut coordinate	Exon	CDS cut position	CDS cut position %	Strand	Start coordinate	End coordinate	crRNA	GC content	PAM
2596	12193035	6	724	52.2	-	12193032	12193051	GGGGCCCAUUGGGAGCAGGA	70	AGG
2597	12192933	6	622	44.9	-	12192930	12192949	UGCCCCUGGGGCCAUACUCC	70	GGG
2598	12193093	6	782	56.4	+	12193076	12193095	GGCGACUUCGCUCUUCCAGU	60	TGG
2599	12193013	6	702	50.6	-	12193010	12193029	GAGGUGCUUGGAGCAGUGCU	60	GGG
2600	12192967	6	656	47.3	-	12192964	12192983	GGGAUCGUGUGGACACUGGC	65	TGG
2601	12193061	6	750	54.1	-	12193058	12193077	CCAGUGCUCCCUUCAGCUGG	65	GGG
2602	12192947	6	636	45.9	-	12192944	12192963	UGGGGUAAGUGUACUGCCCC	60	TGG
2603	12193064	6	753	54.3	+	12193047	12193066	GCCCCAGCCCCCCAGCUGAA	75	GGG
2604	12193062	6	751	54.2	-	12193059	12193078	GCCAGUGCUCCCUUCAGCUG	65	GGG
2605	12193063	6	752	54.3	-	12193060	12193079	CGCCAGUGCUCCCUUCAGCU	65	GGG
2606	12193045	6	734	53	-	12193042	12193061	CUGGGGGGCUGGGGCCCAUU	75	GGG
2607	12193975	7	808	58.3	+	12193958	12193977	GAUUGUGGGUGUGACAGCCU	55	TGG
2608	12193039	6	728	52.5	-	12193036	12193055	GGCUGGGGCCCAUUGGGAGC	75	AGG
2609	12193072	6	761	54.9	+	12193055	12193074	CCCCCAGCUGAAGGGAGCAC	70	TGG
2610	12193001	6	690	49.8	-	12192998	12193017	GCAGUGCUGGGUUCUGGAGU	60	TGG
2611	12193064	6	753	54.3	-	12193061	12193080	UCGCCAGUGCUCCCUUCAGC	65	TGG
2612	12193041	6	730	52.7	+	12193024	12193043	CACCUCCUUCCUGCUCCCAA	60	TGG
2613	12193025	6	714	51.5	-	12193022	12193041	GGGAGCAGGAAGGAGGUGCU	65	TGG
2614	12193014	6	703	50.7	-	12193011	12193030	GGAGGUGCUUGGAGCAGUGC	65	TGG
2615	12192921	6	610	44	-	12192918	12192937	CAUACUCCGGGUGGGGGACG	70	TGG
2616	12193055	6	744	53.7	-	12193052	12193071	CUCCCUUCAGCUGGGGGGCU	70	GGG
2617	12193007	6	696	50.2	-	12193004	12193023	CUUGGAGCAGUGCUGGGUUC	60	TGG
2618	12193063	6	752	54.3	+	12193046	12193065	GGCCCCAGCCCCCCAGCUGA	80	AGG
2619	12193046	6	735	53	-	12193043	12193062	GCUGGGGGGCUGGGGCCCAU	80	TGG
2620	12193054	6	743	53.6	-	12193051	12193070	UCCCUUCAGCUGGGGGGCUG	70	GGG
2621	12193042	6	731	52.7	+	12193025	12193044	ACCUCCUUCCUGCUCCCAAU	55	GGG
2622	12193056	6	745	53.8	-	12193053	12193072	GCUCCCUUCAGCUGGGGGGC	75	TGG
2623	12206953	10	1319	95.2	+	12206936	12206955	GAGACGCCAGAGACCCUGCU	65	GGG
2624	12206925	10	1291	93.1	-	12206922	12206941	CGUCUCCAGCUGUGACCGAA	60	AGG
2625	12206999	10	1365	98.5	+	12206982	12207001	CCCUUGGAGUGCCUGAUGCU	60	GGG
2626	12206988	10	1354	97.7	-	12206985	12207004	CCCAGCAUCAGGCACUCCAA	60	GGG
2627	12206931	10	1297	93.6	+	12206914	12206933	AUGUGCCUUUCGGUCACAGC	55	TGG
2628	12206989	10	1355	97.8	-	12206986	12207005	UCCCAGCAUCAGGCACUCCA	60	AGG
2629	12206955	10	1321	95.3	-	12206952	12206971	CUCUUCGGUGCUCCCCAGCA	65	GGG
2630	12206970	10	1336	96.4	-	12206967	12206986	AAGGGGCAGGGGCUUCUCUU	60	CGG
2631	12206987	10	1353	97.6	-	12206984	12207003	CCAGCAUCAGGCACUCCAAG	60	GGG
2632	12206921	10	1287	92.9	+	12206904	12206923	CCAAGGAGGAAUGUGCCUUU	50	CGG
2633	12206956	10	1322	95.4	-	12206953	12206972	UCUCUUCGGUGCUCCCCAGC	65	AGG
2634	12206999	10	1365	98.5	-	12206996	12207015	CUGGGCUUCAUCCCAGCAUC	60	AGG
2635	12206982	10	1348	97.3	-	12206979	12206998	AUCAGGCACUCCAAGGGGCA	60	GGG
2636	12206983	10	1349	97.3	+	12206966	12206985	GAAGAGAAGCCCCUGCCCCU	65	TGG
2637	12206983	10	1349	97.3	-	12206980	12206999	CAUCAGGCACUCCAAGGGGC	65	AGG
2638	12206952	10	1318	95.1	+	12206935	12206954	GGAGACGCCAGAGACCCUGC	70	TGG
2639	12206981	10	1347	97.2	-	12206978	12206997	UCAGGCACUCCAAGGGGCAG	65	GGG
2640	12206948	10	1314	94.8	-	12206945	12206964	GUGCUCCCCAGCAGGGUCUC	70	TGG
2641	12206998	10	1364	98.4	+	12206981	12207000	CCCCUUGGAGUGCCUGAUGC	65	TGG
2642	12206954	10	1320	95.2	+	12206937	12206956	AGACGCCAGAGACCCUGCUG	65	GGG

FIG. 39E

SEQ ID NO:	MIT	CFD	Elevation	Off-Target	Offtarget #	Azimuth	DeepSpCas9	CrisprScan	Doench	Lindel	inDelphi	Frameshift	Precision	Graf Motifs	Bioscore	30_OOF	OOF_70	Overall	Interpretation predictions
2396	87	93	44	75	56	57	56	56	56	84	60	72	68	OK	57	65	73	68	Knockout
2397	80	92	42	71	122	44	30	97	57	77	85	81	60	OK	50	64	76	70	Knockout
2398	96	95	49	90	41	57	63	33	51	77	79	78	50	OK	32	66	79	70	Knockout
2399	76	87	35	66	128	60	60	57	59	90	96	93	76	OK	46	63	80	73	Knockout
2400	70	83	44	66	187	45	65	68	59	84	93	88	64	OK	51	62	77	71	Knockout
2401	89	93	51	78	84	53	48	42	48	90	93	91	63	OK	51	63	84	72	Knockout
2402	88	95	47	77	155	67	67	32	55	73	79	76	59	OK	57	66	76	69	Knockout
2403	56	82	52	63	231	69	71	49	63	87	89	88	60	OK	55	63	76	71	Knockout
2404	75	85	44	68	110	71	66	69	69	82	72	77	64	OK	51	68	73	71	Knockout
2405	74	89	52	72	172	47	50	85	61	76	80	78	61	OK	44	66	75	70	Knockout
2406	62	83	58	68	240	59	50	65	58	76	85	80	54	OK	64	63	74	69	Knockout
2407	74	89	59	74	155	65	65	35	55	75	87	81	60	OK	53	64	77	70	Knockout
2408	96	98	41	78	37	47	59	48	51	76	81	79	48	OK	54	65	78	69	Knockout
2409	85	92	41	73	63	48	47	46	47	90	94	92	67	OK	52	60	82	71	Knockout
2410	68	86	47	67	143	65	55	60	60	80	78	79	54	OK	51	64	73	69	Knockout
2411	88	94	44	75	79	49	61	72	61	77	90	84	54	OK	52	68	79	73	Knockout
2412	77	90	38	68	142	43	53	59	52	82	88	85	59	OK	59	60	77	68	Knockout
2413	81	89	53	74	135	69	59	44	57	84	80	72	59	OK	51	66	73	68	Knockout
2414	76	90	64	77	121	62	53	36	50	75	79	77	41	OK	65	63	77	68	Knockout
2415	88	93	52	78	112	46	24	41	37	85	89	87	53	OK	49	57	82	67	Knockout
2416	96	97	45	79	38	54	46	60	53	83	72	67	48	OK	51	66	73	67	Knockout
2417	76	91	38	68	95	41	45	70	52	73	86	80	52	TT	57	60	74	67	Knockout
2418	68	86	60	71	241	50	48	44	47	76	87	82	50	OK	60	59	77	67	Knockout
2419	66	84	36	62	162	56	52	86	65	73	73	73	51	OK	50	63	68	67	Knockout
2420	46	69	42	52	337	54	56	71	60	76	82	79	51	OK	44	56	66	64	Knockout
2421	76	89	53	73	179	55	38	37	43	76	78	77	50	OK	53	58	75	64	Knockout
2422	75	85	49	70	190	66	59	40	55	69	68	68	44	OK	64	62	69	64	Knockout
2423	75	86	37	66	147	47	29	45	40	77	93	85	67	OK	48	53	76	64	Knockout
2424	72	85	57	71	133	51	39	29	40	80	84	82	50	OK	64	55	77	64	Knockout
2425	73	86	53	71	179	48	38	35	40	82	78	80	64	OK	54	56	75	64	Knockout
2426	70	89	45	68	165	53	63	24	47	80	74	77	39	OK	65	57	72	64	Knockout
2427	68	82	44	65	187	45	28	65	46	77	77	77	54	GGC	65	55	71	63	Knockout
2428	80	87	35	67	109	40	16	40	32	83	96	89	72	GGC	46	50	78	63	Knockout
2429	85	86	35	69	142	57	56	48	54	74	61	67	44	OK	48	61	68	63	Knockout
2430	69	84	38	64	151	33	25	61	40	78	93	86	67	OK	50	52	75	63	Knockout
2431	58	85	44	63	164	53	48	58	53	74	65	70	46	OK	55	58	66	62	Knockout
2432	67	83	49	66	179	57	64	49	57	66	61	64	65	OK	65	62	65	62	Knockout
2433	64	76	84	68	222	48	21	17	29	87	91	89	59	OK	49	48	79	62	Knockout
2434	72	86	37	65	133	33	39	65	46	74	79	76	56	OK	43	55	71	62	Knockout
2435	70	89	47	69	176	33	36	38	36	80	85	82	46	OK	54	52	76	62	Knockout
2436	68	81	61	70	194	52	48	34	45	73	67	70	54	OK	56	57	70	62	Knockout
2437	91	95	45	77	62	36	38	32	35	77	74	75	52	OK	70	56	76	62	Knockout
2438	71	88	38	66	214	43	59	29	44	73	72	73	46	OK	52	55	69	61	Knockout
2439	78	91	37	69	130	39	35	65	46	76	80	68	43	OK	47	58	68	61	Knockout
2440	75	90	38	68	90	28	42	48	39	75	80	77	54	OK	57	53	73	61	Knockout
2441	60	75	38	58	342	37	44	54	45	70	83	77	63	OK	67	51	67	60	Knockout
2442	73	85	33	64	229	29	29	63	40	75	79	77	51	OK	33	52	70	60	Knockout
2443	57	79	38	58	246	32	40	35	36	81	84	87	67	OK	46	47	73	60	Knockout
2444	92	97	40	76	63	32	41	66	46	65	50	58	69	OK	53	61	67	60	Knockout
2445	83	93	41	72	102	36	24	55	39	62	73	68	54	OK	56	55	70	59	Knockout

FIG. 39F

SEQ ID NO:	MIT	CFD	Elevation	Off7	Offtarget #	Azimuth	DeepSpCas9	CrispScan	Off9	Lindel	inDelphi	Frameshift	Precision	Graf Motifs	Bioscore	Off7_OOF	Off7_FS	Off9_OOF	Off9_FS	Interference predictions
2446	92	97	42	77	90	34	22	40	32	71	65	68	46	OK	48	54	72	59		Knockout
2447	90	94	44	76	76	30	49	73	51	59	38	49	65	OK	45	63	62	58		Knockout
2448	77	86	37	67	115	46	33	70	50	59	56	58	58	OK	58	58	62	58		Knockout
2449	41	64	32	46	436	45	53	60	53	69	80	74	46	OK	62	49	60	58		Knockout
2450	49	72	43	55	395	55	62	67	61	54	53	53	49	OK	62	58	54	56		Knockout
2451	51	80	35	55	276	41	40	42	41	66	69	69	46	OK	48	48	62	55		Knockout
2452	72	87	53	71	129	51	39	15	35	59	48	53	56	OK	61	53	62	53		Knockout
2453	26	44	64	45	832	45	23	55	41	71	71	71	46	GGC	56	43	58	52		Knockout
2454	54	92	37	61	88	36	37	35	36	71	48	60	60	OK	47	48	60	52		Knockout
2455	56	83	44	61	238	40	38	23	34	62	39	51	63	OK	65	47	56	48		Knockout
2456	82	92	53	76	71	39	46	76	53	76	77	78	56	OK	50	65	77	69		Knockout or soluble receptor decoy
2457	76	87	40	68	101	58	67	85	70	69	76	72	51	OK	59	69	70	70		Knockout or soluble receptor decoy
2458	79	91	60	77	157	71	58	54	61	62	84	83	42	OK	56	69	80	74		Knockout or soluble receptor decoy
2459	83	89	46	73	86	56	64	55	58	80	90	85	63	OK	49	66	79	72		Knockout or soluble receptor decoy
2460	71	83	38	64	182	72	71	60	68	80	81	80	52	OK	51	66	72	71		Knockout or soluble receptor decoy
2461	95	98	39	77	29	75	64	63	67	79	76	77	54	OK	47	72	77	74		Knockout or soluble receptor decoy
2462	93	97	54	81	47	44	54	54	51	76	79	77	58	OK	47	66	79	70		Knockout or soluble receptor decoy
2463	81	93	56	77	98	62	63	39	55	76	77	77	62	OK	45	66	77	69		Knockout or soluble receptor decoy
2464	87	92	46	75	93	63	66	50	60	83	90	86	58	OK	54	67	81	74		Knockout or soluble receptor decoy
2465	82	93	43	73	57	56	64	62	61	85	87	86	46	OK	47	67	79	73		Knockout or soluble receptor decoy
2466	64	80	61	68	191	62	57	49	56	76	70	73	44	OK	43	62	71	66		Knockout or soluble receptor decoy
2467	80	94	50	75	60	45	38	26	36	83	92	88	62	OK	49	56	81	66		Knockout or soluble receptor decoy
2468	79	89	40	69	133	49	27	52	43	81	92	87	65	OK	49	56	78	66		Knockout or soluble receptor decoy
2469	96	96	43	78	37	50	45	43	46	74	67	70	44	OK	47	62	74	65		Knockout or soluble receptor decoy
2470	52	85	52	63	240	61	38	44	48	86	84	85	62	OK	51	55	74	65		Knockout or soluble receptor decoy
2471	82	91	36	70	101	46	58	48	51	71	79	75	47	OK	53	60	72	65		Knockout or soluble receptor decoy
2472	88	95	37	73	91	44	44	44	44	73	76	74	61	GGC	48	59	74	64		Knockout or soluble receptor decoy
2473	83	90	36	70	91	37	45	52	45	75	81	78	53	OK	34	57	74	64		Knockout or soluble receptor decoy
2474	49	68	56	58	284	59	47	50	52	81	86	84	46	OK	48	55	71	64		Knockout or soluble receptor decoy
2475	57	85	47	63	239	39	51	51	47	81	80	81	48	OK	34	55	72	64		Knockout or soluble receptor decoy
2476	97	97	41	78	27	52	46	30	43	65	78	71	47	OK	41	60	75	64		Knockout or soluble receptor decoy
2477	66	81	53	67	181	45	41	29	38	83	83	83	57	OK	43	52	75	63		Knockout or soluble receptor decoy
2478	83	94	41	73	105	51	49	56	52	63	61	62	49	OK	50	62	67	62		Knockout or soluble receptor decoy
2479	86	92	52	77	60	42	13	12	22	64	91	88	59	TT	52	50	82	62		Knockout or soluble receptor decoy
2480	56	79	48	61	271	46	53	41	47	76	81	79	53	OK	35	54	70	62		Knockout or soluble receptor decoy
2481	89	95	40	75	51	24	26	55	35	66	79	72	48	TT	53	55	73	61		Knockout or soluble receptor decoy
2482	86	94	44	75	91	28	32	43	34	73	64	69	66	OK	50	54	72	59		Knockout or soluble receptor decoy
2483	76	90	53	73	124	70	73	40	61	74	83	78	58	OK	50	67	76	71		Membrane-bound receptor
2484	94	96	44	78	28	63	61	84	69	84	79	82	48	OK	39	74	80	76		Membrane-bound receptor
2485	94	97	52	81	22	48	44	43	45	76	89	82	63	OK	40	63	82	69		Membrane-bound receptor
2486	86	94	45	75	71	64	63	36	54	81	86	83	57	OK	38	65	79	71		Membrane-bound receptor
2487	89	90	47	75	113	53	58	74	62	79	84	82	43	OK	37	68	78	73		Membrane-bound receptor
2488	85	89	48	74	141	62	60	38	53	85	85	85	53	OK	28	64	80	71		Membrane-bound receptor
2489	71	89	52	71	193	72	68	59	66	76	87	82	59	OK	60	68	76	73		Membrane-bound receptor
2490	95	96	43	79	26	54	68	39	54	65	81	73	55	OK	60	66	76	68		Membrane-bound receptor
2491	63	83	49	65	220	51	55	55	54	86	89	89	64	OK	40	59	77	69		Membrane-bound receptor
2492	89	94	39	74	42	60	44	67	57	77	84	80	61	OK	29	66	77	71		Membrane-bound receptor
2493	91	94	44	76	67	59	45	63	56	82	89	86	65	TT	31	66	81	73		Membrane-bound receptor
2494	62	75	49	62	279	70	68	75	71	77	80	78	56	OK	43	67	70	70		Membrane-bound receptor
2495	73	90	59	74	141	47	65	61	58	77	73	75	50	OK	38	66	74	69		Membrane-bound receptor

FIG. 39G

SEQ ID NO:	MIT	CFD	Elevation	CFD	Offtarget #	Azimuth	DeepSpCas9	CrispScan	CFD	Lindel	inDelphi	Frameshift	Precision	Graf Motifs	Bioscore	OOF	OOF	OOF	Interference predictions
2496	90	92	51	78	98	54	29	64	49	77	83	80	49	OK	41	63	79	69	Membrane-bound receptor
2497	82	93	47	74	79	54	50	63	56	76	70	73	59	OK	50	65	74	68	Membrane-bound receptor
2498	70	85	60	72	167	58	55	48	54	74	82	78	58	OK	42	63	75	68	Membrane-bound receptor
2499	49	74	53	59	325	57	65	50	57	85	93	89	67	OK	58	58	74	68	Membrane-bound receptor
2500	73	82	48	68	148	57	37	65	53	84	83	83	54	OK	43	60	76	68	Membrane-bound receptor
2501	83	91	43	72	68	53	47	41	47	84	84	84	64	OK	35	60	78	68	Membrane-bound receptor
2502	94	97	43	78	47	44	46	56	49	79	70	75	50	GGC	39	63	76	67	Membrane-bound receptor
2503	61	84	45	63	200	56	66	45	56	75	88	81	65	OK	26	60	72	67	Membrane-bound receptor
2504	54	72	45	57	284	58	67	87	71	75	64	70	62	OK	41	64	63	66	Membrane-bound receptor
2505	93	94	47	78	32	49	46	53	49	68	71	70	50	OK	30	64	74	66	Membrane-bound receptor
2506	69	81	59	70	191	59	59	39	52	76	73	74	45	OK	36	61	72	66	Membrane-bound receptor
2507	77	89	47	71	100	52	68	36	52	77	72	75	63	OK	42	62	73	66	Membrane-bound receptor
2508	96	98	34	77	16	47	54	47	49	69	74	71	55	OK	40	63	74	66	Membrane-bound receptor
2509	33	64	45	47	517	74	73	62	70	77	85	81	54	OK	56	58	64	66	Membrane-bound receptor
2510	44	66	42	51	485	63	65	57	62	83	85	84	46	OK	51	56	67	66	Membrane-bound receptor
2511	86	92	35	71	79	42	62	41	48	83	76	79	46	OK	39	60	75	66	Membrane-bound receptor
2512	64	78	45	62	246	50	52	76	59	70	75	73	64	OK	40	61	67	65	Membrane-bound receptor
2513	72	89	38	66	177	44	41	60	48	80	82	81	49	OK	31	57	74	65	Membrane-bound receptor
2514	83	91	47	74	78	49	33	44	42	74	84	79	51	OK	44	58	76	65	Membrane-bound receptor
2515	44	64	34	47	393	62	63	59	61	83	88	86	54	OK	38	54	67	65	Membrane-bound receptor
2516	91	95	43	76	49	44	47	38	43	76	73	74	45	OK	37	60	75	65	Membrane-bound receptor
2517	80	87	36	68	137	58	55	77	63	68	63	65	44	OK	33	66	67	65	Membrane-bound receptor
2518	57	76	37	57	350	56	62	64	61	79	77	78	42	OK	48	59	67	65	Membrane-bound receptor
2519	64	86	34	61	204	50	50	53	51	77	88	82	63	OK	31	56	72	65	Membrane-bound receptor
2520	90	91	41	74	98	48	57	47	51	88	73	70	45	OK	39	62	72	65	Membrane-bound receptor
2521	89	91	38	70	75	42	31	40	38	82	86	84	46	OK	62	54	77	64	Membrane-bound receptor
2522	89	92	59	77	75	63	49	43	52	69	60	64	48	OK	52	64	71	64	Membrane-bound receptor
2523	93	96	43	77	50	30	9	76	38	68	83	76	65	TT	44	58	76	64	Membrane-bound receptor
2524	39	63	30	44	664	56	70	61	63	81	89	85	62	OK	36	53	65	64	Membrane-bound receptor
2525	79	93	59	77	96	54	39	56	50	81	69	65	72	TT	49	63	71	64	Membrane-bound receptor
2526	92	96	43	77	80	29	25	65	40	75	76	76	48	TT	31	58	76	64	Membrane-bound receptor
2527	56	78	49	61	267	64	63	52	60	71	74	73	51	OK	27	60	67	64	Membrane-bound receptor
2528	60	78	49	62	195	61	65	40	55	71	80	75	62	OK	41	59	69	64	Membrane-bound receptor
2529	78	91	56	75	140	45	39	47	44	71	77	74	50	OK	39	59	74	64	Membrane-bound receptor
2530	53	78	40	57	316	61	55	44	73	56	60	58	46	OK	38	65	57	63	Membrane-bound receptor
2531	94	95	55	81	59	40	19	55	38	72	68	70	50	OK	50	60	76	63	Membrane-bound receptor
2532	48	72	65	61	363	40	55	26	40	82	90	86	57	OK	49	51	73	62	Membrane-bound receptor
2533	60	77	34	57	378	56	29	56	47	83	79	81	47	OK	33	52	69	62	Membrane-bound receptor
2534	47	70	38	52	513	38	59	80	59	67	83	75	59	OK	41	55	63	62	Membrane-bound receptor
2535	88	94	61	81	73	42	37	44	41	82	66	64	65	OK	60	61	73	62	Membrane-bound receptor
2536	81	92	53	75	84	53	49	14	39	66	70	68	45	OK	60	57	71	61	Membrane-bound receptor
2537	56	80	38	58	306	44	49	59	51	77	71	74	52	OK	36	54	66	61	Membrane-bound receptor
2538	58	73	59	63	239	57	33	34	41	78	82	80	60	OK	39	52	72	61	Membrane-bound receptor
2539	86	89	38	72	102	56	62	39	52	51	64	58	45	OK	39	62	65	60	Membrane-bound receptor
2540	48	67	43	53	427	49	45	29	41	79	89	84	49	OK	50	47	68	59	Membrane-bound receptor
2541	87	90	36	71	131	27	14	57	33	69	79	74	49	TT	31	52	73	59	Membrane-bound receptor
2542	63	79	53	65	177	34	48	53	45	70	65	67	51	TT	32	55	66	59	Membrane-bound receptor
2543	52	67	33	51	331	41	46	50	46	77	85	81	57	OK	33	48	66	59	Membrane-bound receptor
2544	43	70	32	48	505	30	55	72	52	74	77	75	56	OK	38	50	62	59	Membrane-bound receptor
2545	81	92	36	70	80	33	26	45	35	80	61	71	52	OK	42	52	70	58	Membrane-bound receptor

FIG. 39H

SEQ ID NO:	MIT	CFD	Elevation	Off-target #	Azimuth	DeepSpCas9	CrisprScan	Off-target #	Lindel	inDelphi	Frameshift	Precision	Graf Motifs	Bioscore	Off-target #	Off-target #	Off-target #	Membrane-bound receptor / Soluble decoy receptor
2546	55	78	38	57	279	34	41	34	36	81	80	81	62	OK	38	47	69	58	Membrane-bound receptor
2547	63	78	45	62	236	50	40	62	51	71	54	62	51	OK	49	56	62	58	Membrane-bound receptor
2548	57	83	38	59	221	41	37	51	43	70	75	73	43	OK	36	51	66	58	Membrane-bound receptor
2549	46	60	32	46	402	34	19	58	37	85	90	87	57	GGC	33	41	67	57	Membrane-bound receptor
2550	30	63	29	41	604	44	62	41	49	82	81	81	61	OK	47	45	61	57	Membrane-bound receptor
2551	62	84	38	61	203	45	34	42	40	73	65	69	59	OK	41	51	65	57	Membrane-bound receptor
2552	34	68	30	44	535	56	54	72	61	60	71	65	68	OK	38	53	55	57	Membrane-bound receptor
2553	43	78	45	55	343	44	55	42	47	78	60	69	68	OK	48	51	62	57	Membrane-bound receptor
2554	67	80	52	66	196	52	44	12	36	66	66	66	46	OK	42	51	66	56	Membrane-bound receptor
2555	31	72	28	44	447	42	36	44	41	83	86	84	60	OK	55	42	64	56	Membrane-bound receptor
2556	42	71	47	53	694	37	17	42	32	78	90	84	60	OK	34	43	69	56	Membrane-bound receptor
2557	64	83	46	64	158	33	8	31	24	79	72	75	53	OK	32	44	70	55	Membrane-bound receptor
2558	65	77	31	58	268	33	26	47	35	68	77	72	50	OK	28	47	65	55	Membrane-bound receptor
2559	30	61	26	39	723	46	53	66	55	70	72	71	57	OK	48	47	55	55	Membrane-bound receptor
2560	59	74	51	61	273	40	39	34	38	71	57	64	50	OK	34	49	63	54	Membrane-bound receptor
2561	29	59	26	38	788	54	32	66	51	71	73	72	57	OK	44	44	55	54	Membrane-bound receptor
2562	53	70	39	54	310	44	33	32	36	77	68	72	55	OK	37	45	63	54	Membrane-bound receptor
2563	75	84	61	73	189	40	34	1	25	60	60	60	46	OK	41	49	67	53	Membrane-bound receptor
2564	55	70	50	58	278	46	34	25	35	65	63	64	46	OK	38	47	61	52	Membrane-bound receptor
2565	32	69	23	41	468	41	25	64	43	64	79	71	67	OK	41	42	56	52	Membrane-bound receptor
2566	39	69	38	49	532	33	27	64	41	69	56	62	51	GGC	33	45	56	51	Membrane-bound receptor
2567	47	61	29	46	439	35	47	73	52	59	52	56	57	OK	33	49	51	51	Membrane-bound receptor
2568	21	45	11	26	886	33	44	81	53	63	73	68	57	OK	36	39	47	49	Membrane-bound receptor
2569	52	74	38	55	317	30	25	49	35	55	57	56	44	OK	46	45	55	48	Membrane-bound receptor
2570	29	52	29	37	770	27	9	63	33	72	71	71	57	GGC	36	35	54	47	Membrane-bound receptor
2571	43	65	37	48	468	34	25	80	46	56	38	48	54	OK	34	47	48	47	Membrane-bound receptor
2572	25	54	30	36	827	33	25	52	37	68	52	60	53	OK	34	36	48	44	Membrane-bound receptor
2573	24	40	14	26	###	37	24	88	50	59	50	54	53	OK	38	38	40	43	Membrane-bound receptor
2574	30	63	27	40	606	35	52	17	35	56	34	46	62	OK	44	37	43	40	Membrane-bound receptor
2575	86	92	47	75	126	39	42	89	57	75	81	78	48	OK	39	66	76	70	Soluble decoy receptor
2576	82	93	45	77	74	49	59	70	59	71	81	76	47	OK	35	66	76	71	Soluble decoy receptor
2577	86	92	41	74	64	53	51	57	54	84	75	79	53	OK	47	64	76	69	Soluble decoy receptor
2578	83	90	45	73	76	62	59	89	73	73	67	70	48	OK	47	73	71	72	Soluble decoy receptor
2579	82	89	54	75	96	56	59	56	57	82	91	87	60	OK	48	66	81	73	Soluble decoy receptor
2580	78	85	49	71	117	57	43	79	60	76	82	79	51	OK	34	65	75	70	Soluble decoy receptor
2581	74	86	48	69	192	46	31	74	50	88	92	90	63	TT	39	60	80	70	Soluble decoy receptor
2582	57	71	35	54	243	63	62	72	66	87	89	88	63	OK	31	60	71	69	Soluble decoy receptor
2583	68	87	59	71	167	49	48	88	62	76	64	70	46	TT	46	67	71	68	Soluble decoy receptor
2584	65	86	49	67	158	57	42	62	54	77	89	83	64	OK	42	60	75	68	Soluble decoy receptor
2585	82	86	39	69	149	43	38	89	57	75	75	75	55	OK	39	63	72	67	Soluble decoy receptor
2586	47	69	46	54	387	56	45	62	54	91	97	94	62	OK	48	54	74	67	Soluble decoy receptor
2587	89	90	43	74	103	40	54	62	52	74	79	76	57	OK	31	63	75	67	Soluble decoy receptor
2588	89	94	40	74	60	39	41	43	41	85	82	84	57	OK	41	58	79	66	Soluble decoy receptor
2589	76	87	44	69	201	40	27	73	47	78	87	83	59	OK	41	58	76	66	Soluble decoy receptor
2590	82	91	51	75	96	38	57	66	54	80	61	71	56	OK	44	64	73	66	Soluble decoy receptor
2591	72	90	47	70	135	42	49	47	46	76	87	82	53	OK	40	58	76	66	Soluble decoy receptor
2592	74	84	48	69	285	42	38	53	44	76	89	82	53	OK	39	56	75	65	Soluble decoy receptor
2593	75	86	37	66	124	56	42	62	53	73	80	76	61	OK	39	60	71	65	Soluble decoy receptor
2594	76	87	60	74	146	63	56	86	68	51	54	52	52	OK	44	71	63	65	Soluble decoy receptor
2595	86	93	43	74	74	41	49	50	47	82	69	75	45	OK	32	60	75	65	Soluble decoy receptor

FIG. 39I

SEQ ID NO:	MIT	CFD	Elevation	GUIDE	Offtarget #	Azimuth	DeepSpCas9	CrisprScan	GN	Lindel	inDelphi	Frameshift	Precision	Graf Motifs	Bioscore	GUIDE_SEQ	GUIDE_SEQ + PAM	OVERHANG	Interference with Function
2596	52	69	42	54	381	58	59	55	57	79	81	80	58	OK	42	56	67	64	Soluble decoy receptor
2597	80	82	47	73	187	40	37	35	37	79	76	78	46	OK	41	55	75	63	Soluble decoy receptor
2598	78	86	56	77	27	55	32	20	36	77	78	77	51	OK	52	56	77	63	Soluble decoy receptor
2599	30	51	45	42	703	54	61	72	62	83	85	84	64	OK	38	52	63	63	Soluble decoy receptor
2600	73	84	44	67	134	29	46	36	37	82	90	86	65	OK	40	52	77	63	Soluble decoy receptor
2601	60	74	35	56	234	54	50	47	50	78	80	79	44	OK	31	53	68	62	Soluble decoy receptor
2602	86	90	47	75	93	25	50	56	44	73	59	66	50	OK	42	59	71	62	Soluble decoy receptor
2603	55	68	32	52	415	55	47	40	47	89	84	86	66	OK	32	49	69	62	Soluble decoy receptor
2604	59	80	48	62	263	49	58	50	52	72	66	69	42	OK	26	57	66	61	Soluble decoy receptor
2605	70	86	53	70	176	40	35	25	33	78	79	79	56	OK	26	52	74	61	Soluble decoy receptor
2606	68	83	34	62	277	26	12	89	46	70	79	75	56	TT	45	54	68	61	Soluble decoy receptor
2607	69	87	49	68	200	49	38	54	47	74	61	67	45	GGC	45	58	68	61	Soluble decoy receptor
2608	52	77	59	63	368	38	44	45	42	77	71	74	41	OK	35	53	68	60	Soluble decoy receptor
2609	57	78	48	61	280	49	58	36	48	68	67	68	44	OK	39	54	64	59	Soluble decoy receptor
2610	50	66	52	56	465	46	52	51	50	65	67	66	47	OK	35	53	61	57	Soluble decoy receptor
2611	78	88	48	71	119	32	28	20	27	65	77	71	50	OK	27	49	71	56	Soluble decoy receptor
2612	47	59	47	51	509	42	35	43	40	77	73	75	41	OK	37	46	63	55	Soluble decoy receptor
2613	19	44	13	25	####	53	42	56	50	87	92	90	66	OK	38	38	58	55	Soluble decoy receptor
2614	48	67	27	47	424	30	51	39	40	70	78	74	51	OK	31	44	61	54	Soluble decoy receptor
2615	74	88	35	66	116	40	29	57	42	55	52	54	49	OK	36	54	60	54	Soluble decoy receptor
2616	52	69	38	53	298	15	1	52	22	77	93	85	71	OK	33	37	69	53	Soluble decoy receptor
2617	40	52	41	44	554	25	28	55	36	72	83	77	55	TT	32	40	61	53	Soluble decoy receptor
2618	40	65	33	46	494	45	47	27	40	75	73	74	48	OK	26	43	60	53	Soluble decoy receptor
2619	44	69	23	45	543	24	7	82	38	76	73	74	50	OK	43	41	60	52	Soluble decoy receptor
2620	29	50	28	36	667	39	29	54	41	78	80	79	64	OK	30	38	57	52	Soluble decoy receptor
2621	39	77	31	49	284	40	30	29	33	68	75	72	53	OK	38	41	60	51	Soluble decoy receptor
2622	43	63	26	44	351	16	9	16	14	74	93	84	72	OK	34	29	64	47	Soluble decoy receptor
2623	67	88	39	65	170	57	55	70	61	79	76	78	65	OK	47	63	71	68	Wildtype-like
2624	58	67	61	62	375	59	36	52	49	91	87	89	53	OK	50	56	76	67	Wildtype-like
2625	68	83	60	70	221	46	55	52	51	83	75	79	62	OK	38	61	75	67	Wildtype-like
2626	75	80	56	70	200	55	51	59	55	78	65	72	47	OK	38	63	71	66	Wildtype-like
2627	83	92	51	75	90	50	35	31	39	82	84	83	49	OK	47	57	79	66	Wildtype-like
2628	69	77	44	63	249	56	65	26	49	89	81	85	62	OK	38	56	74	66	Wildtype-like
2629	68	81	44	64	156	50	41	68	53	85	74	80	56	OK	43	59	72	66	Wildtype-like
2630	57	77	42	59	344	40	34	72	49	89	86	92	71	TT	40	54	75	66	Wildtype-like
2631	53	87	42	61	167	66	62	49	59	76	76	76	54	OK	52	60	68	65	Wildtype-like
2632	72	84	57	71	177	39	22	51	37	80	84	82	42	TT	50	54	77	64	Wildtype-like
2633	77	89	60	75	125	35	24	42	34	73	79	76	49	OK	43	54	76	62	Wildtype-like
2634	65	86	49	66	229	50	43	55	49	68	71	68	54	OK	46	58	67	61	Wildtype-like
2635	65	82	48	65	172	48	42	47	46	78	80	69	56	OK	45	55	67	60	Wildtype-like
2636	51	74	34	53	361	52	57	47	52	82	64	73	54	OK	45	53	63	59	Wildtype-like
2637	69	84	47	67	162	40	44	35	40	72	68	70	52	OK	45	53	68	59	Wildtype-like
2638	64	77	39	60	272	49	56	28	44	69	68	69	42	OK	47	52	64	58	Wildtype-like
2639	58	73	38	56	258	50	51	49	50	69	55	62	64	OK	52	53	59	56	Wildtype-like
2640	34	78	33	48	271	42	21	56	40	76	84	80	57	TT	47	44	64	56	Wildtype-like
2641	65	84	52	67	181	26	20	27	24	66	76	71	58	OK	46	46	69	54	Wildtype-like
2642	54	81	37	57	233	67	55	52	52	51	45	48	57	OK	44	58	53	54	Wildtype-like

FIG. 39J

SEQ ID NO:	Genomic cut coordinate	Exon	CDS cut position %	Strand	Start coordinate	End coordinate	crRNA	GC content	PAM
2643	6384597	2	8	-	6384593	6384612	UGGUUCUCCGACGCAUAUGG	55	AGG
2644	6384619	2	9.7	+	6384601	6384620	GUCGGAGAACCAGACCUGCA	60	GGG
2645	6384655	2	12.5	-	6384651	6384670	GGAGCAGCAGAUGCGGUGCU	65	GGG
2646	6385031	3	15.4	-	6385027	6385046	GCUACAUUUAGCUGAGACAU	40	AGG
2647	6385059	3	17.6	-	6385055	6385074	AUGUGGCACAAACUGUGUCC	50	CGG
2648	6385262	4	27.1	+	6385244	6385263	UUGCCCCCUGCACAAGCAAA	55	CGG
2649	6384410	1	3.9	-	6384406	6384425	CCGAAGAGGCCCAGCACCAG	70	AGG
2650	6384600	2	8.3	-	6384596	6384615	GUCUGGUUCUCCGACGCAUA	55	TGG
2651	6384654	2	12.4	-	6384650	6384669	GAGCAGCAGAUGCGGUGCUG	65	GGG
2652	6385240	4	25.4	-	6385236	6385255	UGCAGGGGGCAAUCUCCUCG	65	AGG
2653	6385094	3	20.3	-	6385090	6385109	GUAGUUCCAGUGCUCGUUGU	50	AGG
2654	6384424	1	5	-	6384420	6384439	AUGCUGCCAGGAGCCCGAAG	65	AGG
2655	6385254	4	26.5	-	6385250	6385269	CUUCCGUUUGCUUGUGCAGG	55	GGG
2656	6384656	2	12.5	-	6384652	6384671	GGGAGCAGCAGAUGCGGUGC	70	TGG
2657	6384390	1	2.4	-	6384386	6384405	AGGCCCCCAGGCCAGGCCGG	85	GGG
2658	6385051	3	17	+	6385033	6385052	CAGCUAAAUGUAGCCGCAUC	50	CGG
2659	6385085	3	19.8	-	6385081	6385100	GUGCUCGUUGUAGGAAUUCU	45	CGG
2660	6384374	1	1.1	-	6384370	6384389	CCGGGGGCAGAGGUGGCCCA	80	AGG
2661	6385255	4	26.5	-	6385251	6385270	UCUUCCGUUUGCUUGUGCAG	50	GGG
2662	6385278	4	28.3	-	6385274	6385293	UCCCGGCUGGCAGCGGCACU	75	GGG
2663	6385052	3	17	+	6385034	6385053	AGCUAAAUGUAGCCGCAUCC	50	GGG
2664	6385121	3	22.3	-	6385117	6385136	GGGGCGGCACAGCUGGCAGA	75	TGG
2665	6384450	1	7	+	6384432	6384451	GGCAGCAUCGCAGCCCCAGG	75	CGG
2666	6385076	3	18.9	-	6385072	6385091	GUAGGAAUUCUCGGCACAUG	50	TGG
2667	6384618	2	9.6	+	6384600	6384619	CGUCGGAGAACCAGACCUGC	65	AGG
2668	6384625	2	10.2	+	6384607	6384626	GAACCAGACCUGCAGGGACC	65	AGG
2669	6385116	3	21.9	-	6385112	6385131	GGCACAGCUGGCAGAUGGUC	65	AGG
2670	6384398	1	3	+	6384380	6384399	CUGCCCCCGGCCUGGCCUGG	85	GGG
2671	6384436	1	5.9	-	6384432	6384451	CCUGGGGCUGCGAUGCUGCC	75	AGG
2672	6384421	1	4.7	+	6384403	6384422	CCUCUGGUGCUGGGCCUCUU	65	CGG
2673	6385099	3	20.6	+	6385081	6385100	AGAAUUCCUACAACGAGCAC	45	TGG
2674	6385053	3	17.1	-	6385049	6385068	CACAAACUGUGUCCCGGAUG	55	CGG
2675	6385143	3	24	+	6385125	6385144	CUGUGCCGCCCCUGUGACCC	75	AGG
2676	6384429	1	5.4	+	6384411	6384430	GCUGGGCCUCUUCGGGCUCC	75	TGG
2677	6384385	1	2	+	6384367	6384386	CCUUGGGCCACCUCUGCCCC	75	CGG
2678	6384447	1	6.7	+	6384429	6384448	CCUGGCAGCAUCGCAGCCCC	75	AGG
2679	6384370	1	0.8	-	6384366	6384385	GGGCAGAGGUGGCCCAAGGC	75	AGG
2680	6384412	1	4.1	+	6384394	6384413	GCCUGGGGGCCUCUGGUGCU	75	GGG
2681	6384680	2	14.4	+	6384662	6384681	UGCUGCUCCCCGCUGCCCGCC	80	AGG
2682	6384402	1	3.3	-	6384398	6384417	GCCCAGCACCAGAGGCCCCC	80	AGG
2683	6385279	4	28.4	-	6385275	6385294	UUCCCGGCUGGCAGCGGCAC	75	TGG
2684	6384617	2	9.6	-	6384613	6384632	UUUCCUGGUCCCUGCAGGUC	60	TGG
2685	6384391	1	2.4	-	6384387	6384406	GAGGCCCCCAGGCCAGGCCG	85	GGG
2686	6385128	3	22.9	-	6385124	6385143	GGUCACAGGGGCGGCACAGC	75	TGG
2687	6384393	1	2.6	-	6384389	6384408	CAGAGGCCCCCAGGCCAGGC	80	CGG
2688	6384622	2	9.9	-	6384618	6384637	UUCCUUUUCCUGGUCCCUGC	55	AGG
2689	6384631	2	10.8	+	6384613	6384632	GACCUGCAGGGACCAGGAAA	60	AGG
2690	6384397	1	2.9	-	6384393	6384412	GCACCAGAGGCCCCCAGGCC	80	AGG
2691	6384662	2	13	-	6384658	6384677	GGCAGCGGGAGCAGCAGAUG	70	CGG
2692	6384390	1	2.4	+	6384372	6384391	GGCCACCUCUGCCCCCGGCC	85	TGG

FIG. 40A

SEQ ID NO:	Genomic cut coordinate	Exon	CDS cut position %	Strand	Start coordinate	End coordinate	crRNA	GC content	PAM
2693	6384632	2	10.7	-	6384628	6384647	GCUCAUAGUAUUCCUUUUCC	40	TGG
2694	6384411	1	4	+	6384393	6384412	GGCCUGGGGGCCUCUGGUGC	80	TGG
2695	6384405	1	3.5	+	6384387	6384406	CGGCCUGGCCUGGGGGCCUC	85	TGG
2696	6384422	1	4.6	+	6384404	6384423	CUCUGGUGCUGGGCCUCUUC	65	GGG
2697	6384396	1	2.8	+	6384378	6384397	CUCUGCCCCCGGCCUGGCCU	80	GGG
2698	6385321	4	31.6	-	6385317	6385336	GCUCGCAGUGUGUACACUCG	60	AGG
2699	6386104	5	39	-	6386100	6386119	UGGAAGUGCCCGGCCUUGCA	65	GGG
2700	6386362	6	44.6	-	6386358	6386377	GAGCUGCCUCCACCAGACCU	65	TGG
2701	6386364	6	44.8	+	6386346	6386365	GUGUGAGAACCAAGGUCUGG	55	TGG
2702	6385291	4	29.3	-	6385287	6385306	CAGCACAGAACAUUCCCGGC	60	TGG
2703	6385375	4	35.7	+	6385357	6385376	GGCACUGAAGCCGAGCUCAA	60	AGG
2704	6385357	4	34.3	-	6385353	6385372	GCUCGGCUUCAGUGCCAGGC	70	GGG
2705	6385295	4	29.6	-	6385291	6385310	CAGGCAGCACAGAACAUUCC	55	CGG
2706	6385358	4	34.4	-	6385354	6385373	AGCUCGGCUUCAGUGCCAGG	65	CGG
2707	6386114	5	39.8	-	6386110	6386129	GGAGGUAUUCUGGAAGUGCC	55	CGG
2708	6386394	6	47.1	-	6386390	6386409	UUUGCAGGUUGUGUCGGACU	50	GGG
2709	6386384	6	46.3	-	6386380	6386399	GUGUCGGACUGGGCAGUGCC	70	TGG
2710	6386102	5	38.8	+	6386084	6386103	CAACCACUGCGUCCCCUGCA	65	AGG
2711	6385354	4	34.1	+	6385336	6385355	CUACUUUCUGACUGCCCGCC	60	TGG
2712	6386107	5	39.2	+	6386089	6386108	ACUGCGUCCCCUGCAAGGCC	70	GGG
2713	6386361	6	44.6	+	6386343	6386362	CAGGUGUGAGAACCAAGGUC	55	TGG
2714	6386103	5	38.9	-	6386099	6386118	GGAAGUGCCCGGCCUUGCAG	70	GGG
2715	6385361	4	34.6	-	6385357	6385376	UUGAGCUCGGCUUCAGUGCC	60	AGG
2716	6386094	5	38.2	-	6386090	6386109	CGGCCUUGCAGGGGACGCAG	75	TGG
2717	6386409	6	48.2	-	6386405	6386424	UGGCUCUAAUGGAUUUUUGC	40	AGG
2718	6385287	4	29	+	6385269	6385288	GACCCAGUGCCGCUGCCAGC	75	CGG
2719	6385288	4	29.1	+	6385270	6385289	ACCCAGUGCCGCUGCCAGCC	75	GGG
2720	6385308	4	30.6	+	6385290	6385309	GGGAAUGUUCUGUGCUGCCU	55	GGG
2721	6386400	6	47.6	-	6386396	6386415	UGGAUUUUUGCAGGUUGUGU	40	CGG
2722	6385307	4	30.5	+	6385289	6385308	CGGGAAUGUUCUGUGCUGCC	60	TGG
2723	6385285	4	28.8	-	6385281	6385300	AGAACAUUCCCGGCUGGCAG	60	CGG
2724	6386105	5	39.1	-	6386101	6386120	CUGGAAGUGCCCGGCCUUGC	70	AGG
2725	6386138	5	41.6	-	6386134	6386153	GGGCUGGCAGCGGGCGCUGG	85	GGG
2726	6386367	6	45	+	6386349	6386368	UGAGAACCAAGGUCUGGUGG	55	AGG
2727	6386395	6	47.2	-	6386391	6386410	UUUUGCAGGUUGUGUCGGAC	50	TGG
2728	6386377	6	45.8	+	6386359	6386378	GGUCUGGUGGAGGCAGCUCC	70	AGG
2729	6386124	5	40.5	-	6386120	6386139	CGCUGGGGGAGGAGGUAUUC	65	TGG
2730	6386140	5	41.7	-	6386136	6386155	UGGGGCUGGCAGCGGGCGCU	80	GGG
2731	6386158	5	43.1	+	6386140	6386159	CCCGCUGCCAGCCCCACACC	80	AGG
2732	6386106	5	39.1	+	6386088	6386107	CACUGCGUCCCCUGCAAGGC	70	CGG
2733	6386147	5	42.3	-	6386143	6386162	CCUGGUGUGGGGCUGGCAGC	75	GGG
2734	6386148	5	42.4	-	6386144	6386163	ACCUGGUGUGGGGCUGGCAG	70	CGG
2735	6386141	5	41.8	-	6386137	6386156	GUGGGGCUGGCAGCGGGCGC	85	TGG
2736	6386139	5	41.7	-	6386135	6386154	GGGGCUGGCAGCGGGCGCUG	85	GGG
2737	6386135	5	41.4	-	6386131	6386150	CUGGCAGCGGGCGCUGGGGG	85	AGG
2738	6390140	9	63.4	+	6390122	6390141	CAAUCCUGUAGCUGGAAGCU	50	GGG
2739	6390154	9	64.4	-	6390150	6390169	AAGUAUGGAUGGGCCUUCGG	55	AGG
2740	6390164	9	65.2	-	6390160	6390179	CAAGUCAGGGAAGUAUGGAU	45	GGG
2741	6390177	9	66.2	-	6390173	6390192	GCAGUGGCUGUACCAAGUCA	55	GGG
2742	6390240	9	71	-	6390236	6390255	CCUCCAAAACUGGGGCUGCG	65	GGG

FIG. 40B

SEQ ID NO:	Genomic cut coordinate	Exon	CDS cut position %	Strand	Start coordinate	End coordinate	crRNA	GC content	PAM
2743	6390293	9	75.1	+	6390275	6390294	GAGUCCUCUGGACCUGACCA	60	GGG
2744	6390679	10	80.2	+	6390661	6390680	ACCAAUGGCAUUCAUGUCAC	45	CGG
2745	6390687	10	80.8	-	6390683	6390702	AGUGAUAGUCAUAGACCCGC	50	CGG
2746	6390734	10	84.4	+	6390716	6390735	UCUACAAUGGACCAGUACUG	45	GGG
2747	6390777	10	87.7	-	6390773	6390792	AAUGGGGUAUGGAGGUUCGG	55	GGG
2748	6390778	10	87.8	-	6390774	6390793	GAAUGGGGUAUGGAGGUUCG	55	GGG
2749	6390682	10	80.4	+	6390664	6390683	AAUGGCAUUCAUGUCACCGG	50	CGG
2750	6390801	10	89.5	+	6390783	6390802	AUACCCCAUUCCCGAAGAGG	55	GGG
2751	6390736	10	84.6	+	6390718	6390737	UACAAUGGACCAGUACUGGG	50	GGG
2752	6390785	10	88.3	-	6390781	6390800	UCUUCGGGAAUGGGGUAUGG	55	AGG
2753	6390157	9	64.7	-	6390153	6390172	GGGAAGUAUGGAUGGGCCUU	55	CGG
2754	6390226	9	70	+	6390208	6390227	AUGUUUCCCCAGUAUCCACU	45	GGG
2755	6390221	9	69.6	-	6390217	6390236	GGGGAGCCCAGUGGAUACUG	65	GGG
2756	6390314	9	76.7	+	6390296	6390315	GGAGCCGCAGUUGGAACCCG	70	GGG
2757	6390766	10	86.9	-	6390762	6390781	GAGGUUCGGGGGUAGCUGGG	70	AGG
2758	6390178	9	66.3	-	6390174	6390193	AGCAGUGGCUGUACCAAGUC	55	AGG
2759	6390800	10	89.4	+	6390782	6390801	CAUACCCCAUUCCCGAAGAG	55	GGG
2760	6390307	9	76.1	-	6390303	6390322	UGCUCCCCGGGGUUCCAACUG	65	CGG
2761	6390202	9	68.1	-	6390198	6390217	GGGGAAACAUCUCCAGAAAU	45	GGG
2762	6390820	10	91	-	6390816	6390835	GGGGUGUAGAGAGCCCGGGA	70	GGG
2763	6390749	10	85.8	-	6390745	6390764	GGGAGGUCUCCAGGACCCGG	75	TGG
2764	6390821	10	91.1	-	6390817	6390836	UGGGGUGUAGAGAGCCCGGG	70	AGG
2765	6390165	9	65.3	-	6390161	6390180	CCAAGUCAGGGAAGUAUGGA	50	TGG
2766	6390798	10	89.3	+	6390780	6390799	UCCAUACCCCAUUCCCGAAG	55	AGG
2767	6390825	10	91.4	-	6390821	6390840	CUGGUGGGGUGUAGAGAGCC	65	CGG
2768	6390824	10	91.3	-	6390820	6390839	UGGUGGGGUGUAGAGAGCCC	65	GGG
2769	6390799	10	89.4	+	6390781	6390800	CCAUACCCCAUUCCCGAAGA	55	GGG
2770	6390793	10	88.9	-	6390789	6390808	GGUCCCCCUCUUCGGGAAUG	65	GGG
2771	6390840	10	92.5	-	6390836	6390855	AGCCUUGCCAUCUUCCUGGU	55	GGG
2772	6390669	10	79.4	-	6390665	6390684	GCCGGUGACAUGAAUGCCAU	55	TGG
2773	6390169	9	65.6	-	6390165	6390184	UGUACCAAGUCAGGGAAGUA	45	TGG
2774	6390683	10	80.5	+	6390665	6390684	AUGGCAUUCAUGUCACCGGC	55	GGG
2775	6390844	10	92.8	+	6390826	6390845	UCUACACCCCACCAGGAAGA	55	TGG
2776	6390336	9	78.4	+	6390318	6390337	GAGCAGAGCCAGGUGGCCCA	70	CGG
2777	6390139	9	63.3	+	6390121	6390140	CCAAUCCUGUAGCUGGAAGC	55	TGG
2778	6390128	9	62.5	-	6390124	6390143	CCAGCUUCCAGCUACAGGAU	55	TGG
2779	6390312	9	76.5	+	6390294	6390313	AGGGAGCCGCAGUUGGAACC	65	CGG
2780	6390769	10	87.1	-	6390765	6390784	AUGGAGGUUCGGGGGUAGCU	60	GGG
2781	6390837	10	92.3	+	6390819	6390838	CGGGCUCUCUACACCCCACC	70	AGG
2782	6390779	10	87.8	-	6390775	6390794	GGAAUGGGGUAUGGAGGUUC	55	GGG
2783	6390292	9	75	+	6390274	6390293	AGAGUCCUCUGGACCUGACC	60	AGG
2784	6390299	9	75.5	-	6390295	6390314	GGGUUCCAACUGCGGCUCCC	70	TGG
2785	6390700	10	81.8	+	6390682	6390701	GGCGGGUCUAUGACUAUCAC	55	TGG
2786	6390839	10	92.4	-	6390835	6390854	GCCUUGCCAUCUUCCUGGUG	60	GGG
2787	6388821	8	60.9	+	6388803	6388822	GCUGCUCAAGAGGCGUCCGC	70	AGG
2788	6390733	10	84.3	+	6390715	6390734	AUCUACAAUGGACCAGUACU	40	GGG
2789	6390152	9	64.3	+	6390134	6390153	UGGAAGCUGGGAGCCUCCGA	65	AGG
2790	6388470	7	56.5	-	6388466	6388485	AGGGUGGCUCUUCCAGAUGC	60	AGG
2791	6390795	10	89.1	-	6390791	6390810	AGGGUCCCCCUCUUCGGGAA	65	TGG
2792	6390735	10	84.5	+	6390717	6390736	CUACAAUGGACCAGUACUGG	50	GGG

FIG. 40C

SEQ ID NO:	Genomic cut coordinate	Exon	CDS cut position %	Strand	Start coordinate	End coordinate	crRNA	GC content	PAM
2793	6390251	9	71.9	+	6390233	6390252	CCCCGCAGCCCCAGUUUUGG	70	AGG
2794	6390721	10	83.4	+	6390703	6390722	GGCAACAUCUACAUCUACAA	40	TGG
2795	6390127	9	62.4	-	6390123	6390142	CAGCUUCCAGCUACAGGAUU	50	GGG
2796	6390808	10	90.1	+	6390790	6390809	AUUCCCGAAGAGGGGGACCC	65	TGG
2797	6388501	7	58.9	+	6388483	6388502	CCUUCUCUCUGCAGGAAACU	50	GGG
2798	6390305	9	76	+	6390287	6390306	CCUGACCAGGGAGCCGCAGU	70	TGG
2799	6390132	9	62.8	+	6390114	6390133	GAGGGACCCAAUCCUGUAGC	60	TGG
2800	6390222	9	69.6	-	6390218	6390237	CGGGGAGCCCAGUGGAUACU	65	GGG
2801	6390849	10	93.2	+	6390831	6390850	ACCCCACCAGGAAGAUGGCA	60	AGG
2802	6390313	9	76.6	+	6390295	6390314	GGGAGCCGCAGUUGGAACCC	70	GGG
2803	6390758	10	86.2	-	6390754	6390773	GGGGUAGCUGGGAGGUCUCC	70	AGG
2804	6390734	10	84.4	-	6390730	6390749	CCCGGUGGUCCCCCCCAGUAC	75	TGG
2805	6390193	9	67.4	-	6390189	6390208	UCUCCAGAAAUGGGUAGCAG	50	TGG
2806	6388469	7	58	-	6388485	6388504	CCAGUUUCCUGCAGAGAGAA	50	GGG
2807	6390744	10	85.2	+	6390726	6390745	ACCAGUACUGGGGGGGACCAC	65	CGG
2808	6390223	9	69.7	-	6390219	6390238	GCGGGGAGCCCAGUGGAUAC	70	TGG
2809	6390752	10	85.8	-	6390748	6390767	GCUGGGAGGUCUCCAGGACC	70	CGG
2810	6390225	9	69.9	+	6390207	6390226	GAUGUUUCCCCAGUAUCCAC	50	TGG
2811	6390201	9	68	+	6390183	6390202	CAGCCACUGCUACCCAUUUC	55	TGG
2812	6390794	10	89	-	6390790	6390809	GGGUCCCCCUCUUCGGGAAU	65	GGG
2813	6390770	10	87.2	-	6390766	6390785	UAUGGAGGUUCGGGGGUAGC	60	TGG
2814	6390271	9	73.4	-	6390267	6390286	UCCAGAGGACUCUGCUGUUG	55	CGG
2815	6390230	9	70.3	-	6390226	6390245	UGGGGCUGCGGGGAGCCCAG	80	TGG
2816	6390176	9	66.1	+	6390158	6390177	CCAUCCAUACUUCCCUGACU	50	TGG
2817	6390801	10	89.5	-	6390797	6390816	AGGGCCAGGGUCCCCCUCUU	70	CGG
2818	6390203	9	68.2	-	6390199	6390218	UGGGGAAACAUCUCCAGAAA	45	TGG
2819	6390249	9	71.7	-	6390245	6390264	GCACCCCUGCCUCCAAAACU	60	GGG
2820	6390745	10	85.2	+	6390727	6390748	CCAGUACUGGGGGGACCACC	70	GGG
2821	6390780	10	87.9	-	6390776	6390795	GGGAAUGGGGUAUGGAGGUU	55	CGG
2822	6388490	7	58	-	6388486	6388505	CCCAGUUUCCUGCAGAGAGA	55	AGG
2823	6388486	7	57.7	-	6388482	6388501	GUUUCCUGCAGAGAGAAGGG	55	TGG
2824	6390256	9	72.2	+	6390238	6390257	CAGCCCCAGUUUUGGAGGCA	60	GGG
2825	6390818	10	90.8	+	6390800	6390819	AGGGGGACCCUGGCCCUCCC	80	GGG
2826	6390788	10	88.5	-	6390784	6390803	CCCUCUUCGGGAAUGGGGUA	60	TGG
2827	6390281	9	74.2	+	6390263	6390282	GCCGCAACAGCAGAGUCCUC	65	TGG
2828	6390294	9	75.2	-	6390290	6390309	CCAACUGCGGCUCCCUGGUC	70	AGG
2829	6390751	10	85.7	+	6390733	6390752	CUGGGGGGACCACCGGGUCC	80	TGG
2830	6390814	10	90.5	-	6390810	6390829	UAGAGAGCCCGGGAGGGCCA	70	GGG
2831	6390841	10	92.6	-	6390837	6390856	AAGCCUUGCCAUCUUCCUGG	55	TGG
2832	6390286	9	74.5	-	6390282	6390301	GGCUCCCUGGUCAGGUCCAG	70	AGG
2833	6390732	10	84.3	+	6390714	6390733	CAUCUACAAUGGACCAGUAC	45	TGG
2834	6390248	9	71.6	+	6390230	6390249	GCUCCCCGCAGCCCCAGUUU	70	TGG
2835	6390320	9	77.1	-	6390316	6390335	GGCCACCUGGCUCUGCUCCC	75	CGG
2836	6390133	9	62.8	-	6390129	6390148	GGCUCCCAGCUUCCAGCUAC	65	AGG
2837	6390815	10	90.6	-	6390811	6390830	GUAGAGAGCCCGGGAGGGCC	75	AGG
2838	6390844	10	92.8	-	6390840	6390859	GCCAAGCCUUGCCAUCUUCC	60	TGG
2839	6388493	7	58.3	+	6388475	6388494	AGAGCCACCCUUCUCUCUGC	60	AGG
2840	6390241	9	71.1	-	6390237	6390256	GCCUCCAAAACUGGGGCUGC	65	GGG
2841	6390319	9	77.1	-	6390315	6390334	GCCACCUGGCUCUGCUCCCC	75	GGG
2842	6390800	10	89.4	-	6390796	6390815	GGGCCAGGGUCCCCCUCUUC	75	GGG

FIG. 40D

SEQ ID NO:	Genomic cut coordinate	Exon	CDS cut position %	Strand	Start coordinate	End coordinate	crRNA	GC content	PAM
2843	6390242	9	71.2	-	6390238	6390257	UGCCUCCAAAACUGGGGCUG	60	CGG
2844	6390817	10	90.7	+	6390799	6390818	GAGGGGGACCCUGGCCCUCC	80	CGG
2845	6390255	9	72.2	+	6390237	6390256	GCAGCCCCAGUUUUGGAGGC	65	AGG
2846	6388500	7	58.8	+	6388482	6388501	CCCUUCUCUCUGCAGGAAAC	55	TGG
2847	6388407	7	51.7	-	6388403	6388422	CAGAACGGCCAGCAUCAGCA	60	TGG
2848	6386440	6	50.6	+	6386422	6386441	CCACUGCCCCCAGAGAUGUC	65	AGG
2849	6388422	7	52.8	-	6388418	6388437	GAAGGCCAGUGGCAGCAGAA	60	CGG
2850	6388428	7	53.3	+	6388410	6388429	GCUGGCCGUUCUGCUGCCAC	70	TGG
2851	6386429	6	49.8	-	6386425	6386444	CCUGACAUCUCUGGGGGCAG	65	TGG
2852	6386420	6	49.1	-	6386416	6386435	UCUGGGGGCAGUGGCUCUAA	60	TGG
2853	6390880	10	95.6	+	6390862	6390881	CUAGCGGAGACAGAGCACUG	60	TGG
2854	6390901	10	97.2	+	6390883	6390902	GGUGCCACACCCUCUAACAG	60	GGG
2855	6390900	10	97.1	+	6390882	6390901	UGGUGCCACACCCUCUAACA	55	GGG
2856	6390899	10	97	+	6390881	6390900	GUGGUGCCACACCCUCUAAC	60	AGG
2857	6390864	10	94.3	+	6390846	6390865	UGGCAAGGCUUGGCACCUAG	60	CGG
2858	6390868	10	94.6	-	6390864	6390883	CACAGUGCUCUGUCUCCGCU	60	AGG
2859	6390913	10	98.1	-	6390909	6390928	GGGUGAUAAAUUGGUUCCUU	40	GGG
2860	6390914	10	98.2	-	6390910	6390929	UGGGUGAUAAAUUGGUUCCU	40	TGG
2861	6390894	10	96.6	-	6390890	6390909	UGGGCCCCUGUUAGAGGGUG	65	TGG
2862	6390922	10	98.8	-	6390918	6390937	GUCAGUCAUGGGUGAUAAAU	40	TGG
2863	6390900	10	97.1	-	6390896	6390915	GUUCCUUGGGCCCCUGUUAG	60	AGG
2864	6390908	10	97.7	+	6390890	6390909	CACCCUCUAACAGGGGCCCA	65	AGG
2865	6390899	10	97	-	6390895	6390914	UUCCUUGGGCCCCUGUUAGA	55	GGG
2866	6390854	10	93.6	+	6390836	6390855	ACCAGGAAGAUGGCAAGGCU	55	TGG

FIG. 40E

SEQ ID NO:	MIT	CFD	Elevation	CCTop	Offtarget #	Azimuth	DeepSpCas9	CrisprScan	DO	Lindel	inDelphi	Frameshift	Precision	Graf Motifs	Bioscore	Out of Frame	Out of 3	Out of 11	Interpretation predictions
2643	96	98	43	79	19	63	73	59	65	85	90	86	55	OK	42	72	85	77	Knockout
2644	76	90	53	73	120	68	69	51	63	90	85	68	65	OK	48	68	80	74	Knockout
2645	74	84	53	70	254	39	58	51	49	91	88	90	63	OK	60	60	80	70	Knockout
2646	74	88	61	74	116	61	49	48	53	79	88	83	58	OK	56	64	79	70	Knockout
2647	73	88	58	73	166	62	60	60	61	74	83	79	47	OK	61	67	76	71	Knockout
2648	82	92	53	76	110	54	39	69	54	80	86	83	49	OK	50	65	79	71	Knockout
2649	62	89	64	72	181	50	58	68	59	65	82	73	64	OK	58	65	72	68	Knockout
2650	96	96	43	80	23	48	34	42	41	77	83	80	48	OK	47	61	80	67	Knockout
2651	71	82	49	67	263	63	56	74	64	71	65	68	45	OK	55	66	68	67	Knockout
2652	96	91	48	75	106	65	46	43	51	73	70	72	47	OK	63	63	73	66	Knockout
2653	90	96	47	78	45	53	61	47	54	69	75	68	58	TT	63	66	73	66	Knockout
2654	81	84	38	68	156	61	52	68	60	66	71	68	50	OK	51	64	68	65	Knockout
2655	77	88	47	71	116	48	29	54	44	80	84	82	49	OK	60	57	76	65	Knockout
2656	73	87	47	69	368	32	53	44	43	83	85	84	50	OK	61	56	76	65	Knockout
2657	49	62	31	47	485	45	46	100	64	82	78	80	46	OK	48	55	64	64	Knockout
2658	96	96	50	81	34	45	16	71	44	69	61	65	58	OK	60	63	73	64	Knockout
2659	83	89	55	76	78	46	20	59	42	71	80	75	61	TT	57	59	76	64	Knockout
2660	37	65	33	45	587	50	55	80	62	84	88	86	49	OK	55	53	65	64	Knockout
2661	78	71	52	67	225	59	45	45	50	76	72	74	40	OK	60	58	71	64	Knockout
2662	77	90	43	70	118	39	50	54	48	71	70	71	52	OK	64	59	70	63	Knockout
2663	93	96	47	79	47	54	31	29	36	75	68	71	61	OK	59	58	75	63	Knockout
2664	43	68	35	49	435	57	54	53	55	79	84	82	52	OK	73	52	65	62	Knockout
2665	47	71	33	50	332	61	51	73	62	70	76	73	51	OK	46	56	62	62	Knockout
2666	90	94	48	77	55	63	48	58	56	61	44	52	67	OK	48	67	65	62	Knockout
2667	79	92	48	73	71	49	32	13	31	77	78	78	53	OK	48	52	75	61	Knockout
2668	55	75	47	59	301	51	61	32	48	73	77	75	57	OK	52	53	67	61	Knockout
2669	57	75	42	58	366	41	53	61	52	70	75	73	46	OK	75	55	65	61	Knockout
2670	33	52	37	41	755	46	43	74	54	82	89	86	56	OK	55	47	63	60	Knockout
2671	62	80	34	59	350	37	35	58	43	79	76	78	62	GGC	33	51	68	60	Knockout
2672	62	75	57	65	333	19	7	62	29	82	87	85	66	TT	47	47	75	60	Knockout
2673	92	94	42	76	68	52	51	19	41	70	59	65	43	OK	71	58	70	60	Knockout
2674	89	94	51	78	95	50	38	60	49	65	43	54	55	OK	62	64	66	60	Knockout
2675	61	80	33	58	214	37	51	49	46	73	81	77	61	OK	53	52	67	60	Knockout
2676	68	80	34	61	330	31	46	51	43	70	75	73	49	OK	50	52	67	59	Knockout
2677	35	65	34	45	561	49	52	52	51	79	79	79	39	OK	36	48	62	58	Knockout
2678	56	78	34	56	309	36	64	61	54	70	58	64	47	OK	43	55	60	58	Knockout
2679	25	75	27	42	642	40	32	51	41	82	91	87	57	OK	47	42	65	57	Knockout
2680	45	71	32	48	435	33	35	56	41	78	85	82	72	OK	50	45	65	57	Knockout
2681	54	68	36	53	397	31	13	45	30	89	88	88	66	OK	61	41	71	57	Knockout
2682	44	66	31	47	479	40	52	35	42	75	87	81	59	OK	45	45	64	57	Knockout
2683	61	92	36	70	138	28	41	51	40	82	53	58	47	OK	64	55	64	56	Knockout
2684	52	78	34	55	270	34	29	52	38	74	76	75	49	OK	51	46	65	56	Knockout
2685	38	61	30	43	584	39	39	58	45	80	77	79	43	OK	48	44	61	56	Knockout
2686	65	85	47	66	241	39	30	36	35	65	68	66	56	OK	70	50	66	56	Knockout
2687	27	53	27	36	628	26	36	66	43	79	94	86	69	OK	57	39	61	55	Knockout
2688	54	67	44	55	486	37	21	20	28	80	77	78	51	OK	44	40	67	53	Knockout
2689	48	72	43	54	381	51	52	49	51	60	50	55	49	OK	50	53	55	53	Knockout
2690	33	66	29	43	602	39	15	44	33	78	89	83	57	GGC	47	38	63	53	Knockout
2691	22	49	21	31	916	47	54	73	58	67	58	63	43	OK	68	44	47	50	Knockout
2692	40	59	33	44	596	37	10	32	26	79	80	80	48	GGC	47	35	62	50	Knockout

FIG. 40F

SEQ ID NO:	MIT	CFD	Elevation	CCTop	Off-target #	Azimuth	DeepSpCas9	CrispRGen	CRISPOR	Lindel	inDelphi	Frameshift	Precision	Graf Motifs	Bioscore	GUIDE-seq	GUIDE-Tag	Consensus	Intended Knockout Predictions
2693	59	78	64	67	211	30	21	2	16	58	69	63	64	TT	50	42	65	49	Knockout
2694	46	67	31	48	578	11	25	43	26	71	75	73	62	OK	50	37	60	49	Knockout
2695	27	44	14	28	698	25	15	72	37	73	78	75	47	OK	53	33	52	47	Knockout
2696	45	69	40	51	544	20	15	41	25	63	68	65	51	TT	50	28	58	47	Knockout
2697	21	46	18	26	806	14	29	34	26	76	92	84	65	GGC	46	27	58	46	Knockout
2698	94	95	50	80	32	60	53	31	48	80	81	80	41	OK	53	64	80	69	Knockout or soluble decoy receptor
2699	84	90	45	73	95	51	48	49	49	68	89	88	62	OK	61	61	81	70	Knockout or soluble decoy receptor
2700	66	89	49	68	217	54	63	59	59	85	93	89	59	OK	62	63	76	72	Knockout or soluble decoy receptor
2701	66	78	53	66	194	64	61	39	55	84	91	87	51	OK	64	60	77	69	Knockout or soluble decoy receptor
2702	77	88	53	73	125	55	54	46	52	78	85	82	51	OK	48	62	77	69	Knockout or soluble decoy receptor
2703	83	89	55	76	99	57	45	43	48	82	86	84	59	OK	49	62	80	69	Knockout or soluble decoy receptor
2704	62	83	36	60	196	52	53	68	58	83	86	86	56	OK	58	59	73	68	Knockout or soluble decoy receptor
2705	58	82	48	63	285	51	48	61	53	82	91	87	60	TT	52	58	75	68	Knockout or soluble decoy receptor
2706	73	85	45	68	208	56	62	52	57	75	83	79	52	OK	55	62	73	68	Knockout or soluble decoy receptor
2707	72	79	53	68	179	57	51	47	52	81	86	84	62	GGC	64	60	76	68	Knockout or soluble decoy receptor
2708	91	97	44	77	64	47	46	75	56	63	74	69	43	OK	54	67	73	67	Knockout or soluble decoy receptor
2709	58	85	47	63	160	43	60	47	50	87	91	89	65	GGC	50	57	76	67	Knockout or soluble decoy receptor
2710	70	83	47	67	150	59	50	45	51	86	81	84	63	OK	60	59	75	67	Knockout or soluble decoy receptor
2711	90	93	48	77	73	39	23	53	38	77	86	81	64	OK	44	58	79	66	Knockout or soluble decoy receptor
2712	67	82	38	62	194	49	52	54	52	82	80	81	46	GGC	55	57	72	65	Knockout or soluble decoy receptor
2713	62	79	43	61	344	58	58	60	59	73	79	76	42	OK	63	60	69	65	Knockout or soluble decoy receptor
2714	76	84	38	66	180	57	61	55	58	87	70	68	38	OK	61	62	67	64	Knockout or soluble decoy receptor
2715	76	88	35	66	109	37	42	62	47	81	78	79	62	GGC	43	57	73	64	Knockout or soluble decoy receptor
2716	73	77	38	63	196	57	54	65	65	64	60	62	44	OK	55	64	62	63	Knockout or soluble decoy receptor
2717	77	85	61	74	147	32	24	32	29	61	91	86	57	TT	48	52	80	63	Knockout or soluble decoy receptor
2718	66	83	38	62	181	40	30	33	34	86	94	90	61	OK	44	48	76	62	Knockout or soluble decoy receptor
2719	54	73	38	55	283	44	18	49	37	91	96	93	65	GGC	44	46	74	62	Knockout or soluble decoy receptor
2720	58	76	56	63	267	49	30	46	42	82	78	80	54	GGC	47	52	72	62	Knockout or soluble decoy receptor
2721	47	78	66	64	266	51	29	43	41	72	84	78	51	OK	60	52	71	61	Knockout or soluble decoy receptor
2722	75	84	53	71	134	32	40	27	33	84	74	79	63	GGC	47	52	75	61	Knockout or soluble decoy receptor
2723	49	82	35	55	188	56	57	50	54	73	74	74	52	OK	50	55	64	61	Knockout or soluble decoy receptor
2724	74	84	44	67	166	28	12	46	26	80	90	85	63	TT	48	48	76	60	Knockout or soluble decoy receptor
2725	37	69	33	46	655	36	47	93	59	73	76	74	48	OK	56	52	60	60	Knockout or soluble decoy receptor
2726	66	80	49	65	208	60	56	70	63	82	51	52	55	OK	63	64	58	60	Knockout or soluble decoy receptor
2727	94	95	49	79	75	31	3	26	20	76	79	77	42	OK	53	50	78	59	Knockout or soluble decoy receptor
2728	43	74	46	54	368	35	54	56	48	70	75	72	56	OK	48	51	63	58	Knockout or soluble decoy receptor
2729	70	78	60	69	210	20	9	46	22	77	91	84	56	TT	50	48	77	58	Knockout or soluble decoy receptor
2730	57	77	32	55	431	25	23	75	41	89	84	77	59	OK	55	48	66	58	Knockout or soluble decoy receptor
2731	41	89	34	48	537	47	40	43	43	86	74	80	60	OK	61	48	64	57	Knockout or soluble decoy receptor
2732	47	81	43	57	190	38	29	27	31	78	86	82	55	OK	48	44	69	57	Knockout or soluble decoy receptor
2733	32	59	28	40	733	33	45	65	48	70	83	76	55	OK	61	44	56	55	Knockout or soluble decoy receptor
2734	27	57	18	34	581	37	46	63	49	74	82	78	49	OK	61	41	56	54	Knockout or soluble decoy receptor
2735	43	82	35	47	715	9	20	58	29	76	76	76	48	OK	52	38	61	51	Knockout or soluble decoy receptor
2736	22	58	12	30	825	39	41	74	51	68	75	71	46	OK	55	41	51	51	Knockout or soluble decoy receptor
2737	34	53	31	39	702	23	24	67	45	72	83	87	49	OK	51	42	53	50	Knockout or soluble decoy receptor
2738	66	82	58	69	168	54	56	34	48	91	97	94	73	OK	37	58	82	70	Membrane-bound decoy receptor
2739	89	93	49	77	61	63	61	79	66	77	86	81	58	OK	46	72	79	75	Membrane-bound decoy receptor
2740	79	83	53	72	179	55	47	53	52	85	89	87	51	OK	46	62	79	70	Membrane-bound decoy receptor
2741	74	86	53	71	172	65	69	66	67	79	83	81	51	OK	55	69	76	73	Membrane-bound decoy receptor
2742	79	88	48	72	124	60	66	44	57	92	83	88	67	OK	32	64	80	72	Membrane-bound decoy receptor

FIG. 40G

SEQ ID NO:	MIT	CFD	Elevation	CFD	Offtarget #	Azimuth	DeepSpCas9	CrispScan	CFD	Lindel	inDelphi	Frameshift	Precision	Graf Motifs	Bioscore	CFD	Graf	Consensus	Membrane-bound decoy receptor
2743	63	88	52	68	177	66	72	54	64	74	88	81	59	OK	44	66	74	71	Membrane-bound decoy receptor
2744	68	87	66	74	141	53	55	57	55	79	84	81	58	OK	53	64	77	70	Membrane-bound decoy receptor
2745	94	95	41	77	41	64	64	47	56	86	85	85	49	OK	43	67	81	73	Membrane-bound decoy receptor
2746	87	91	60	79	85	61	63	45	56	73	75	74	63	OK	55	69	77	70	Membrane-bound decoy receptor
2747	82	85	46	71	140	57	64	79	67	80	86	84	58	OK	45	69	77	74	Membrane-bound decoy receptor
2748	77	88	61	75	147	49	62	61	57	84	89	86	57	TT	46	66	81	73	Membrane-bound decoy receptor
2749	90	95	54	80	83	67	60	68	66	74	68	71	45	OK	53	72	75	72	Membrane-bound decoy receptor
2750	82	93	47	77	73	66	66	53	62	78	76	77	47	OK	43	69	77	72	Membrane-bound decoy receptor
2751	81	90	53	75	85	72	61	49	67	77	66	72	65	OK	54	71	73	71	Membrane-bound decoy receptor
2752	73	85	48	69	151	60	59	64	61	76	88	82	57	OK	48	65	75	71	Membrane-bound decoy receptor
2753	73	88	60	73	185	47	43	75	55	79	80	78	47	TT	38	64	76	69	Membrane-bound decoy receptor
2754	73	83	60	72	173	59	57	40	52	83	83	83	50	OK	50	62	77	69	Membrane-bound decoy receptor
2755	58	78	53	62	312	64	70	73	69	85	85	75	61	OK	45	65	68	69	Membrane-bound decoy receptor
2756	87	90	36	71	102	63	67	71	67	71	63	67	46	OK	43	69	69	68	Membrane-bound decoy receptor
2757	62	72	42	59	249	49	53	76	60	80	88	84	66	OK	45	59	71	68	Membrane-bound decoy receptor
2758	80	91	49	73	140	37	35	69	47	78	89	83	56	OK	54	60	78	68	Membrane-bound decoy receptor
2759	87	93	51	77	75	62	64	42	56	70	71	71	56	OK	43	67	74	68	Membrane-bound decoy receptor
2760	83	92	46	74	87	59	57	52	58	70	79	74	58	OK	47	65	74	68	Membrane-bound decoy receptor
2761	60	83	65	69	247	44	44	55	48	81	88	85	52	OK	49	59	77	67	Membrane-bound decoy receptor
2762	66	75	38	60	271	61	43	79	61	77	84	81	46	OK	48	60	70	67	Membrane-bound decoy receptor
2763	70	75	34	60	224	67	66	73	60	78	86	72	42	OK	45	64	66	67	Membrane-bound decoy receptor
2764	66	76	32	58	239	60	39	63	64	74	86	80	53	OK	49	61	69	67	Membrane-bound decoy receptor
2765	71	85	61	72	231	50	43	25	39	85	91	88	65	OK	46	56	80	67	Membrane-bound decoy receptor
2766	86	91	57	78	77	60	49	37	49	75	73	74	41	OK	48	63	76	67	Membrane-bound decoy receptor
2767	61	73	49	61	306	47	36	86	56	79	87	83	55	GGC	45	59	72	67	Membrane-bound decoy receptor
2768	55	72	38	55	338	58	55	79	64	79	82	81	44	OK	37	60	68	67	Membrane-bound decoy receptor
2769	86	95	58	80	97	55	53	46	51	68	72	70	55	OK	47	65	75	67	Membrane-bound decoy receptor
2770	90	93	46	76	66	57	48	54	53	68	75	71	59	OK	51	65	74	67	Membrane-bound decoy receptor
2771	64	79	57	67	202	46	55	51	51	80	85	82	64	OK	48	59	75	67	Membrane-bound decoy receptor
2772	87	94	61	81	55	55	45	65	56	73	80	67	47	OK	48	68	74	67	Membrane-bound decoy receptor
2773	61	85	55	67	193	51	62	47	53	81	82	82	55	OK	53	60	74	67	Membrane-bound decoy receptor
2774	89	93	53	78	65	59	47	45	50	70	76	73	52	OK	45	64	76	67	Membrane-bound decoy receptor
2775	59	81	58	66	213	53	69	42	55	75	76	76	56	OK	56	60	71	66	Membrane-bound decoy receptor
2776	48	66	40	51	509	51	74	72	66	82	78	80	48	OK	44	59	66	66	Membrane-bound decoy receptor
2777	72	88	53	71	135	45	29	28	34	88	93	93	71	OK	37	52	82	66	Membrane-bound decoy receptor
2778	81	88	53	74	165	44	49	46	46	79	77	78	43	OK	38	60	76	66	Membrane-bound decoy receptor
2779	73	89	41	68	169	45	61	63	58	72	75	73	54	OK	41	62	71	66	Membrane-bound decoy receptor
2780	78	83	45	68	130	42	37	68	49	75	84	80	54	OK	40	59	74	66	Membrane-bound decoy receptor
2781	80	76	42	59	173	55	43	63	54	81	85	83	60	OK	53	57	71	65	Membrane-bound decoy receptor
2782	65	83	56	68	254	28	47	86	54	72	77	74	44	TT	46	61	71	65	Membrane-bound decoy receptor
2783	71	85	48	68	163	50	55	36	47	78	81	80	52	OK	44	57	74	65	Membrane-bound decoy receptor
2784	71	89	52	71	130	44	43	32	40	82	89	86	61	OK	37	55	78	65	Membrane-bound decoy receptor
2785	96	98	43	79	26	54	52	37	48	84	74	69	62	OK	56	63	74	65	Membrane-bound decoy receptor
2786	64	75	63	67	235	54	52	61	56	76	85	71	50	OK	57	62	69	65	Membrane-bound decoy receptor
2787	90	90	36	72	310	57	38	46	47	76	77	76	46	OK	51	59	74	65	Membrane-bound decoy receptor
2788	94	91	61	79	117	42	50	43	45	72	69	71	61	OK	58	62	75	65	Membrane-bound decoy receptor
2789	53	70	54	59	319	54	52	57	54	80	76	78	44	OK	45	57	69	64	Membrane-bound decoy receptor
2790	65	79	62	69	197	55	64	48	56	82	71	67	58	OK	56	62	68	64	Membrane-bound decoy receptor
2791	84	93	43	73	160	32	29	66	42	79	74	77	47	OK	42	58	75	64	Membrane-bound decoy receptor
2792	86	93	58	79	84	60	55	44	53	69	52	61	52	OK	55	68	70	64	Membrane-bound decoy receptor

FIG. 40H

SEQ ID NO:	RIT	CFD	Elevation	CCTop	Offinder #	Azimuth	DeepSpCas9	CrispScan	CFD	Lindel	inDelphi	Frameshift	Precision	Graf Motifs	Bioscore	CCTop	CRISTA	Consensus	Membrane-bound decoy receptor
2793	73	82	44	66	159	46	51	40	46	76	83	79	59	OK	43	56	73	64	Membrane-bound decoy receptor
2794	77	80	61	78	139	52	47	23	41	71	83	77	58	OK	64	58	76	64	Membrane-bound decoy receptor
2795	77	88	60	75	181	42	42	61	48	68	71	70	48	OK	36	52	72	64	Membrane-bound decoy receptor
2796	86	91	37	71	73	49	29	31	36	76	85	82	59	OK	43	54	77	63	Membrane-bound decoy receptor
2797	55	76	60	64	340	45	42	50	46	79	80	80	56	OK	54	55	72	63	Membrane-bound decoy receptor
2798	79	93	43	71	156	52	45	57	51	63	68	65	50	OK	45	61	68	63	Membrane-bound decoy receptor
2799	78	87	51	72	123	47	45	42	45	67	71	69	51	OK	39	58	71	62	Membrane-bound decoy receptor
2800	69	86	45	67	144	32	20	64	39	76	86	81	66	OK	45	53	74	62	Membrane-bound decoy receptor
2801	57	67	49	58	330	62	52	28	47	83	79	81	45	OK	53	52	69	62	Membrane-bound decoy receptor
2802	58	74	34	55	230	59	63	51	58	68	80	74	60	OK	43	57	65	62	Membrane-bound decoy receptor
2803	64	73	49	62	275	39	23	49	37	82	87	85	51	OK	48	50	73	61	Membrane-bound decoy receptor
2804	89	94	46	76	76	42	27	55	41	68	63	65	55	OK	58	59	71	61	Membrane-bound decoy receptor
2805	71	82	53	69	210	61	61	41	54	65	58	61	47	OK	52	61	65	61	Membrane-bound decoy receptor
2806	29	59	48	45	467	54	34	60	49	88	89	89	58	OK	65	47	67	61	Membrane-bound decoy receptor
2807	80	87	47	71	111	45	42	78	55	56	58	57	49	OK	39	63	64	61	Membrane-bound decoy receptor
2808	79	92	49	73	134	25	29	37	30	76	86	81	57	OK	45	52	77	61	Membrane-bound decoy receptor
2809	56	77	42	58	364	48	51	63	54	77	83	70	43	OK	36	56	64	61	Membrane-bound decoy receptor
2810	55	76	51	61	182	49	58	33	47	78	75	77	42	OK	37	54	69	61	Membrane-bound decoy receptor
2811	75	89	53	73	177	17	12	39	23	84	94	89	60	TT	49	48	61	61	Membrane-bound decoy receptor
2812	91	95	50	79	84	26	28	46	33	75	82	68	54	OK	51	56	74	60	Membrane-bound decoy receptor
2813	81	87	35	68	108	24	24	48	32	70	88	79	63	OK	39	50	74	60	Membrane-bound decoy receptor
2814	65	78	44	62	238	55	59	67	60	88	81	57	53	OK	44	61	60	60	Membrane-bound decoy receptor
2815	30	50	27	36	662	61	52	60	64	80	81	81	45	OK	36	50	58	60	Membrane-bound decoy receptor
2816	68	82	60	70	179	54	43	24	40	72	70	71	48	OK	55	55	70	60	Membrane-bound decoy receptor
2817	68	84	46	66	249	26	33	75	33	75	88	81	63	TT	42	49	73	60	Membrane-bound decoy receptor
2818	52	75	65	64	288	35	20	53	36	79	80	79	41	OK	41	50	72	60	Membrane-bound decoy receptor
2819	54	78	70	67	302	41	41	33	38	71	77	74	55	OK	45	53	71	60	Membrane-bound decoy receptor
2820	76	85	36	66	130	51	45	63	53	58	83	81	58	OK	40	59	63	60	Membrane-bound decoy receptor
2821	48	73	57	59	507	34	27	73	45	72	74	73	44	OK	47	52	66	59	Membrane-bound decoy receptor
2822	39	60	56	52	404	46	31	38	38	86	89	88	54	OK	63	45	70	59	Membrane-bound decoy receptor
2823	36	57	21	38	504	67	64	44	58	61	82	82	52	OK	56	48	60	59	Membrane-bound decoy receptor
2824	35	57	68	53	572	44	32	65	47	79	71	75	45	OK	40	50	64	58	Membrane-bound decoy receptor
2825	44	69	28	47	467	43	17	69	43	78	89	84	66	OK	47	45	65	58	Membrane-bound decoy receptor
2826	74	85	38	66	127	37	18	43	33	75	74	74	48	OK	53	49	70	58	Membrane-bound decoy receptor
2827	77	87	56	73	120	43	42	33	39	61	59	60	47	OK	49	56	67	58	Membrane-bound decoy receptor
2828	70	68	34	64	141	35	27	55	39	72	73	72	43	OK	44	52	68	58	Membrane-bound decoy receptor
2829	75	84	37	65	205	39	21	66	42	62	73	67	48	OK	37	54	66	58	Membrane-bound decoy receptor
2830	50	67	40	52	269	53	56	64	58	88	52	60	56	OK	31	55	56	57	Membrane-bound decoy receptor
2831	49	36	40	42	1230	54	54	54	54	78	73	75	44	OK	48	48	59	57	Membrane-bound decoy receptor
2832	55	75	42	57	338	54	42	60	52	61	82	61	53	OK	51	55	59	57	Membrane-bound decoy receptor
2833	86	94	50	77	82	44	16	33	31	64	65	64	54	OK	58	54	71	57	Membrane-bound decoy receptor
2834	68	87	34	63	189	29	21	45	32	70	75	72	51	TT	46	47	68	56	Membrane-bound decoy receptor
2835	41	67	37	48	473	35	46	46	42	71	82	77	54	OK	43	45	62	56	Membrane-bound decoy receptor
2836	60	79	50	63	278	46	43	41	43	62	57	59	51	OK	39	53	61	55	Membrane-bound decoy receptor
2837	51	68	36	52	298	32	38	50	40	77	70	73	48	GGC	34	46	62	55	Membrane-bound decoy receptor
2838	51	77	64	64	281	34	32	13	26	69	82	76	65	TT	56	45	70	55	Membrane-bound decoy receptor
2839	43	72	39	51	297	49	47	27	41	72	75	74	43	OK	54	46	62	55	Membrane-bound decoy receptor
2840	40	68	55	57	362	32	43	35	37	66	74	67	56	OK	32	47	62	54	Membrane-bound decoy receptor
2841	38	60	37	45	573	41	42	62	48	67	68	67	37	OK	43	47	56	54	Membrane-bound decoy receptor
2842	66	83	47	65	277	29	8	69	35	84	83	58	47	TT	47	50	62	53	Membrane-bound decoy receptor

FIG. 40I

SEQ ID NO:	MIT	CFD	Elevation	CFD	Offtarget #	Azimuth	DeepSpCas9	CrisprScan	CFD	Lindel	inDelphi	Frameshift	Precision	Graf Motifs	Bioscore				Isoform prediction
2843	34	73	33	47	322	42	41	48	44	58	71	62	56	OK	32	45	54	51	Membrane-bound decoy receptor
2844	29	65	15	38	471	30	16	69	36	77	82	79	53	OK	32	37	56	51	Membrane-bound decoy receptor
2845	34	63	65	54	460	36	24	41	34	62	69	65	57	OK	41	44	60	51	Membrane-bound decoy receptor
2846	41	66	37	48	409	34	19	23	29	77	84	81	54	OK	55	37	64	51	Membrane-bound decoy receptor
2847	67	77	53	66	264	63	69	43	58	77	55	66	63	OK	59	62	66	63	Soluble decoy receptor
2848	63	76	43	61	395	49	49	39	46	84	81	82	64	OK	45	53	72	63	Soluble decoy receptor
2849	44	68	32	48	440	56	59	58	58	78	62	70	57	OK	52	53	59	59	Soluble decoy receptor
2850	66	85	53	68	191	38	58	58	51	61	41	51	50	OK	47	60	60	57	Soluble decoy receptor
2851	44	61	70	58	456	44	44	64	51	80	58	59	46	OK	40	54	58	56	Soluble decoy receptor
2852	71	80	48	66	203	32	21	59	37	55	86	60	46	OK	43	52	63	55	Soluble decoy receptor
2853	60	81	47	63	176	76	81	56	72	91	93	92	60	OK	56	67	77	75	Wildtype-like
2854	87	95	53	78	84	64	69	37	57	75	89	82	57	OK	38	67	80	72	Wildtype-like
2855	82	94	56	77	100	49	54	45	49	84	87	88	53	OK	39	63	82	71	Wildtype-like
2856	89	94	57	80	71	34	38	43	38	80	92	86	64	OK	39	59	83	68	Wildtype-like
2857	82	85	52	66	163	69	41	59	56	77	82	79	44	OK	50	61	73	67	Wildtype-like
2858	82	84	53	73	158	54	30	55	46	83	81	82	53	OK	56	60	76	67	Wildtype-like
2859	78	86	61	75	135	36	30	58	41	76	83	80	52	TT	38	58	77	65	Wildtype-like
2860	76	88	61	74	152	37	29	29	32	80	91	85	63	TT	38	53	80	64	Wildtype-like
2861	61	69	53	61	280	40	40	56	57	77	74	75	44	OK	39	59	68	64	Wildtype-like
2862	78	88	60	75	101	23	16	57	31	86	87	86	53	OK	44	53	81	64	Wildtype-like
2863	74	87	43	68	120	40	21	45	35	79	90	85	57	OK	39	52	76	63	Wildtype-like
2864	64	82	46	64	163	55	45	54	51	78	71	75	46	OK	41	58	69	63	Wildtype-like
2865	63	79	36	59	232	40	28	58	42	78	92	85	60	OK	42	51	72	62	Wildtype-like
2866	75	49	58	41	1281	50	49	58	52	84	90	87	59	OK	53	46	64	60	Wildtype-like

FIG. 40J

SEQ ID NO:	Genomic cut coordinate	Exon	CDS cut position	CDS cut position %	Strand	Start coordinate	End coordinate	crRNA	GC content	PAM
2867	1214095	1	32	3.8	+	1214078	1214097	GCAGAGCCGCACACGGCCCG	80	CGG
2868	1214090	1	37	4.4	-	1214087	1214106	GCUGGGCCGCGGGCCGUGUG	85	CGG
2869	1214088	1	39	4.7	+	1214071	1214090	AGGAGGAGCAGAGCCGCACA	65	CGG
2870	1214048	1	79	9.5	+	1214031	1214050	GACACAGUGGAGCCCCGUCA	65	CGG
2871	1214035	1	92	11	+	1214018	1214037	GGUAGGUGUCCCCGACACAG	65	TGG
2872	1214033	1	94	11.3	-	1214030	1214049	GACGGGGCUCCACUGUGUCG	70	GGG
2873	1213749	2	181	21.7	-	1213746	1213765	CUGCAGCCGCUCCCAGAACA	65	CGG
2874	1213733	2	197	23.6	-	1213730	1213749	AACACGGUGUGCCGUCCGUG	65	CGG
2875	1213733	2	197	23.6	+	1213716	1213735	AGAAGCCCGGCCCGCACGGA	75	CGG
2876	1213732	2	198	23.7	-	1213729	1213748	ACACGGUGUGCCGUCCGUGC	70	GGG
2877	1213729	2	201	24.1	+	1213712	1213731	UUGUAGAAGCCCGGCCCGCA	65	CGG
2878	1213678	2	252	30.2	+	1213661	1213680	CUGAGGUUACACCACGUGCA	55	GGG
2879	1213066	3	295	35.4	-	1213063	1213082	UGAGCGGAAGCAGCUGUGCA	60	CGG
2880	1213054	3	307	36.8	+	1213037	1213056	GCGGCAGACUGUGUCCUGUG	65	TGG
2881	1213013	3	348	41.7	+	1212996	1213015	CCAGGCUUGUAGCUGUCCAG	60	GGG
2882	1213012	3	349	41.8	+	1212995	1213014	UCCAGGCUUGUAGCUGUCCA	55	GGG
2883	1213002	3	359	43	-	1212999	1213018	CCCCUGGACAGCUACAAGCC	65	TGG
2884	1214050	1	77	9.2	-	1214047	1214066	CUGGGGCUGAGCACCGUGAC	70	GGG
2885	1213727	2	203	24.3	-	1213724	1213743	GUGUGCCGUCCGUGCGGGCC	80	GGG
2886	1213678	2	252	30.2	-	1213675	1213694	AGCCGUGCAAGCCCUGCACG	70	TGG
2887	1214051	1	76	9.1	-	1214048	1214067	CCUGGGGCUGAGCACCGUGA	70	CGG
2888	1213032	3	329	39.4	-	1213029	1213048	ACAGUCUGCCGCUGCCGGGC	75	GGG
2889	1213720	2	210	25.2	+	1213703	1213722	ACCACGUCGUUGUAGAAGCC	55	CGG
2890	1214013	1	114	13.7	+	1213996	1214015	UGGCAGCACCGGUCGUUGCU	65	GGG
2891	1213057	3	304	36.5	-	1213054	1213073	GCAGCUGUGCACGGCCACAC	70	AGG
2892	1214049	1	78	9.4	-	1214046	1214065	UGGGGCUGAGCACCGUGACG	70	GGG
2893	1214010	1	117	14	-	1214007	1214026	ACACCUACCCCAGCAACGAC	60	CGG
2894	1213033	3	328	39.3	-	1213030	1213049	CACAGUCUGCCGCUGCCGGG	75	CGG
2895	1213749	2	181	21.7	+	1213732	1213751	CGGACGGCACACCGUGUUCU	65	GGG
2896	1213728	2	202	24.2	-	1213725	1213744	GGUGUGCCGUCCGUGCGGGC	80	CGG
2897	1213687	2	243	29.1	+	1213670	1213689	CACCACGUGCAGGGCUUGCA	65	CGG
2898	1213692	2	238	28.5	+	1213675	1213694	CGUGCAGGGCUUGCACGGCU	70	TGG
2899	1213992	1	135	16.2	-	1213989	1214008	ACCGGUGCUGCCACGAGUGC	70	AGG
2900	1214018	1	109	13.1	+	1214001	1214020	GCACCGGUCGUUGCUGGGGU	70	AGG
2901	1213036	3	325	39	-	1213033	1213052	GGACACAGUCUGCCGCUGCC	70	GGG
2902	1213748	2	182	21.8	+	1213731	1213750	ACGGACGGCACACCGUGUUC	65	TGG
2903	1213029	3	332	39.8	+	1213012	1213031	CCAGGGGCUGGGUGCCCGCC	85	CGG
2904	1213677	2	253	30.3	+	1213660	1213679	ACUGAGGUUACACCACGUGC	55	AGG
2905	1213011	3	350	42	+	1212994	1213013	CUCCAGGCUUGUAGCUGUCC	60	AGG
2906	1214014	1	113	13.5	+	1213997	1214016	GGCAGCACCGGUCGUUGCUG	70	GGG
2907	1213035	3	326	39.1	+	1213018	1213037	GCUGGGUGCCCGCCCGGCAG	85	CGG
2908	1213017	3	344	41.2	+	1213000	1213019	GCUUGUAGCUGUCCAGGGGC	65	TGG
2909	1213754	2	176	21.1	+	1213737	1213756	GGCACACCGUGUUCUGGGAG	65	CGG
2910	1214012	1	115	13.8	+	1213995	1214014	GUGGCAGCACCGGUCGUUGC	70	TGG
2911	1214074	1	53	6.4	-	1214071	1214090	UGUGCGGCUCUGCUCCUCCU	65	GGG
2912	1213710	2	220	26.4	-	1213707	1213726	GCCGGGCUUCUACAACGACG	65	TGG
2913	1213018	3	343	41.1	+	1213001	1213020	CUUGUAGCUGUCCAGGGGCU	60	GGG
2914	1214062	1	65	7.8	+	1214045	1214064	CCGUCACGGUGCUCAGCCCC	75	AGG
2915	1212996	3	365	43.8	-	1212993	1213012	GACAGCUACAAGCCUGGAGU	55	TGG
2916	1214100	1	27	3.2	-	1214097	1214116	GGGCUCGGCGGCUGGGCCGC	90	GGG

FIG. 41A

SEQ ID NO:	Genomic cut coordinate	Exon	CDS cut position	CDS cut position %	Strand	Start coordinate	End coordinate	crRNA	GC content	PAM
2917	1214002	1	125	15	+	1213985	1214004	GCCUGCACUCGUGGCAGCAC	70	CGG
2918	1213018	3	343	41.1	-	1213015	1213034	CCGGGGCGGGCACCCAGCCCC	90	TGG
2919	1214101	1	26	3.1	-	1214098	1214117	GGGGCUCGGCGGCUGGGCCG	90	CGG
2920	1213037	3	324	38.8	-	1213034	1213053	AGGACACAGUCUGCCGCUGC	65	CGG
2921	1214075	1	52	6.2	-	1214072	1214091	GUGUGCGGCUCUGCUCCUCC	70	TGG
2922	1213763	2	167	20	+	1213746	1213765	UGUUCUGGGAGCGGCUGCAG	65	CGG
2923	1214071	1	56	6.7	+	1214054	1214073	UGCUCAGCCCCAGGCCCAGG	75	AGG
2924	1214067	1	60	7.2	-	1214064	1214083	CUCUGCUCCUCCUGGGCCUG	70	GGG
2925	1214069	1	58	7	-	1214066	1214085	GGCUCUGCUCCUCCUGGGCC	75	TGG
2926	1212685	4	389	46.6	+	1212668	1212687	CUGGGGAGAAGUGCCCUGGA	65	GGG
2927	1212668	4	406	48.7	+	1212651	1212670	GCAGGCCUGGUUGUCGCCUG	70	GGG
2928	1212109	5	466	55.9	+	1212092	1212111	GCUAUUGCUGGCCGGCUGCA	65	GGG
2929	1212101	5	474	56.8	+	1212084	1212103	GCGUCCGAGCUAUUGCUGGC	65	CGG
2930	1212079	5	496	59.5	-	1212076	1212095	UAGCUCGGACGCAAUCUGUG	55	AGG
2931	1212094	5	481	57.7	-	1212091	1212110	GCAGCCGGCCAGCAAUAGCU	65	CGG
2932	1212662	4	412	49.4	-	1212659	1212678	CUUCUCCCCAGGCGACAACC	65	AGG
2933	1212127	5	448	53.7	+	1212110	1212129	CAGGGUGUGCUUCCCAGCCA	65	AGG
2934	1212684	4	390	46.8	+	1212667	1212686	CCUGGGGAGAAGUGCCCUGG	70	AGG
2935	1212667	4	407	48.8	+	1212650	1212669	UGCAGGCCUGGUUGUCGCCU	65	GGG
2936	1212666	4	408	48.9	+	1212649	1212668	UUGCAGGCCUGGUUGUCGCC	65	TGG
2937	1212097	5	478	57.3	+	1212080	1212099	GAUUGCGUCCGAGCUAUUGC	55	TGG
2938	1212681	4	393	47.1	+	1212664	1212683	UCGCCUGGGGAGAAGUGCCC	70	TGG
2939	1212690	4	384	46	+	1212673	1212692	GAGAAGUGCCCUGGAGGGCA	65	GGG
2940	1212687	4	387	46.4	-	1212684	1212703	ACUGUGCCCCCUGCCCUCCA	70	GGG
2941	1212673	4	401	48.1	-	1212670	1212689	CCUCCAGGGCACUUCUCCCC	70	AGG
2942	1212109	5	466	55.9	-	1212106	1212125	UGGGAAGCACACCCUGCAGC	65	CGG
2943	1212692	4	382	45.8	+	1212675	1212694	GAAGUGCCCUGGAGGGCAGG	70	GGG
2944	1212108	5	467	56	+	1212091	1212110	AGCUAUUGCUGGCCGGCUGC	65	AGG
2945	1212655	4	419	50.2	+	1212638	1212657	UGGUCCAGGGCUUGCAGGCC	70	TGG
2946	1212691	4	383	45.9	+	1212674	1212693	AGAAGUGCCCUGGAGGGCAG	65	GGG
2947	1212650	4	424	50.8	+	1212633	1212652	UCACUUGGUCCAGGGCUUGC	60	AGG
2948	1212689	4	385	46.2	+	1212672	1212691	GGAGAAGUGCCCUGGAGGGC	70	AGG
2949	1212648	4	426	51.1	-	1212645	1212664	ACAACCAGGCCUGCAAGCCC	65	TGG
2950	1212688	4	386	46.3	-	1212685	1212704	GACUGUGCCCCCUGCCCUCC	75	AGG
2951	1211754	6	712	85.4	+	1211737	1211756	GUCCCUCCGGAGCAGGUACA	65	GGG
2952	1211601	7	787	94.4	+	1211584	1211603	GGCCUGCUCCUCUUGGAUGG	65	GGG
2953	1211598	7	790	94.7	-	1211595	1211614	UUUCCGGACCCCCAUCCAAG	60	AGG
2954	1211720	6	746	89.4	+	1211703	1211722	CAGGGGGCUUGUGGGCAUCG	70	GGG
2955	1211721	6	745	89.3	+	1211704	1211723	AGGGGGCUUGUGGGCAUCGG	70	GGG
2956	1211599	7	789	94.6	+	1211582	1211601	UCGGCCUGCUCCUCUUGGAU	60	GGG
2957	1211722	6	744	89.2	+	1211705	1211724	GGGGGCUUGUGGGCAUCGGG	75	GGG
2958	1211598	7	790	94.7	+	1211581	1211600	GUCGGCCUGCUCCUCUUGGA	65	TGG
2959	1211600	7	788	94.5	+	1211583	1211602	CGGCCUGCUCCUCUUGGAUG	65	GGG
2960	1211746	6	720	86.3	-	1211743	1211762	UGGCCCUGUACCUGCUCCGG	70	AGG
2961	1211745	6	721	86.5	-	1211742	1211761	GGCCCUGUACCUGCUCCGGA	70	GGG
2962	1211718	6	748	89.7	+	1211701	1211720	ACCAGGGGGCUUGUGGGCAU	65	CGG
2963	1211741	6	725	86.9	+	1211724	1211743	GGGGCAGCCUCUGGUCCCUC	75	CGG
2964	1211606	7	782	93.8	+	1211589	1211608	GCUCCUCUUGGAUGGGGGUC	65	CGG
2965	1211719	6	747	89.6	+	1211702	1211721	CCAGGGGGCUUGUGGGCAUC	70	GGG
2966	1211708	6	758	90.9	-	1211705	1211724	CCCGAUGCCCACAAGCCCCC	75	TGG

FIG. 41B

SEQ ID NO:	Genomic cut coordinate	Exon	CDS cut position	CDS cut position %	Strand	Start coordinate	End coordinate	crRNA	GC content	PAM
2967	1211594	7	794	95.2	+	1211577	1211596	GGGCGUCGGCCUGCUCCUCU	75	TGG
2968	1211749	6	717	86	-	1211746	1211765	UGCUGGCCCCUGUACCUGCUC	65	CGG
2969	1211732	6	734	88	+	1211715	1211734	GGGCAUCGGGGGGCAGCCUC	80	TGG
2970	1211592	7	796	95.4	-	1211589	1211608	GACCCCCAUCCAAGAGGAGC	65	AGG
2971	1211773	6	693	83.1	+	1211756	1211775	AGGGCCAGCAGGAUGGCCAG	70	GGG
2972	1211737	6	729	87.4	-	1211734	1211753	ACCUGCUCCGGAGGGACCAG	70	AGG
2973	1211747	6	719	86.2	+	1211730	1211749	GCCUCUGGUCCCUCCGGAGC	75	AGG
2974	1211772	6	694	83.2	+	1211755	1211774	CAGGGCCAGCAGGAUGGCCA	70	GGG
2975	1211766	6	700	83.9	+	1211749	1211768	CAGGUACAGGGCCAGCAGGA	65	TGG
2976	1211762	6	704	84.4	+	1211745	1211764	GGAGCAGGUACAGGGCCAGC	70	AGG
2977	1211753	6	713	85.5	+	1211736	1211755	GGUCCCUCCGGAGCAGGUAC	70	AGG
2978	1211771	6	695	83.3	+	1211754	1211773	ACAGGGCCAGCAGGAUGGCC	70	AGG
2979	1211766	6	700	83.9	-	1211763	1211782	GGGCCCCCUGGCCAUCCUGC	80	TGG
2980	1211778	6	688	82.5	-	1211775	1211794	GCUGGGGCUGCUGGGCCCCC	85	TGG
2981	1211786	6	680	81.5	-	1211783	1211802	GGCCUGGUGCUGGGGCUGCU	75	GGG
2982	1211962	5	613	73.5	+	1211945	1211964	GGGGACCUCCACGGGCCGGG	85	TGG
2983	1211946	5	629	75.4	-	1211943	1211962	CGGCCCGUGGAGGUCCCCGG	85	GGG
2984	1211825	6	641	76.9	+	1211808	1211827	CCAGGAUGGCGGCAACCGCA	70	CGG
2985	1211947	5	628	75.3	-	1211944	1211963	CCGGCCCGUGGAGGUCCCCG	85	GGG
2986	1211956	5	619	74.2	-	1211953	1211972	ACCCUCCACCCGGCCCGUGG	80	AGG
2987	1211977	5	598	71.7	+	1211960	1211979	CCGGGUGGAGGGUCCCUGUG	75	AGG
2988	1212027	5	548	65.7	+	1212010	1212029	CAGUGAUGGGCCUGGCCGGG	75	GGG
2989	1211999	5	576	69.1	+	1211982	1212001	GUUCUGGGCCAGGCUUCAGU	60	GGG
2990	1212026	5	549	65.8	+	1212009	1212028	ACAGUGAUGGGCCUGGCCGG	70	GGG
2991	1212052	5	523	62.7	+	1212035	1212054	CUGGGUCUCCUGGGGCUGCG	75	TGG
2992	1211959	5	616	73.9	-	1211956	1211975	GGGACCCUCCACCCGGCCCG	85	TGG
2993	1212074	5	501	60.1	-	1212071	1212090	CGGACGCAAUCUGUGAGGAC	60	AGG
2994	1212073	5	502	60.2	-	1212070	1212089	GGACGCAAUCUGUGAGGACA	55	GGG
2995	1211980	5	595	71.3	-	1211977	1211996	AGCCUGGCCCAGAACCUCAC	65	AGG
2996	1211979	5	596	71.5	-	1211976	1211995	GCCUGGCCCAGAACCUCACA	65	GGG
2997	1212014	5	561	67.3	+	1211997	1212016	UCAGUGGGCUGGACAGUGAU	55	GGG
2998	1211959	5	616	73.9	+	1211942	1211961	CCCGGGGACCUCCACGGGCC	85	GGG
2999	1212023	5	552	66.2	+	1212006	1212025	UGGACAGUGAUGGGCCUGGC	65	CGG
3000	1211814	6	652	78.2	-	1211811	1211830	CCGUGCGGUUGCCGCCAUCC	75	TGG
3001	1211966	5	609	73	+	1211949	1211968	ACCUCCACGGGCCGGGUGGA	75	GGG
3002	1211958	5	617	74	+	1211941	1211960	CCCCGGGGACCUCCACGGGC	85	CGG
3003	1211949	5	626	75.1	-	1211946	1211965	ACCCGGCCCGUGGAGGUCCC	80	CGG
3004	1212039	5	536	64.3	-	1212036	1212055	ACGCAGCCCCAGGAGACCCA	70	GGG
3005	1211984	5	591	70.9	+	1211967	1211986	GAGGGUCCCUGUGAGGUUCU	60	GGG
3006	1211814	6	652	78.2	+	1211797	1211816	CAGGCCCAGGCCCAGGAUGG	75	CGG
3007	1212013	5	562	67.4	+	1211996	1212015	UUCAGUGGGCUGGACAGUGA	55	TGG
3008	1211998	5	577	69.2	+	1211981	1212000	GGUUCUGGGCCAGGCUUCAG	65	TGG
3009	1211996	5	579	69.4	-	1211993	1212012	CUGUCCAGCCCACUGAAGCC	65	TGG
3010	1211948	5	627	75.2	-	1211945	1211964	CCCGGGCCCGUGGAGGUCCCC	85	GGG
3011	1212025	5	550	65.9	+	1212008	1212027	GACAGUGAUGGGCCUGGCCG	70	GGG
3012	1212059	5	516	61.9	+	1212042	1212061	UCCUGGGGCUGCGUGGCUGG	75	GGG
3013	1212024	5	551	66.1	+	1212007	1212026	GGACAGUGAUGGGCCUGGCC	70	GGG
3014	1212058	5	517	62	+	1212041	1212060	CUCCUGGGGCUGCGUGGCUG	75	GGG
3015	1211965	5	610	73.1	+	1211948	1211967	GACCUCCACGGGCCGGGUGG	80	AGG
3016	1212019	5	556	66.7	+	1212002	1212021	GGGCUGGACAGUGAUGGGCC	70	TGG

FIG. 41C

SEQ ID NO:	Genomic cut coordinate	Exon	CDS cut position	CDS cut position %	Strand	Start coordinate	End coordinate	crRNA	GC content	PAM
3017	1212057	5	518	62.1	+	1212040	1212059	UCUCCUGGGGCUGCGUGGCU	70	GGG
3018	1212026	5	549	65.8	-	1212023	1212042	AGACCCAGGGCCCCCCGGCC	85	AGG
3019	1211983	5	592	71	+	1211966	1211985	GGAGGGUCCCUGUGAGGUUC	65	TGG
3020	1212044	5	531	63.7	+	1212027	1212046	GGGGGGCCCUGGGUCUCCUG	80	GGG
3021	1212056	5	519	62.2	+	1212039	1212058	GUCUCCUGGGGCUGCGUGGC	75	TGG
3022	1212034	5	541	64.9	+	1212017	1212036	GGGCCUGGCCGGGGGGCCCU	90	GGG
3023	1212031	5	544	65.2	-	1212028	1212047	CCAGGAGACCCAGGGCCCCC	80	CGG
3024	1212003	5	572	68.6	+	1211986	1212005	UGGGCCAGGCUUCAGUGGGC	70	TGG
3025	1212040	5	535	64.1	-	1212037	1212056	CACGCAGCCCCAGGAGACCC	75	AGG
3026	1211989	5	586	70.3	+	1211972	1211991	UCCCUGUGAGGUUCUGGGCC	65	AGG
3027	1211813	6	653	78.3	-	1211810	1211829	CGUGCGGUUGCCGCCAUCCU	70	GGG
3028	1212043	5	532	63.8	+	1212026	1212045	CGGGGGGCCCUGGGUCUCCU	80	GGG
3029	1212049	5	526	63.1	-	1212046	1212065	CCCCCCAGCCACGCAGCCCC	85	AGG
3030	1212033	5	542	65	+	1212016	1212035	UGGGCCUGGCCGGGGGGCCC	90	TGG
3031	1211807	6	659	79	-	1211804	1211823	GUUGCCGCCAUCCUGGGCCU	70	GGG
3032	1211808	6	658	78.9	-	1211805	1211824	GGUUGCCGCCAUCCUGGGCC	75	TGG
3033	1211795	6	671	80.5	-	1211792	1211811	CUGGGCCUGGGCCUGGUGCU	75	GGG
3034	1212042	5	533	63.9	+	1212025	1212044	CCGGGGGGCCCUGGGUCUCC	85	TGG
3035	1211802	6	664	79.6	-	1211799	1211818	CGCCAUCCUGGGCCUGGGCC	80	TGG
3036	1211568	7	820	98.3	+	1211551	1211570	AGGUCAGAUCUUGGCCAGGG	60	TGG
3037	1211559	7	829	99.4	+	1211542	1211561	GGUGGGCCCAGGUCAGAUCU	65	TGG
3038	1211565	7	823	98.7	+	1211548	1211567	CCCAGGUCAGAUCUUGGCCA	60	GGG
3039	1211564	7	824	98.8	+	1211547	1211566	GCCCAGGUCAGAUCUUGGCC	65	AGG
3040	1211571	7	817	98	-	1211568	1211587	GGCCGACGCCCACUCCACCC	80	TGG
3041	1211580	7	808	96.9	+	1211563	1211582	GGCCAGGGUGGAGUGGGCGU	75	CGG

FIG. 41D

SEQ ID NO:	MIT	CFD	Elevation	OOF	Offtarget #	Azimuth	DeepSpCas9	CrispScan	OK	Lindel	inDelphi	Frameshift	Precision	Graf Motifs	Bioscore	OOF / OOF	OOF / FS	OOF / FS+1	Indel/frame/+1 predictions
2867	82	91	35	69	127	46	62	59	56	85	93	89	56	OK	40	63	79	71	Knockout
2868	58	88	39	62	260	43	51	80	58	91	93	92	66	OK	49	60	77	71	Knockout
2869	67	76	61	68	371	56	68	66	63	82	89	86	53	OK	50	66	77	72	Knockout
2870	89	92	48	76	106	61	63	72	65	80	75	77	49	OK	53	71	77	73	Knockout
2871	82	91	43	72	96	62	73	57	64	80	91	86	65	OK	53	68	79	74	Knockout
2872	84	91	38	71	82	61	65	55	60	73	84	78	51	OK	56	66	75	70	Knockout
2873	65	85	62	71	251	59	68	74	67	74	80	77	53	OK	47	69	74	72	Knockout
2874	97	98	40	78	22	56	55	57	56	78	78	78	62	OK	46	67	76	71	Knockout
2875	90	97	42	76	70	56	54	75	62	72	78	75	60	OK	46	69	76	71	Knockout
2876	95	96	45	79	30	49	59	59	56	82	78	80	51	OK	51	68	80	72	Knockout
2877	94	96	37	76	44	57	46	75	59	71	81	76	59	OK	49	68	76	70	Knockout
2878	84	92	50	75	88	65	71	58	65	83	79	81	63	OK	64	70	78	74	Knockout
2879	56	83	49	63	239	58	72	47	59	95	95	95	66	OK	57	61	79	72	Knockout
2880	68	87	68	74	156	70	71	76	72	88	83	85	66	OK	56	73	80	77	Knockout
2881	68	82	53	68	203	64	61	68	64	78	84	81	49	OK	49	66	74	71	Knockout
2882	68	80	60	69	221	48	57	46	50	87	92	90	61	OK	44	60	80	70	Knockout
2883	75	87	53	72	185	52	44	37	44	89	94	91	60	GGC	38	58	82	69	Knockout
2884	80	93	37	70	207	39	42	81	54	80	80	80	65	OK	48	62	75	68	Knockout
2885	90	96	44	77	60	41	30	71	47	73	79	76	54	GGC	40	62	76	67	Knockout
2886	81	96	48	75	64	61	56	47	55	72	70	71	50	OK	59	65	73	67	Knockout
2887	73	77	45	65	282	47	60	84	64	73	70	72	51	OK	48	64	68	67	Knockout
2888	72	82	35	63	157	44	51	70	55	80	86	83	46	OK	50	59	73	67	Knockout
2889	94	97	41	77	27	57	43	45	48	73	81	77	54	GGC	50	63	77	67	Knockout
2890	96	96	44	78	45	42	44	49	45	73	80	76	59	OK	55	62	77	66	Knockout
2891	60	74	41	58	322	57	49	60	55	78	91	84	65	OK	55	57	71	66	Knockout
2892	92	91	37	73	113	58	61	60	60	65	63	64	45	OK	53	66	69	66	Knockout
2893	90	96	37	74	81	55	62	40	52	74	68	71	52	OK	59	63	72	66	Knockout
2894	46	60	62	56	434	52	58	74	61	74	83	79	51	OK	50	59	67	65	Knockout
2895	93	97	41	77	26	42	20	48	37	77	85	81	57	TT	47	57	79	65	Knockout
2896	90	96	40	75	64	40	44	46	43	78	75	77	51	OK	32	59	76	65	Knockout
2897	74	86	57	72	119	47	49	44	47	79	67	73	66	OK	52	60	73	64	Knockout
2898	85	92	47	75	84	46	42	67	52	82	51	66	59	OK	44	63	70	64	Knockout
2899	90	95	37	74	85	46	41	46	44	70	79	74	52	OK	55	59	74	64	Knockout
2900	79	91	40	70	72	44	48	67	53	68	69	69	50	OK	50	61	69	64	Knockout
2901	80	86	49	72	152	54	55	37	49	83	60	71	73	GGC	59	60	72	64	Knockout
2902	97	99	37	78	24	29	26	45	33	74	80	77	48	TT	47	55	77	63	Knockout
2903	58	68	34	53	527	40	27	86	54	71	90	81	70	OK	47	54	67	63	Knockout
2904	79	90	45	71	70	52	61	32	48	62	70	66	48	OK	59	60	69	62	Knockout
2905	70	80	52	67	198	37	33	40	37	77	90	84	54	OK	44	52	75	62	Knockout
2906	91	91	39	74	84	56	57	52	55	58	58	58	42	OK	57	64	66	62	Knockout
2907	66	86	47	66	309	32	50	84	55	72	54	63	50	OK	51	61	65	61	Knockout
2908	71	83	49	68	165	24	37	41	34	79	81	80	51	OK	49	51	74	61	Knockout
2909	62	83	31	59	144	55	47	53	52	75	70	73	45	OK	42	55	66	61	Knockout
2910	96	98	38	77	68	22	29	38	30	73	82	78	55	TT	53	53	77	61	Knockout
2911	54	81	64	66	228	47	56	58	54	62	66	59	67	TT	50	60	63	60	Knockout
2912	97	99	46	81	25	67	71	41	60	49	32	41	61	OK	54	70	61	60	Knockout
2913	69	82	45	65	176	33	38	65	45	70	67	68	52	OK	49	55	67	60	Knockout
2914	64	87	48	66	145	44	53	62	53	70	53	61	47	OK	38	60	64	60	Knockout
2915	68	85	53	69	163	55	51	40	49	65	55	60	49	OK	43	59	64	59	Knockout
2916	51	70	38	53	419	29	30	80	46	73	78	75	53	OK	46	50	64	58	Knockout

FIG. 41E

SEQ ID NO:	MIT	CFD	Elevation	23-7	Offtarget #	Azimuth	DeepSpCas9	CrispScan	0-1	Lindel	inDelphi	Frameshift	Precision	Graf Motifs	Bioscore	23-7	0-1	Overall	Interference predictions
2917	71	86	45	68	182	41	57	58	52	57	49	53	45	OK	58	60	60	58	Knockout
2918	44	71	51	55	421	35	39	75	50	68	63	65	52	OK	49	52	60	57	Knockout
2919	44	67	28	46	622	23	26	65	38	74	79	76	47	OK	47	42	61	54	Knockout
2920	50	85	45	60	541	47	57	56	53	62	33	48	69	OK	58	57	54	54	Knockout
2921	62	80	47	63	196	31	36	30	32	60	48	54	55	OK	50	48	59	50	Knockout
2922	39	68	40	49	394	60	55	73	63	52	28	38	77	OK	50	56	43	50	Knockout
2923	29	51	26	35	680	58	57	61	59	54	60	57	56	OK	57	47	46	50	Knockout
2924	27	50	32	36	910	45	46	69	53	70	49	59	67	OK	56	45	48	50	Knockout
2925	25	53	10	29	688	19	13	16	17	65	37	51	67	GGC	44	23	40	32	Knockout
2926	51	71	40	54	370	62	63	91	72	84	91	87	63	OK	53	63	71	71	Knockout or soluble decoy receptor
2927	87	95	45	76	154	50	53	94	66	80	82	81	45	OK	41	71	78	74	Knockout or soluble decoy receptor
2928	85	91	49	75	85	44	64	57	55	89	78	83	61	OK	45	65	79	71	Knockout or soluble decoy receptor
2929	94	97	46	79	21	55	48	40	48	90	93	91	68	OK	41	63	85	73	Knockout or soluble decoy receptor
2930	92	96	51	80	32	69	72	59	67	85	83	84	65	OK	53	73	82	77	Knockout or soluble decoy receptor
2931	87	90	47	75	106	50	56	56	54	75	79	77	55	OK	44	64	76	69	Knockout or soluble decoy receptor
2932	84	87	41	71	137	51	49	39	46	82	91	87	69	OK	48	59	79	68	Knockout or soluble decoy receptor
2933	50	71	47	56	315	47	45	74	55	86	89	88	54	OK	45	56	72	66	Knockout or soluble decoy receptor
2934	49	70	33	51	414	57	57	75	63	80	85	82	45	OK	53	57	66	65	Knockout or soluble decoy receptor
2935	87	89	45	74	146	34	33	42	36	79	88	84	54	GGC	40	55	79	65	Knockout or soluble decoy receptor
2936	90	90	45	75	100	24	21	49	31	68	93	81	65	OK	40	53	78	62	Knockout or soluble decoy receptor
2937	96	96	50	81	14	45	43	9	29	73	77	75	65	TT	47	55	78	62	Knockout or soluble decoy receptor
2938	67	82	48	66	229	37	26	63	42	79	70	75	46	OK	45	54	70	61	Knockout or soluble decoy receptor
2939	43	60	37	47	430	40	52	71	54	83	84	83	47	OK	42	51	65	61	Knockout or soluble decoy receptor
2940	39	62	28	43	468	50	57	72	60	80	83	81	62	OK	52	51	62	61	Knockout or soluble decoy receptor
2941	58	77	45	60	343	46	49	60	52	73	59	66	44	OK	44	56	63	59	Knockout or soluble decoy receptor
2942	57	81	44	61	285	50	44	51	48	61	74	67	52	OK	44	54	64	59	Knockout or soluble decoy receptor
2943	21	45	24	30	622	42	59	79	60	79	87	83	61	OK	42	45	56	58	Knockout or soluble decoy receptor
2944	86	92	48	75	90	28	29	32	30	69	71	70	47	OK	44	53	73	58	Knockout or soluble decoy receptor
2945	56	79	53	63	345	24	11	47	27	82	81	82	46	GGC	42	45	72	57	Knockout or soluble decoy receptor
2946	35	51	36	41	529	45	46	63	51	80	80	80	58	OK	42	46	60	57	Knockout or soluble decoy receptor
2947	66	79	48	64	198	24	32	22	26	67	82	74	66	TT	52	45	69	55	Knockout or soluble decoy receptor
2948	40	63	38	47	439	34	42	40	39	77	83	80	44	OK	34	43	64	55	Knockout or soluble decoy receptor
2949	58	84	51	64	240	46	62	22	43	67	50	58	50	OK	57	54	61	55	Knockout or soluble decoy receptor
2950	32	54	20	35	588	25	16	37	26	72	72	72	46	OK	41	31	54	44	Knockout or soluble decoy receptor
2951	83	92	45	73	79	56	56	56	56	74	60	67	66	OK	67	65	70	65	Membrane-bound decoy
2952	72	80	49	67	218	63	61	53	59	86	90	88	59	OK	46	63	76	71	Membrane-bound decoy
2953	86	94	37	72	79	66	57	35	53	87	89	88	48	OK	35	62	80	71	Membrane-bound decoy
2954	75	84	39	66	175	44	58	71	58	80	86	83	61	OK	37	62	75	69	Membrane-bound decoy
2955	74	86	38	66	191	39	50	91	60	78	86	82	65	OK	36	63	74	69	Membrane-bound decoy
2956	78	92	53	74	99	32	42	60	45	84	89	87	45	OK	46	60	81	69	Membrane-bound decoy
2957	56	75	32	54	345	48	46	90	61	80	84	82	58	OK	37	58	68	66	Membrane-bound decoy
2958	65	87	48	67	114	35	55	43	44	84	92	88	59	OK	35	55	77	66	Membrane-bound decoy
2959	70	89	49	69	133	42	46	51	46	82	84	83	53	OK	48	58	76	66	Membrane-bound decoy
2960	73	84	37	65	152	57	54	72	61	65	63	64	42	OK	40	63	64	63	Membrane-bound decoy
2961	79	84	36	66	123	54	61	43	53	72	71	71	51	OK	40	60	69	63	Membrane-bound decoy
2962	65	81	47	64	208	33	31	93	52	72	69	71	51	OK	25	58	67	62	Membrane-bound decoy
2963	52	79	42	58	356	49	35	71	52	73	73	73	54	OK	36	55	65	61	Membrane-bound decoy
2964	61	78	43	61	280	42	19	72	44	75	73	74	44	OK	40	53	67	60	Membrane-bound decoy
2965	60	81	33	58	262	31	23	74	43	71	80	75	56	OK	37	50	67	59	Membrane-bound decoy
2966	56	84	37	59	175	46	53	35	45	73	72	73	52	OK	30	52	66	59	Membrane-bound decoy

FIG. 41F

SEQ ID NO:	MIT	CFD	Elevation	CFF	Offtarget #	Azimuth	DeepSpCas9	CrispScan	DS	Lindel	inDelphi	Frameshift	Precision	Graf Motifs	Bioscore	DS_OFF	OFF_FS	OFF_FRAME	interference predictions
2967	69	86	35	63	132	37	26	57	40	74	68	71	47	TT	38	52	67	58	Membrane-bound decoy
2968	61	77	43	60	310	49	53	52	51	61	49	55	45	OK	48	56	58	56	Membrane-bound decoy
2969	55	81	33	56	278	35	23	68	42	68	70	69	46	OK	36	49	63	56	Membrane-bound decoy
2970	71	83	53	69	171	48	54	18	40	65	53	59	48	OK	41	55	64	56	Membrane-bound decoy
2971	47	67	27	47	552	57	55	74	62	65	55	60	48	OK	46	54	53	56	Membrane-bound decoy
2972	39	60	37	45	602	57	61	68	62	64	53	59	52	OK	44	54	52	55	Membrane-bound decoy
2973	74	85	32	64	196	41	36	42	40	63	59	61	42	OK	47	52	62	55	Membrane-bound decoy
2974	38	63	31	44	674	51	57	66	58	70	50	60	48	OK	39	51	52	54	Membrane-bound decoy
2975	26	61	29	39	502	53	58	56	56	68	55	62	63	OK	46	47	50	52	Membrane-bound decoy
2976	40	65	32	46	506	51	58	54	54	51	58	55	57	OK	53	50	50	52	Membrane-bound decoy
2977	76	84	37	66	140	34	38	37	36	56	39	47	58	OK	57	51	56	50	Membrane-bound decoy
2978	37	63	23	41	481	39	44	50	44	66	45	56	51	GGC	39	43	48	47	Membrane-bound decoy
2979	49	73	32	51	356	33	41	25	33	59	44	51	58	OK	48	42	51	45	Membrane-bound decoy
2980	24	44	17	28	1134	24	26	67	39	62	63	62	56	OK	41	34	45	43	Membrane-bound decoy
2981	17	41	5	21	1009	34	28	47	36	79	63	71	72	OK	46	29	46	43	Membrane-bound decoy
2982	78	84	38	67	151	48	45	74	56	79	86	83	62	OK	36	61	75	68	Soluble decoy receptor
2983	77	87	42	69	123	62	52	105	73	79	76	78	43	OK	39	71	73	73	Soluble decoy receptor
2984	88	90	38	72	110	50	51	62	54	78	80	79	61	OK	36	63	76	68	Soluble decoy receptor
2985	67	85	33	62	127	52	56	74	61	86	78	82	49	OK	39	61	72	68	Soluble decoy receptor
2986	77	86	36	66	139	57	45	66	56	81	79	80	51	OK	45	61	73	67	Soluble decoy receptor
2987	49	76	48	58	302	61	32	101	65	79	80	80	65	OK	39	61	69	67	Soluble decoy receptor
2988	61	72	37	57	398	46	42	82	57	84	92	88	62	OK	39	57	72	67	Soluble decoy receptor
2989	69	81	49	66	206	45	49	59	51	80	79	79	54	OK	47	59	73	66	Soluble decoy receptor
2990	65	79	36	60	213	40	49	75	55	81	86	83	49	OK	39	57	72	66	Soluble decoy receptor
2991	45	58	28	44	496	56	61	67	61	90	88	88	65	OK	27	53	66	65	Soluble decoy receptor
2992	68	83	40	64	206	53	43	60	52	77	84	80	51	OK	35	58	72	65	Soluble decoy receptor
2993	90	96	54	80	39	49	44	54	49	71	63	67	50	OK	53	65	73	65	Soluble decoy receptor
2994	75	89	55	73	118	64	43	43	50	71	73	72	55	OK	53	62	73	65	Soluble decoy receptor
2995	70	81	42	64	258	52	38	55	48	81	87	84	61	OK	41	56	74	65	Soluble decoy receptor
2996	64	75	53	64	289	62	56	29	49	77	78	78	49	OK	41	57	71	64	Soluble decoy receptor
2997	58	71	41	57	265	44	54	68	55	80	81	80	64	OK	49	56	68	64	Soluble decoy receptor
2998	72	86	39	66	224	45	27	67	46	75	85	80	51	GGC	35	56	73	64	Soluble decoy receptor
2999	48	74	44	55	339	36	50	64	50	81	94	88	72	OK	31	53	71	64	Soluble decoy receptor
3000	89	96	44	76	46	32	13	42	29	83	93	88	59	OK	51	52	82	64	Soluble decoy receptor
3001	79	87	37	68	123	46	21	52	40	82	84	83	64	OK	35	54	75	63	Soluble decoy receptor
3002	75	81	37	64	183	36	29	56	40	79	89	84	48	OK	35	52	74	63	Soluble decoy receptor
3003	68	82	43	64	142	36	37	60	44	79	84	81	59	OK	37	54	73	63	Soluble decoy receptor
3004	54	77	48	60	302	59	72	62	64	75	46	61	56	OK	37	62	60	62	Soluble decoy receptor
3005	65	77	52	65	257	34	35	70	46	70	83	77	57	TT	40	55	71	62	Soluble decoy receptor
3006	24	58	12	31	801	49	54	90	64	80	93	87	58	OK	51	48	59	61	Soluble decoy receptor
3007	57	76	49	61	252	44	39	61	48	75	75	75	51	OK	36	54	68	61	Soluble decoy receptor
3008	48	75	43	55	365	48	45	51	48	75	85	80	62	OK	45	52	68	61	Soluble decoy receptor
3009	67	89	49	68	220	46	47	26	38	76	79	77	59	GGC	35	53	73	61	Soluble decoy receptor
3010	72	85	36	64	178	33	33	67	44	75	68	71	46	OK	39	54	68	60	Soluble decoy receptor
3011	56	77	34	56	282	27	36	62	42	79	86	83	49	OK	31	49	69	60	Soluble decoy receptor
3012	32	68	20	40	570	30	60	74	55	78	84	81	48	OK	33	47	61	59	Soluble decoy receptor
3013	43	70	40	51	420	35	34	49	39	81	90	85	53	GGC	31	45	68	59	Soluble decoy receptor
3014	49	64	33	49	542	26	39	72	46	80	86	83	51	OK	22	47	66	59	Soluble decoy receptor
3015	72	83	37	64	151	33	17	63	38	73	78	76	51	OK	34	51	70	59	Soluble decoy receptor
3016	51	69	41	54	524	50	46	49	48	78	64	71	47	GGC	43	51	62	58	Soluble decoy receptor

FIG. 41G

SEQ ID NO:	MIT	CFD	Elevation	CFD	Offtarget #	Azimuth	DeepSpCas9	CnnpScan	OOF	Lindel	inDelphi	Framesshift	Precision	Graf Motifs	Bioscore	OOF	CFD	Overlap	Understanding predictions
3017	59	72	29	53	376	30	4	68	34	78	89	83	52	OK	21	44	68	57	Soluble decoy receptor
3018	56	74	40	57	388	35	2	48	28	85	87	86	51	GGC	31	42	71	57	Soluble decoy receptor
3019	64	80	48	64	237	8	34	41	28	73	78	75	48	TT	33	46	70	56	Soluble decoy receptor
3020	38	65	28	44	543	47	53	92	64	67	46	57	54	OK	35	54	50	55	Soluble decoy receptor
3021	57	81	34	57	372	13	9	36	19	84	84	89	67	OK	21	38	73	55	Soluble decoy receptor
3022	42	58	34	45	756	30	18	86	45	69	79	74	48	OK	29	45	59	55	Soluble decoy receptor
3023	33	51	29	38	823	45	46	50	47	75	82	78	53	OK	36	42	58	54	Soluble decoy receptor
3024	60	69	36	55	340	37	37	39	38	72	70	71	52	OK	38	46	63	54	Soluble decoy receptor
3025	39	71	30	47	462	42	61	35	46	60	69	65	70	OK	37	46	56	52	Soluble decoy receptor
3026	48	65	41	51	350	38	23	27	29	72	69	71	44	GGC	42	40	61	50	Soluble decoy receptor
3027	86	96	38	74	36	38	30	58	42	83	91	87	61	TT	51	58	81	68	Soluble decoy receptor
3028	47	69	34	50	384	31	15	60	35	64	66	65	73	TT	27	43	58	50	Soluble decoy receptor
3029	30	57	23	37	787	36	59	47	47	60	64	62	45	OK	31	42	49	49	Soluble decoy receptor
3030	40	55	31	42	786	19	7	51	26	72	79	76	48	OK	29	34	59	48	Soluble decoy receptor
3031	45	79	30	51	166	37	42	47	42	67	27	47	74	GGC	40	47	49	47	Soluble decoy receptor
3032	39	78	30	49	216	27	30	22	26	70	39	54	65	GGC	40	36	52	43	Soluble decoy receptor
3033	18	43	12	24	1680	22	36	62	40	68	63	66	63	OK	46	32	45	43	Soluble decoy receptor
3034	39	53	36	43	569	19	9	51	26	67	44	55	63	OK	28	35	49	41	Soluble decoy receptor
3035	28	56	26	37	597	34	0	37	24	53	28	40	71	GGC	44	30	33	34	Soluble decoy receptor
3036	63	79	53	65	203	61	59	67	60	75	75	75	58	OK	41	67	70	70	Wildtype-like
3037	64	83	49	65	265	42	44	45	44	79	92	86	57	OK	8	55	76	65	Wildtype-like
3038	67	82	52	67	190	53	57	52	54	71	72	72	47	OK	43	60	69	64	Wildtype-like
3039	72	84	48	68	168	44	45	32	40	79	84	81	46	GGC	43	54	75	63	Wildtype-like
3040	70	89	36	65	138	59	66	28	51	67	78	73	63	OK	50	58	69	63	Wildtype-like
3041	49	66	37	51	623	47	42	64	51	70	61	65	43	OK	31	51	58	56	Wildtype-like

FIG. 41H

SEQ ID NO:	Genomic cut coordinate	Exon	CDS cut position	CDS cut position %	Strand	Start coordinate	End coordinate	crRNA	GC content	PAM
3042	62348191	2	99	5.3	-	62348188	62348207	UGCUUCUCACUGGUACAUGG	50	AGG
3043	62348194	2	102	5.5	-	62348191	62348210	UAAUGCUUCUCACUGGUACA	40	TGG
3044	62348217	2	125	6.8	+	62348200	62348219	GAGAAGCAUUAUGAGCAUCU	40	GGG
3045	62348221	2	129	7	+	62348204	62348223	AGCAUUAUGAGCAUCUGGGA	45	CGG
3046	62349847	3	193	10.4	-	62349844	62349863	GGGCAGACAUACACUGUCAG	55	AGG
3047	62349863	3	209	11.3	+	62349846	62349865	GACAGUGUAUGUCUGCCCUG	55	TGG
3048	62349867	3	213	11.5	-	62349864	62349883	AAGUAUUCAUCCGGGCCACA	50	GGG
3049	62354435	4	328	17.7	-	62354432	62354451	CGUGCACGCGCAGCGCCGGG	85	GGG
3050	62325381	1	29	1.6	-	62325378	62325397	GCAGCAGCGCGAACAGCGGG	75	CGG
3051	62354431	4	324	17.5	+	62354414	62354433	CCGGCAACAGCACGACCCCC	75	CGG
3052	62349868	3	214	11.6	-	62349865	62349884	CAAGUAUUCAUCCGGGCCAC	55	AGG
3053	62354439	4	332	17.9	-	62354436	62354455	CAGCCGUGCACGCGCAGCGC	80	CGG
3054	62354411	4	304	16.4	-	62354408	62354427	CGUGCUGUUGCCGGCGACCA	70	CGG
3055	62348244	2	152	8.2	+	62348227	62348246	UGCUGUAACAAAUGUGAACC	40	AGG
3056	62354436	4	329	17.8	-	62354433	62354452	CCGUGCACGCGCAGCGCCGG	85	GGG
3057	62349880	3	226	12.2	+	62349863	62349882	CUGUGGCCCGGAUGAAUACU	55	TGG
3058	62354438	4	331	17.9	-	62354435	62354454	AGCCGUGCACGCGCAGCGCC	80	GGG
3059	62349868	3	214	11.6	+	62349851	62349870	UGUAUGUCUGCCCUGUGGCC	60	CGG
3060	62354437	4	330	17.8	-	62354434	62354453	GCCGUGCACGCGCAGCGCCG	85	GGG
3061	62325385	1	33	1.8	-	62325382	62325401	AGCAGCAGCAGCGCGAACAG	65	CGG
3062	62354402	4	295	15.9	-	62354399	62354418	GCCGGCGACCACGGCCACCA	80	GGG
3063	62349875	3	221	11.9	-	62349872	62349891	AGCUAUCCAAGUAUUCAUCC	40	GGG
3064	62354420	4	313	16.9	-	62354417	62354436	CCGGGGGGUCGUGCUGUUGC	75	CGG
3065	62325362	1	10	0.5	-	62325359	62325378	GCGGCGCCGCCGGGCGCGCG	100	GGG
3066	62325371	1	19	1	-	62325368	62325387	GAACAGCGGGCGGCGCCGCC	85	GGG
3067	62354412	4	305	16.5	+	62354395	62354414	GCCCUGGUGGCCGUGGUCGC	80	CGG
3068	62349876	3	222	12	-	62349873	62349892	CAGCUAUCCAAGUAUUCAUC	40	CGG
3069	62325372	1	20	1.1	-	62325369	62325388	CGAACAGCGGGCGGCGCCGC	85	CGG
3070	62348216	2	124	6.7	+	62348199	62348218	UGAGAAGCAUUAUGAGCAUC	40	TGG
3071	62349932	3	278	15	+	62349915	62349934	CUGCAUAAAGUUUGUGAUAC	35	AGG
3072	62325384	1	32	1.7	-	62325381	62325400	GCAGCAGCAGCGCGAACAGC	70	GGG
3073	62325415	1	63	3.4	+	62325398	62325417	UGCUCUGCGCGCUGCUCGCC	75	CGG
3074	62325364	1	12	0.6	-	62325361	62325380	GGGCGGCGCCGCCGGGCGCG	100	CGG
3075	62354403	4	296	16	-	62354400	62354419	UGCCGGCGACCACGGCCACC	80	AGG
3076	62354405	4	298	16.1	+	62354388	62354407	AGGCAAGGCCCUGGUGGCCG	75	TGG
3077	62325363	1	11	0.6	-	62325360	62325379	GGCGGCGCCGCCGGGCGCGC	100	GGG
3078	62354447	4	340	18.4	+	62354430	62354449	CCCCCGGCGCUGCGCGUGCA	85	CGG
3079	62354493	4	386	20.9	-	62354490	62354509	GCGCGCACUCGGUGUUGCGG	75	CGG
3080	62358287	5	467	25.2	-	62358284	62358303	CAUCAGAGAAGUAGCCUGCA	50	AGG
3081	62358319	5	499	27	-	62358316	62358335	CCAGGGUCUGCAUUUGUCCG	60	TGG
3082	62360004	6	571	30.8	+	62359987	62360006	UGGGACAGAGAAAUCCGAUG	50	CGG
3083	62360007	6	574	31	-	62360004	62360023	AGAAGAACUGCAAACCGCAU	45	CGG
3084	62358316	5	496	26.8	-	62358313	62358332	GGGUCUGCAUUUGUCCGUGG	60	AGG
3085	62358282	5	462	25	-	62358279	62358298	GAGAAGUAGCCUGCAAGGCA	55	AGG
3086	62354496	4	389	21	-	62354493	62354512	CCGGCGCGCACUCGGUGUUG	75	CGG
3087	62354452	4	345	18.6	+	62354435	62354454	GGCGCUGCGCGUGCACGGCU	80	GGG
3088	62354507	4	400	21.6	+	62354490	62354509	CCGCAACACCGAGUGCGCGC	75	CGG
3089	62358330	5	510	27.6	+	62358313	62358332	CCACGGACAAAUGCAGACCC	60	TGG
3090	62354461	4	354	19.1	+	62354444	62354463	CGUGCACGGCUGGGUACCAC	70	TGG
3091	62359969	6	536	29	-	62359966	62359985	GAUGUUCUACUCUCUUUCCA	40	AGG

FIG. 42A

SEQ ID NO:	Genomic cut coordinate	Exon	CDS cut position	CDS cut position %	Strand	Start coordinate	End coordinate	crRNA	GC content	PAM
3092	62354504	4	397	21.4	-	62354501	62354520	GCCCAGGCCCGGCGCGCACU	85	CGG
3093	62354508	4	401	21.7	+	62354491	62354510	CGCAACACCGAGUGCGCGCC	75	GGG
3094	62354451	4	344	18.6	+	62354434	62354453	CGGCGCUGCGCGUGCACGGC	85	TGG
3095	62359984	6	551	29.8	+	62359967	62359986	GGAAAGAGAGUAGAACAUCA	40	TGG
3096	62359965	6	532	28.7	-	62359962	62359981	UUCUACUCUCUUUCCAAGGA	40	AGG
3097	62359985	6	552	29.8	+	62359968	62359987	GAAAGAGAGUAGAACAUCAU	35	GGG
3098	62358284	5	464	25.1	+	62358267	62358286	GUGUGCAAACCUUGCCUUGC	55	AGG
3099	62354514	4	407	22	+	62354497	62354516	ACCGAGUGCGCGCCGGGCCU	80	GGG
3100	62354468	4	361	19.5	+	62354451	62354470	GGCUGGGUACCACUGGAGCC	70	AGG
3101	62354466	4	359	19.4	-	62354463	62354482	ACUCGCAGUCCUGGCUCCAG	65	TGG
3102	62354475	4	368	19.9	-	62354472	62354491	GGCGGCAGCACUCGCAGUCC	75	TGG
3103	62354513	4	406	21.9	+	62354496	62354515	CACCGAGUGCGCGCCGGGCC	85	TGG
3104	62358313	5	493	26.6	+	62358296	62358315	CUCUGAUGCCUUUUCCUCCA	50	CGG
3105	62358310	5	490	26.5	-	62358307	62358326	GCAUUUGUCCGUGGAGGAAA	50	AGG
3106	62354515	4	408	22	-	62354512	62354531	GGGUGCUGGGCGCCCAGGCC	85	CGG
3107	62366728	8	751	40.6	+	62366711	62366730	UUUGUGGCACUGGAUCAAUG	45	AGG
3108	62366735	8	758	41	+	62366718	62366737	CACUGGAUCAAUGAGGCUUG	50	TGG
3109	62366755	8	778	42	+	62366738	62366757	UGGCCGCCUAAGUGGAGAUA	55	AGG
3110	62368710	9	793	42.8	-	62368707	62368726	ACUGACACAACUGUCACCUG	50	AGG
3111	62368731	9	814	44	+	62368714	62368733	CAGUUGUGUCAGUACACACA	45	CGG
3112	62368741	9	824	44.5	+	62368724	62368743	AGUACACACACGGCAAACUU	45	TGG
3113	62368750	9	833	45	+	62368733	62368752	ACGGCAAACUUUGGUCAGCA	50	GGG
3114	62368855	9	938	50.7	+	62368838	62368857	UGUCAGGGCACAUGUGUAGG	55	AGG
3115	62368873	9	956	51.6	+	62368856	62368875	GGAGGUGGUCCCUACGCACA	65	AGG
3116	62368886	9	969	52.4	+	62368869	62368888	ACGCACAAGGCGAAGAUGCC	60	AGG
3117	62368920	9	1003	54.2	+	62368903	62368922	GGUCAGCAAGACCGAGAUAG	55	AGG
3118	62369087	9	1170	63.2	+	62369070	62369089	GUUUAAGCCAGUGCUUCACG	50	GGG
3119	62369141	9	1224	66.1	-	62369138	62369157	GUCCAAUCAGUCCUGCACAG	55	GGG
3120	62369197	9	1280	69.2	+	62369180	62369199	UUGCAAAAAGAGGUGGACAG	45	TGG
3121	62369214	9	1297	70.1	+	62369197	62369216	CAGUGGCCAUUGCCCGCACU	65	GGG
3122	62369296	9	1379	74.5	+	62369279	62369298	GAGGACUGUGAACCCCUCGU	60	GGG
3123	62369297	9	1380	74.6	-	62369294	62369313	CGUUUUGGGGAACCCACGAG	60	GGG
3124	62369298	9	1381	74.6	-	62369295	62369314	ACGUUUUGGGGAACCCACGA	55	GGG
3125	62369299	9	1382	74.7	-	62369296	62369315	CACGUUUUGGGGAACCCACG	60	AGG
3126	62369310	9	1393	75.3	-	62369307	62369326	GGGCAAGGGUCCACGUUUUG	60	GGG
3127	62369311	9	1394	75.3	+	62369294	62369313	CUCGUGGGUUCCCCAAAACG	60	TGG
3128	62369330	9	1413	76.3	-	62369327	62369346	CCCAUGCCAUAGGCGCACUG	65	GGG
3129	62369430	9	1513	81.7	+	62369413	62369432	GAGGCUCCCAAGCUCAGCGA	65	GGG
3130	62384846	10	1663	89.8	+	62384829	62384848	CUACGUCAGCCAGACCUCGC	65	AGG
3131	62384849	10	1666	90	+	62384832	62384851	CGUCAGCCAGACCUCGCAGG	70	AGG
3132	62384850	10	1667	90.1	+	62384833	62384852	GUCAGCCAGACCUCGCAGGA	65	GGG
3133	62384909	10	1726	93.2	-	62384906	62384925	GAAGGAGUCUCGGCGCGCCA	70	GGG
3134	62384924	10	1741	94.1	+	62384907	62384926	GGCGCGCCGAGACUCCUUCG	75	CGG
3135	62384926	10	1743	94.2	+	62384909	62384928	CGCGCCGAGACUCCUUCGCG	75	GGG
3136	62384927	10	1744	94.2	-	62384924	62384943	GCGCGGGCCGUUCCCCGCGA	85	AGG
3137	62384955	10	1772	95.7	+	62384938	62384957	CCGCGCUUCCCGGACCCGUG	80	CGG
3138	62384968	10	1785	96.4	+	62384951	62384970	ACCCGUGCGGCGGCCCCGAG	85	GGG
3139	62368828	9	911	49.2	+	62368811	62368830	AUGUGCUACCCAGAUCAAGG	50	TGG
3140	62369104	9	1187	64.1	+	62369087	62369106	ACGGGGACACAGAGCACAGU	60	GGG
3141	62369103	9	1186	64.1	+	62369086	62369105	CACGGGGACACAGAGCACAG	65	TGG

FIG. 42B

SEQ ID NO:	Genomic cut coordinate	Exon	CDS cut position	CDS cut position %	Strand	Start coordinate	End coordinate	crRNA	GC content	PAM
3142	62384889	10	1706	92.2	-	62384886	62384905	GGGUCUCCUCCUGCACCGGG	75	CGG
3143	62368989	9	1072	57.9	-	62368986	62369005	GAGGAACAGUAACUGGUCUG	50	TGG
3144	62369340	9	1423	76.9	-	62369337	62369356	AGGGGGAAGGCCCAUGCCAU	65	AGG
3145	62369240	9	1323	71.5	-	62369237	62369256	GUGCAGACAUCUGCCCAGUU	55	GGG
3146	62368962	9	1045	56.5	+	62368945	62368964	GCCCACAGAAGAUGAAUACA	45	TGG
3147	62384808	10	1625	87.8	+	62384791	62384810	GGGCAGGUGAUGAACUUCAA	50	GGG
3148	62369165	9	1248	67.4	-	62369162	62369181	AAGUAGUUUUCAGAGGACAU	35	GGG
3149	62368899	9	982	53.1	+	62368882	62368901	AGAUGCCAGGAUGCUCUCAU	50	TGG
3150	62368988	9	1071	57.9	-	62368985	62369004	AGGAACAGUAACUGGUCUGU	45	GGG
3151	62384877	10	1694	91.5	+	62384860	62384879	GCGGCGGCUGCGGAGCCCAU	80	GGG
3152	62366747	8	770	41.6	+	62366730	62366749	GAGGCUUGUGGCCGCCUAAG	65	TGG
3153	62384958	10	1775	95.9	+	62384941	62384960	CGCUUCCCCGGACCCGUGCGG	80	CGG
3154	62384792	10	1609	86.9	-	62384789	62384808	GAAGUUCAUCACCUGCCCGC	60	TGG
3155	62384780	10	1597	86.3	-	62384777	62384796	CUGCCCGCUGGAGAUGAACG	65	TGG
3156	62369341	9	1424	76.9	+	62369324	62369343	CCCCAGUGCGCCUAUGGCAU	65	GGG
3157	62369331	9	1414	76.4	-	62369328	62369347	GCCCAUGCCAUAGGCGCACU	65	GGG
3158	62368782	9	865	46.7	+	62368765	62368784	AGGUGUCUUACUGCUGACUC	50	TGG
3159	62361788	7	725	39.2	+	62361771	62361790	AAAAAAGGGAAAGCACUCAC	40	AGG
3160	62384910	10	1727	93.3	-	62384907	62384926	CGAAGGAGUCUCGGCGCGCC	75	AGG
3161	62368840	9	923	49.9	+	62368823	62368842	GAUCAAGGUGGUGUCUGUCA	50	GGG
3162	62385015	10	1832	99	+	62384998	62385017	AGGCCGGUGCAGGAGCAAGG	70	CGG
3163	62369143	9	1226	66.2	-	62369140	62369159	GAGUCCAAUCAGUCCUGCAC	55	AGG
3164	62369400	9	1483	80.1	+	62369383	62369402	CAGAGACCAGCCCGAGGAUG	65	GGG
3165	62368852	9	935	50.5	+	62368835	62368854	GUCUGUCAGGGCACAUGUGU	55	AGG
3166	62369142	9	1225	66.2	-	62369139	62369158	AGUCCAAUCAGUCCUGCACA	50	GGG
3167	62368825	9	908	49.1	+	62368808	62368827	GAUAUGUGCUACCCAGAUCA	45	AGG
3168	62384925	10	1742	94.1	+	62384908	62384927	GCGCGCCGAGACUCCUUCGC	75	GGG
3169	62369276	9	1359	73.4	-	62369273	62369292	GGUUCACAGUCCUCCCCAGG	65	AGG
3170	62369357	9	1440	77.8	-	62369354	62369373	CUGCUGGCUUCUUCUUCAGG	55	GGG
3171	62384849	10	1666	90	-	62384846	62384865	CGCCGCCGCGCCCUCCUGCG	90	AGG
3172	62384792	10	1609	86.9	+	62384775	62384794	CACGUUCAUCUCCAGCGGGC	65	AGG
3173	62369295	9	1378	74.4	+	62369278	62369297	GGAGGACUGUGAACCCCUCG	65	TGG
3174	62369239	9	1322	71.4	-	62369236	62369255	UGCAGACAUCUGCCCAGUUG	55	GGG
3175	62369340	9	1423	76.9	+	62369323	62369342	GCCCCAGUGCGCCUAUGGCA	70	TGG
3176	62384858	10	1675	90.5	+	62384841	62384860	GACCUCGCAGGAGGGCGCGG	80	CGG
3177	62369008	9	1091	58.9	-	62369005	62369024	AUUUGCUUCCAGGCUCAGUG	50	AGG
3178	62369429	9	1512	81.7	+	62369412	62369431	GGAGGCUCCCAAGCUCAGCG	70	AGG
3179	62369275	9	1358	73.4	-	62369272	62369291	GUUCACAGUCCUCCCCAGGA	60	GGG
3180	62369376	9	1459	78.8	+	62369359	62369378	AGAAGAAGCCAGCAGGACGG	60	AGG
3181	62369213	9	1296	70	+	62369196	62369215	ACAGUGGCCAUUGCCCGCAC	65	TGG
3182	62368762	9	845	45.7	+	62368745	62368764	GGUCAGCAGGGAGCAUGUGA	60	AGG
3183	62369036	9	1119	60.5	-	62369033	62369052	UCCAGGGGUUCAGAGAAAGG	55	AGG
3184	62369324	9	1407	76	-	62369321	62369340	CCAUAGGCGCACUGGGGCAA	65	GGG
3185	62369083	9	1166	63	-	62369080	62369099	UCUGUGUCCCCGUGAAGCAC	60	TGG
3186	62384807	10	1624	87.7	+	62384790	62384809	CGGGCAGGUGAUGAACUUCA	55	AGG
3187	62369335	9	1418	76.6	+	62369318	62369337	CCCUUGCCCCAGUGCGCCUA	70	TGG
3188	62384881	10	1698	91.7	-	62384878	62384897	UCCUGCACCGGGCGGCCCAU	75	GGG
3189	62368893	9	976	52.7	-	62368890	62368909	GCUGACCAAUGAGAGCAUCC	55	TGG
3190	62368871	9	954	51.5	-	62368868	62368887	GCAUCUUCGCCUUGUGCGUA	55	GGG
3191	62369215	9	1298	70.1	-	62369212	62369231	UGGGGCUGGCUGCCCAGUGC	75	GGG

FIG. 42C

SEQ ID NO:	Genomic cut coordinate	Exon	CDS cut position	CDS cut position %	Strand	Start coordinate	End coordinate	crRNA	GC content	PAM
3192	62369448	9	1531	82.7	-	62369445	62369464	ACCAGGGGAGCUUCCAGACC	65	CGG
3193	62369311	9	1394	75.3	-	62369308	62369327	GGGGCAAGGGUCCACGUUUU	60	GGG
3194	62368920	9	1003	54.2	-	62368917	62368936	GAAGCUGUCUUCCUCUAUCU	45	CGG
3195	62384970	10	1787	96.5	-	62384967	62384986	CCGGCUCCCGCAGCCCCUCG	85	GGG
3196	62369254	9	1337	72.2	+	62369237	62369256	AACUGGGCAGAUGUCUGCAC	55	AGG
3197	62384999	10	1816	98.1	+	62384982	62385001	GCCGGAGAAGGCCUCGAGGC	75	CGG
3198	62369141	9	1224	66.1	+	62369124	62369143	ACUGCACUGAGCCCCUGUGC	65	AGG
3199	62369358	9	1441	77.8	-	62369355	62369374	CCUGCUGGCUUCUUCUUCAG	55	GGG
3200	62369325	9	1408	76.1	-	62369322	62369341	GCCAUAGGCGCACUGGGGCA	70	AGG
3201	62384966	10	1783	96.3	+	62384949	62384968	GGACCCGUGCGGCGGCCCCG	90	AGG
3202	62361752	7	689	37.2	+	62361735	62361754	CUGGUGGCUGCCAUCAUCUU	55	TGG
3203	62369274	9	1357	73.3	+	62369257	62369276	AGGCUGCCGGAACCCUCCUG	70	GGG
3204	62361751	7	688	37.2	-	62361748	62361767	AUAGCAAACGCCAAAGAUGA	40	TGG
3205	62369369	9	1452	78.4	+	62369352	62369371	CCCCUGAAGAAGAAGCCAGC	60	AGG
3206	62368952	9	1035	55.9	-	62368949	62368968	UCCAUGUAUUCAUCUUCUGU	35	GGG
3207	62384995	10	1812	97.9	+	62384978	62384997	GGGAGCCGGAGAAGGCCUCG	75	AGG
3208	62369312	9	1395	75.4	-	62369309	62369328	UGGGGCAAGGGUCCACGUUU	60	TGG
3209	62384919	10	1736	93.8	-	62384916	62384935	CGUUCCCCGCGAAGGAGUCU	65	CGG
3210	62369279	9	1362	73.6	-	62369276	62369295	AGGGGUUCACAGUCCUCCCC	65	AGG
3211	62384822	10	1639	88.5	+	62384805	62384824	CUUCAAGGGCGACAUCAUCG	55	TGG
3212	62369209	9	1292	69.8	-	62369206	62369225	UGGCUGCCCAGUGCGGGCAA	70	TGG
3213	62369277	9	1360	73.5	+	62369260	62369279	CUGCCGGAACCCUCCUGGGG	75	AGG
3214	62384844	10	1661	89.7	-	62384841	62384860	CCGCGCCCUCCUGCGAGGUC	80	TGG
3215	62384967	10	1784	96.4	+	62384950	62384969	GACCCGUGCGGCGGCCCCGA	85	GGG
3216	62384944	10	1761	95.1	-	62384941	62384960	CCGCACGGGUCCGGGAAGCG	80	CGG
3217	62384931	10	1748	94.4	+	62384914	62384933	CGAGACUCCUUCGCGGGGAA	65	CGG
3218	62369464	9	1547	83.6	-	62369461	62369480	AUGCAGGGGACUGGCCACCA	65	GGG
3219	62369332	9	1415	76.4	-	62369329	62369348	GGCCCAUGCCAUAGGCGCAC	70	TGG
3220	62369049	9	1132	61.2	+	62369032	62369051	UCCUUUCUCUGAACCCCUGG	55	AGG
3221	62369411	9	1494	80.7	+	62369394	62369413	CCGAGGAUGGGGCUGAUGGG	70	AGG
3222	62384788	10	1605	86.7	+	62384771	62384790	ACUCCACGUUCAUCUCCAGC	55	GGG
3223	62384953	10	1770	95.6	-	62384950	62384969	UCGGGGCCGCCGCACGGGUC	85	CGG
3224	62369398	9	1481	80	+	62369381	62369400	GCCAGAGACCAGCCCGAGGA	70	TGG
3225	62384882	10	1699	91.8	-	62384879	62384898	CUCCUGCACCGGGCGGCCCA	80	TGG
3226	62369187	9	1270	68.6	+	62369170	62369189	UGAAAACUACUUGCAAAAAG	30	AGG
3227	62369273	9	1356	73.3	+	62369256	62369275	CAGGCUGCCGGAACCCUCCU	70	GGG
3228	62369085	9	1168	63.1	+	62369068	62369087	CAGUUUAAGCCAGUGCUUCA	45	CGG
3229	62385005	10	1822	98.4	+	62384988	62385007	GAAGGCCUCGAGGCCGGUGC	75	AGG
3230	62369269	9	1352	73	-	62369266	62369285	AGUCCUCCCCAGGAGGGUUC	65	CGG
3231	62384958	10	1775	95.9	-	62384955	62384974	GCCCCUCGGGGCCGCCGCAC	90	GGG
3232	62369461	9	1544	83.4	+	62369444	62369463	GGGUCUGGAAGCUCCCCUGG	70	TGG
3233	62368980	9	1063	57.4	-	62368977	62368996	UAACUGGUCUGUGGGCUGGG	60	AGG
3234	62384894	10	1711	92.4	+	62384877	62384896	CAUGGGCCGCCCGGUGCAGG	80	AGG
3235	62368785	9	868	46.9	+	62368768	62368787	UGUCUUACUGCUGACUCUGG	50	AGG
3236	62369086	9	1169	63.2	+	62369069	62369088	AGUUUAAGCCAGUGCUUCAC	45	GGG
3237	62369039	9	1122	60.6	-	62369036	62369055	ACCUCCAGGGGUUCAGAGAA	55	AGG
3238	62361765	7	702	37.9	+	62361748	62361767	UCAUCUUUGGCGUUUGCUAU	40	AGG
3239	62368983	9	1066	57.6	-	62368980	62368999	CAGUAACUGGUCUGUGGGCU	55	GGG
3240	62384855	10	1672	90.3	+	62384838	62384857	CCAGACCUCGCAGGAGGGCG	75	CGG
3241	62369394	9	1477	79.8	+	62369377	62369396	GGAGGCCAGAGACCAGCCCG	75	AGG

FIG. 42D

SEQ ID NO:	Genomic cut coordinate	Exon	CDS cut position	CDS cut position %	Strand	Start coordinate	End coordinate	crRNA	GC content	PAM
3242	62369463	9	1546	83.5	-	62369460	62369479	UGCAGGGGACUGGCCACCAG	70	GGG
3243	62384903	10	1720	92.9	+	62384886	62384905	CCCGGUGCAGGAGGAGACCC	75	TGG
3244	62384787	10	1604	86.7	+	62384770	62384789	AACUCCACGUUCAUCUCCAG	50	CGG
3245	62369446	9	1529	82.6	+	62369429	62369448	GCGAGGGCAGGUGCCGGGUC	80	TGG
3246	62369272	9	1355	73.2	+	62369255	62369274	ACAGGCUGCCGGAACCCUCC	70	TGG
3247	62369425	9	1508	81.5	-	62369422	62369441	CACCUGCCCUCGCUGAGCUU	65	GGG
3248	62384989	10	1806	97.6	-	62384986	62385005	ACCGGCCUCGAGGCCUUCUC	70	CGG
3249	62369238	9	1321	71.4	+	62369221	62369240	AGCCAGCCCCAGCCCCAACU	70	GGG
3250	62384945	10	1762	95.2	+	62384928	62384947	GGGGAACGGCCCGCGCUUCC	80	CGG
3251	62369388	9	1471	79.5	-	62369385	62369404	CCCAUCCUCGGGCUGGUCUC	70	TGG
3252	62369241	9	1324	71.5	-	62369238	62369257	UGUGCAGACAUCUGCCCAGU	55	TGG
3253	62368872	9	955	51.6	-	62368869	62368888	GGCAUCUUCGCCUUGUGCGU	60	AGG
3254	62361773	7	710	38.4	+	62361756	62361775	GGCGUUUGCUAUAGGAAAAA	40	AGG
3255	62361739	7	676	36.5	-	62361736	62361755	AAAGAUGAUGGCAGCCACCA	50	GGG
3256	62368825	9	908	49.1	-	62368822	62368841	GACAGACACCACCUUGAUCU	50	GGG
3257	62368984	9	1067	57.6	-	62368981	62369000	ACAGUAACUGGUCUGUGGGC	55	TGG
3258	62368953	9	1036	56	-	62368950	62368969	GUCCAUGUAUUCAUCUUCUG	40	TGG
3259	62368996	9	1079	58.3	-	62368993	62369012	GCUCAGUGAGGAACAGUAAC	50	TGG
3260	62368749	9	832	44.9	+	62368732	62368751	CACGGCAAACUUUGGUCAGC	55	AGG
3261	62369150	9	1233	66.6	+	62369133	62369152	AGCCCCUGUGCAGGACUGAU	60	TGG
3262	62369408	9	1491	80.6	+	62369391	62369410	AGCCCGAGGAUGGGGCUGAU	65	GGG
3263	62369046	9	1129	61	+	62369029	62369048	ACCUCCUUUCUCUGAACCCC	55	TGG
3264	62369426	9	1509	81.5	-	62369423	62369442	GCACCUGCCCUCGCUGAGCU	70	TGG
3265	62368967	9	1050	56.7	+	62368950	62368969	CAGAAGAUGAAUACAUGGAC	40	AGG
3266	62385007	10	1824	98.5	-	62385004	62385023	GCCCCGCCUUGCUCCUGCAC	75	CGG
3267	62384891	10	1708	92.3	+	62384874	62384893	GCCCAUGGGCCGCCCGGUGC	85	AGG
3268	62384943	10	1760	95.1	-	62384940	62384959	CGCACGGGUCCGGGAAGCGC	80	GGG
3269	62369399	9	1482	80.1	+	62369382	62369401	CCAGAGACCAGCCCGAGGAU	65	GGG
3270	62369018	9	1101	59.5	-	62369015	62369034	GGAGGUGUGGAUUUGCUUCC	55	AGG
3271	62369172	9	1255	67.8	-	62369169	62369188	UUUUUGCAAGUAGUUUUCAG	30	AGG
3272	62369166	9	1249	67.5	-	62369163	62369182	CAAGUAGUUUUCAGAGGACA	40	TGG
3273	62384885	10	1702	92	+	62384868	62384887	UGCGGAGCCCAUGGGCCGCC	80	CGG
3274	62369051	9	1134	61.3	-	62369048	62369067	UCAUUCUCCCCCACCUCCAG	60	GGG
3275	62369216	9	1299	70.2	-	62369213	62369232	CUGGGGCUGGCUGCCCAGUG	75	CGG
3276	62369190	9	1273	68.8	+	62369173	62369192	AAACUACUUGCAAAAAGAGG	35	TGG
3277	62369441	9	1524	82.3	+	62369424	62369443	GCUCAGCGAGGGCAGGUGCC	75	GGG
3278	62384892	10	1709	92.3	-	62384889	62384908	CCAGGGUCUCCUCCUGCACC	70	GGG
3279	62361740	7	677	36.6	-	62361737	62361756	CAAAGAUGAUGGCAGCCACC	55	AGG
3280	62384974	10	1791	96.8	+	62384957	62384976	GCGGCGGCCCCGAGGGGCUG	90	CGG
3281	62384972	10	1789	96.7	-	62384969	62384988	CUCCGGCUCCCGCAGCCCCU	80	CGG
3282	62384952	10	1769	95.6	-	62384949	62384968	CGGGGCCGCCGCACGGGUCC	90	GGG
3283	62368839	9	922	49.8	+	62368822	62368841	AGAUCAAGGUGGUGUCUGUC	50	AGG
3284	62369234	9	1317	71.2	-	62369231	62369250	ACAUCUGCCCAGUUGGGGCU	60	GGG
3285	62361736	7	673	36.4	+	62361719	62361738	CUUCGCGUCUGUGGCCCUGG	70	TGG
3286	62369465	9	1548	83.6	-	62369462	62369481	GAUGCAGGGGACUGGCCACC	70	AGG
3287	62384959	10	1776	95.9	-	62384956	62384975	AGCCCCUCGGGGCCGCCGCA	85	CGG
3288	62369011	9	1094	59.1	+	62368994	62369013	UUACUGUUCCUCACUGAGCC	50	TGG
3289	62384971	10	1788	96.6	-	62384968	62384987	UCCGGCUCCCGCAGCCCCUC	80	GGG
3290	62369261	9	1344	72.6	+	62369244	62369263	CAGAUGUCUGCACAGGCUGC	60	CGG
3291	62369434	9	1517	82	+	62369417	62369436	CUCCCAAGCUCAGCGAGGGC	70	AGG

FIG. 42E

SEQ ID NO:	Genomic cut coordinate	Exon	CDS cut position	CDS cut position %	Strand	Start coordinate	End coordinate	crRNA	GC content	PAM
3292	62368808	9	891	48.1	-	62368805	62368824	UCUGGGUAGCACAUAUCUUC	45	TGG
3293	62369031	9	1114	60.2	-	62369028	62369047	GGGUUCAGAGAAAGGAGGUG	55	TGG
3294	62368858	9	941	50.8	+	62368841	62368860	CAGGGCACAUGUGUAGGAGG	60	TGG
3295	62369353	9	1436	77.6	-	62369350	62369369	UGGCUUCUUCUUCAGGGGGA	55	AGG
3296	62369458	9	1541	83.3	+	62369441	62369460	GCCGGGUCUGGAAGCUCCCC	75	TGG
3297	62384861	10	1678	90.7	+	62384844	62384863	CUCGCAGGAGGGCGCGGCGG	85	CGG
3298	62369479	9	1562	84.4	+	62369462	62369481	GGUGGCCAGUCCCCUGCAUC	70	TGG
3299	62369395	9	1478	79.8	-	62369392	62369411	CAUCAGCCCCAUCCUCGGGC	70	TGG
3300	62369053	9	1136	61.4	+	62369036	62369055	UUCUCUGAACCCCUGGAGGU	55	GGG
3301	62369233	9	1316	71.1	-	62369230	62369249	CAUCUGCCCAGUUGGGGCUG	65	GGG
3302	62384893	10	1710	92.4	-	62384890	62384909	GCCAGGGUCUCCUCCUGCAC	70	CGG
3303	62369235	9	1318	71.2	-	62369232	62369251	GACAUCUGCCCAGUUGGGGC	65	TGG
3304	62384975	10	1792	96.8	+	62384958	62384977	CGGCGGCCCCGAGGGGCUGC	90	GGG
3305	62384876	10	1693	91.5	+	62384859	62384878	GGCGGCGGCUGCGGAGCCCA	85	TGG
3306	62369400	9	1483	80.1	-	62369397	62369416	CCUCCCAUCAGCCCCAUCCU	65	CGG
3307	62369440	9	1523	82.3	+	62369423	62369442	AGCUCAGCGAGGGCAGGUGC	70	CGG
3308	62369052	9	1135	61.3	-	62369049	62369068	GUCAUUCUCCCCCACCUCCA	60	GGG
3309	62361733	7	670	36.2	+	62361716	62361735	UCUCUUCGCGUCUGUGGCCC	65	TGG
3310	62369054	9	1137	61.4	+	62369037	62369056	UCUCUGAACCCCUGGAGGUG	60	GGG
3311	62369373	9	1456	78.7	-	62369370	62369389	GUCUCUGGCCUCCGUCCUGC	70	TGG
3312	62369359	9	1442	77.9	-	62369356	62369375	UCCUGCUGGCUUCUUCUUCA	50	GGG
3313	62369407	9	1490	80.5	+	62369390	62369409	CAGCCCGAGGAUGGGGCUGA	70	TGG
3314	62368826	9	909	49.1	-	62368823	62368842	UGACAGACACCACCUUGAUC	50	TGG
3315	62368979	9	1062	57.4	-	62368976	62368995	AACUGGUCUGUGGGCUGGGA	60	GGG
3316	62384987	10	1804	97.5	+	62384970	62384989	GGGGCUGCGGGAGCCGGAGA	80	AGG
3317	62369052	9	1135	61.3	+	62369035	62369054	UUUCUCUGAACCCCUGGAGG	55	TGG
3318	62384981	10	1798	97.1	+	62384964	62384983	CCCCGAGGGGCUGCGGGAGC	85	CGG
3319	62369399	9	1482	80.1	-	62369396	62369415	CUCCCAUCAGCCCCAUCCUC	65	GGG
3320	62369053	9	1136	61.4	-	62369050	62369069	UGUCAUUCUCCCCCACCUCC	60	AGG
3321	62369360	9	1443	78	-	62369357	62369376	GUCCUGCUGGCUUCUUCUUC	55	AGG
3322	62369229	9	1312	70.9	-	62369226	62369245	UGCCCAGUUGGGGCUGGGGC	75	TGG
3323	62361687	7	624	33.7	-	62361684	62361703	AAACCGGGCAAGUAAACAUG	45	GGG
3324	62361688	7	625	33.8	-	62361685	62361704	UAAACCGGGCAAGUAAACAU	40	GGG
3325	62361727	7	664	35.9	+	62361710	62361729	UCUGCUUCUCUUCGCGUCUG	55	TGG
3326	62361695	7	632	34.1	+	62361678	62361697	GAACCCCAUGUUUACUUGCC	50	CGG
3327	62360044	6	611	33	+	62360027	62360046	CCAGCUAGAAAACCACCAAA	45	TGG
3328	62361702	7	639	34.5	-	62361699	62361718	AGAAGCAGAAUUAUUAAACC	30	GGG
3329	62361689	7	626	33.8	-	62361686	62361705	UUAAACCGGGCAAGUAAACA	40	TGG
3330	62361703	7	640	34.6	-	62361700	62361719	GAGAAGCAGAAUUAUUAAAC	30	CGG
3331	62360033	6	600	32.4	-	62360030	62360049	CCAUUUGGUGGUUUUCUAGC	45	TGG
3332	62385017	10	1834	99.1	+	62385000	62385019	GCCGGUGCAGGAGCAAGGCG	75	GGG
3333	62385029	10	1846	99.7	-	62385026	62385045	CAUGGGGGGCGCUCAAGCCU	70	TGG
3334	62385016	10	1833	99	+	62384999	62385018	GGCCGGUGCAGGAGCAAGGC	75	GGG
3335	62385023	10	1840	99.4	+	62385006	62385025	GCAGGAGCAAGGCGGGGCCA	75	AGG

FIG. 42F

SEQ ID NO:	MIT	CFD	Elevation	DT	Offtarget #	Azimuth	DeepSpCas9	CrispRScan	Ctrl	Lindel	inDelphi	Frameshift	Precision	Graf Motifs	Bioscore	KO_DT	KO_FT	Overlap	Interference modification
3042	78	84	65	76	165	71	71	41	61	90	92	91	59	OK	60	68	83	76	Knockout
3043	71	85	59	72	158	57	64	24	48	84	88	86	61	OK	59	60	78	69	Knockout
3044	67	83	64	71	189	58	49	42	50	82	87	85	57	OK	75	61	78	69	Knockout
3045	72	84	69	72	190	70	48	41	53	85	88	86	45	OK	67	62	79	70	Knockout
3046	70	84	60	71	178	69	68	51	63	78	87	82	58	OK	61	67	77	72	Knockout
3047	71	83	53	69	155	71	51	56	63	86	83	85	54	OK	58	66	77	72	Knockout
3048	89	93	43	76	60	66	62	61	63	91	91	91	63	OK	60	69	83	76	Knockout
3049	86	93	41	73	83	54	60	73	62	81	79	80	48	OK	58	68	77	72	Knockout
3050	78	86	44	69	136	48	58	63	56	77	88	83	52	OK	46	63	76	69	Knockout
3051	86	94	36	72	82	47	49	63	53	81	76	79	51	OK	50	62	75	66	Knockout
3052	84	95	43	77	44	45	36	45	42	75	86	81	60	OK	45	60	78	67	Knockout
3053	88	94	38	73	75	28	43	51	41	83	90	87	53	OK	52	57	80	67	Knockout
3054	94	96	41	78	36	49	55	67	57	81	71	66	65	OK	52	67	72	67	Knockout
3055	76	88	64	76	166	54	43	30	42	77	84	80	52	OK	54	59	78	66	Knockout
3056	80	94	41	72	72	35	49	85	56	71	81	86	44	OK	58	64	69	65	Knockout
3057	81	94	44	76	62	38	29	54	40	73	82	77	63	OK	66	58	77	65	Knockout
3058	83	91	41	72	82	28	23	55	35	85	91	88	59	OK	52	54	80	65	Knockout
3059	52	75	39	55	265	53	48	58	53	78	88	83	60	GGC	45	54	69	64	Knockout
3060	82	92	38	71	98	50	52	57	53	71	65	68	43	OK	58	62	69	64	Knockout
3061	60	89	37	62	383	41	68	58	56	70	75	73	65	OK	54	59	67	64	Knockout
3062	78	91	36	69	102	60	63	57	60	56	66	61	68	OK	53	65	65	63	Knockout
3063	75	88	60	74	117	63	46	16	42	58	75	71	58	OK	63	58	73	63	Knockout
3064	82	92	47	74	81	35	33	74	47	56	77	66	61	TT	46	60	70	62	Knockout
3065	33	73	37	48	713	38	37	86	54	82	82	82	61	OK	37	51	65	61	Knockout
3066	70	90	38	68	155	23	29	63	38	75	81	78	64	OK	46	52	72	61	Knockout
3067	78	85	39	67	201	39	39	52	43	72	72	72	68	OK	52	55	70	61	Knockout
3068	75	85	64	75	172	43	24	45	37	58	69	64	52	OK	62	56	69	59	Knockout
3069	74	93	41	69	95	17	39	60	39	62	68	65	56	OK	47	54	67	58	Knockout
3070	75	87	64	75	168	38	20	30	29	67	73	70	49	OK	75	52	73	56	Knockout
3071	77	90	60	76	128	39	9	40	29	63	75	69	58	OK	56	53	72	59	Knockout
3072	66	84	33	61	469	37	42	45	41	69	76	73	55	OK	50	51	67	58	Knockout
3073	77	87	37	67	121	38	17	55	37	88	70	69	55	OK	46	52	68	58	Knockout
3074	29	61	37	42	984	27	33	72	44	78	77	78	59	OK	43	43	60	55	Knockout
3075	79	91	35	68	109	36	36	26	33	60	47	54	58	OK	54	51	61	52	Knockout
3076	46	66	30	47	465	45	50	68	54	59	38	49	59	OK	46	51	48	50	Knockout
3077	25	57	19	34	971	30	19	45	28	53	71	70	51	OK	38	31	52	44	Knockout
3078	86	93	40	73	118	30	42	66	46	88	86	86	65	OK	63	59	80	68	Knockout or soluble decoy receptor
3079	86	96	37	77	75	53	65	71	63	80	76	78	48	OK	48	70	77	73	Knockout or soluble decoy receptor
3080	70	82	60	71	184	54	63	44	54	90	90	90	65	OK	62	62	80	71	Knockout or soluble decoy receptor
3081	85	89	51	75	123	58	61	60	60	86	85	86	59	OK	62	67	80	73	Knockout or soluble decoy receptor
3082	88	91	59	79	132	76	66	64	69	79	76	78	46	OK	62	74	79	75	Knockout or soluble decoy receptor
3083	90	93	51	78	80	60	32	63	52	80	81	80	46	OK	61	65	79	70	Knockout or soluble decoy receptor
3084	80	92	59	77	150	66	60	84	70	59	73	66	47	OK	54	73	72	71	Knockout or soluble decoy receptor
3085	64	78	49	64	273	54	59	57	57	84	95	89	71	OK	64	60	76	70	Knockout or soluble decoy receptor
3086	94	97	42	78	35	43	49	71	54	89	78	74	52	OK	46	66	76	69	Knockout or soluble decoy receptor
3087	83	93	46	74	101	38	40	65	48	81	83	82	47	OK	59	61	78	68	Knockout or soluble decoy receptor
3088	95	98	41	78	31	40	40	40	40	86	88	87	49	OK	43	59	82	68	Knockout or soluble decoy receptor
3089	66	88	44	66	157	58	70	28	52	77	87	82	57	OK	62	59	74	67	Knockout or soluble decoy receptor
3090	91	97	40	76	60	45	49	50	48	70	70	70	53	OK	61	62	73	65	Knockout or soluble decoy receptor
3091	80	74	61	65	252	59	47	35	47	80	87	84	57	OK	53	56	74	65	Knockout or soluble decoy receptor

FIG. 42G

SEQ ID NO:	MIT	CFD	Elevation	GSS	Offtarget #	Azimuth	DeepSpCas9	CropSeq	CFD	Lindel	inDelphi	Frameshift	Precision	Graf Motifs	Bioscore	Cas-OFFinder	CHOPCHOP	CRISPOR	Intervention prediction
3092	77	89	40	69	221	32	25	63	41	78	84	81	51	OK	53	55	75	64	Knockout or soluble decoy receptor
3093	93	96	37	76	28	30	13	49	31	84	87	85	56	OK	42	53	81	64	Knockout or soluble decoy receptor
3094	88	96	44	76	102	23	17	55	31	78	86	82	52	OK	60	54	79	63	Knockout or soluble decoy receptor
3095	53	87	62	61	404	61	53	17	44	63	81	82	57	OK	61	52	71	62	Knockout or soluble decoy receptor
3096	54	77	59	63	329	45	36	23	35	65	87	86	57	OK	63	49	75	62	Knockout or soluble decoy receptor
3097	60	83	61	68	285	56	45	59	53	61	75	63	69	OK	61	61	66	61	Knockout or soluble decoy receptor
3098	56	86	59	76	156	31	21	22	25	85	94	89	66	TT	62	48	80	61	Knockout or soluble decoy receptor
3099	77	90	35	67	82	27	29	59	38	78	72	75	53	GGC	50	53	71	60	Knockout or soluble decoy receptor
3100	62	81	49	64	244	49	34	37	40	68	74	71	58	GGC	59	52	68	58	Knockout or soluble decoy receptor
3101	62	80	38	60	179	56	56	62	58	59	51	56	47	OK	64	59	57	58	Knockout or soluble decoy receptor
3102	61	91	53	68	148	35	39	36	37	86	68	62	50	OK	54	53	65	56	Knockout or soluble decoy receptor
3103	73	87	40	67	118	20	8	46	22	74	85	79	53	GGC	50	44	73	56	Knockout or soluble decoy receptor
3104	44	58	78	57	506	45	19	44	36	70	72	71	65	OK	48	47	64	55	Knockout or soluble decoy receptor
3105	62	75	53	63	171	50	43	48	47	58	48	53	51	OK	56	55	58	54	Knockout or soluble decoy receptor
3106	37	69	32	46	616	28	8	72	35	70	54	62	60	GGC	51	41	54	48	Knockout or soluble decoy receptor
3107	80	87	61	76	165	69	51	41	54	90	94	92	56	OK	56	65	84	74	Membrane-bound decoy
3108	80	84	56	73	119	62	50	42	51	81	89	85	52	TT	50	62	79	70	Membrane-bound decoy
3109	86	93	42	74	51	57	48	59	55	77	86	82	46	OK	53	64	78	70	Membrane-bound decoy
3110	70	89	53	71	165	76	69	51	65	85	87	86	50	OK	31	68	78	74	Membrane-bound decoy
3111	71	88	59	73	183	71	72	59	67	88	90	89	65	OK	43	70	81	76	Membrane-bound decoy
3112	87	95	53	76	71	50	58	44	51	85	91	88	56	TT	36	64	83	72	Membrane-bound decoy
3113	87	95	60	81	54	64	44	56	55	87	74	80	56	OK	33	66	81	72	Membrane-bound decoy
3114	72	88	56	72	170	62	61	66	63	75	81	78	61	OK	48	67	75	71	Membrane-bound decoy
3115	90	95	48	78	90	63	56	65	62	77	82	79	52	OK	28	70	79	73	Membrane-bound decoy
3116	81	94	57	77	69	53	46	51	50	96	92	89	65	GGC	40	64	83	72	Membrane-bound decoy
3117	91	92	60	81	60	56	59	50	55	80	85	82	59	OK	50	66	82	73	Membrane-bound decoy
3118	82	88	51	74	101	73	66	30	56	83	87	85	45	OK	61	65	79	72	Membrane-bound decoy
3119	77	88	53	73	120	77	73	49	66	85	90	88	64	OK	50	70	80	76	Membrane-bound decoy
3120	59	77	52	63	276	76	51	62	61	90	97	93	66	OK	43	62	78	72	Membrane-bound decoy
3121	91	96	47	78	92	52	55	77	61	81	84	83	47	OK	48	70	80	74	Membrane-bound decoy
3122	85	92	41	73	114	64	53	81	69	79	87	83	62	OK	44	71	78	75	Membrane-bound decoy
3123	87	92	52	77	80	66	43	75	61	77	86	81	57	OK	44	69	79	73	Membrane-bound decoy
3124	95	96	55	82	46	60	46	55	54	83	88	86	63	OK	39	68	84	74	Membrane-bound decoy
3125	89	95	50	78	59	55	39	60	51	84	86	85	54	OK	39	65	82	72	Membrane-bound decoy
3126	91	95	53	80	72	52	18	69	46	82	92	87	61	TT	37	63	83	71	Membrane-bound decoy
3127	87	97	48	77	39	65	71	49	62	79	88	83	56	OK	37	69	80	74	Membrane-bound decoy
3128	91	95	52	76	73	73	73	50	65	91	92	91	63	OK	51	72	86	79	Membrane-bound decoy
3129	84	90	50	75	148	61	74	71	69	78	86	72	44	OK	33	72	73	72	Membrane-bound decoy
3130	92	94	44	77	67	55	49	52	52	86	82	84	62	OK	53	64	80	71	Membrane-bound decoy
3131	91	97	41	76	55	61	57	53	57	76	83	79	51	OK	52	67	78	71	Membrane-bound decoy
3132	83	90	46	73	122	66	60	50	59	87	83	85	55	OK	50	66	79	72	Membrane-bound decoy
3133	94	97	37	76	45	58	57	55	57	80	78	79	41	OK	43	66	77	70	Membrane-bound decoy
3134	95	96	40	78	36	51	63	53	56	85	91	88	63	TT	41	67	83	74	Membrane-bound decoy
3135	94	96	37	77	24	64	59	49	57	77	82	79	46	OK	30	67	76	71	Membrane-bound decoy
3136	88	95	44	76	59	50	45	87	61	83	80	82	50	OK	30	68	79	73	Membrane-bound decoy
3137	90	96	41	76	59	58	50	79	62	81	82	81	52	OK	32	69	79	73	Membrane-bound decoy
3138	83	92	42	72	86	52	29	91	57	87	89	88	53	OK	43	65	80	73	Membrane-bound decoy
3139	78	88	57	74	123	76	77	49	67	73	79	76	56	OK	34	71	75	72	Membrane-bound decoy
3140	58	83	53	65	217	64	55	66	62	76	88	82	51	OK	46	63	73	70	Membrane-bound decoy
3141	48	68	48	55	364	78	72	50	66	87	94	90	65	OK	47	60	72	70	Membrane-bound decoy

FIG. 42H

SEQ ID NO:	MIT	CFD	Elevation	Cnn	OffTarget#	Azimuth	DeepSpCas9	CrispScan	Ctn	Lindel	inDelphi	Frameshift	Precision	Graf Motifs	Bioscore	Cas-OFFinder	Cas-OFFinder	Cas-OFFinder	Interference Predictions
3142	77	82	38	66	203	72	58	72	67	73	82	78	51	OK	47	66	72	70	Membrane-bound decoy
3143	66	83	53	67	228	56	62	48	55	87	90	88	64	OK	41	61	76	70	Membrane-bound decoy
3144	69	87	48	68	179	49	43	78	57	78	84	81	50	OK	44	62	75	69	Membrane-bound decoy
3145	74	90	60	76	154	33	42	73	49	85	82	84	56	OK	43	62	79	69	Membrane-bound decoy
3146	66	80	66	70	201	56	63	32	47	88	89	89	64	OK	56	59	79	69	Membrane-bound decoy
3147	76	87	53	72	159	57	56	71	61	87	78	73	56	OK	53	67	72	69	Membrane-bound decoy
3148	35	74	68	58	317	63	57	67	62	81	90	85	61	OK	44	60	72	69	Membrane-bound decoy
3149	75	87	53	72	155	52	49	58	53	80	84	82	60	OK	48	62	77	69	Membrane-bound decoy
3150	76	84	51	70	164	66	58	46	57	81	80	81	60	OK	38	64	75	69	Membrane-bound decoy
3151	73	90	42	68	179	36	42	91	56	83	82	83	46	OK	38	62	75	69	Membrane-bound decoy
3152	93	94	43	77	66	48	41	81	57	73	73	73	63	OK	46	67	75	69	Membrane-bound decoy
3153	90	95	38	74	70	48	43	57	49	82	82	82	45	OK	44	62	76	69	Membrane-bound decoy
3154	85	92	46	74	78	53	52	27	44	87	88	87	54	OK	52	59	81	69	Membrane-bound decoy
3155	85	91	40	72	99	60	69	65	65	75	68	71	58	OK	54	66	72	69	Membrane-bound decoy
3156	90	93	51	78	67	42	40	49	44	83	87	85	59	OK	44	61	82	69	Membrane-bound decoy
3157	93	96	50	80	49	42	42	32	39	83	86	85	50	OK	52	59	82	68	Membrane-bound decoy
3158	74	88	53	72	139	55	53	54	54	77	79	78	63	OK	46	62	75	68	Membrane-bound decoy
3159	59	68	61	63	429	59	50	51	53	88	90	89	70	OK	55	58	76	68	Membrane-bound decoy
3160	94	96	45	78	38	37	24	55	39	83	91	87	59	OK	43	59	83	68	Membrane-bound decoy
3161	55	77	51	61	274	61	64	73	68	73	81	77	48	OK	38	64	69	68	Membrane-bound decoy
3162	34	48	40	41	560	60	70	82	71	91	93	92	55	OK	36	56	66	68	Membrane-bound decoy
3163	83	94	53	77	76	51	54	50	52	75	76	75	42	OK	49	64	76	68	Membrane-bound decoy
3164	81	84	48	71	199	47	53	80	60	69	74	72	46	OK	37	66	71	68	Membrane-bound decoy
3165	66	83	53	67	170	58	49	54	54	82	86	84	51	OK	46	61	76	68	Membrane-bound decoy
3166	82	92	53	76	107	62	55	26	48	79	84	82	49	OK	48	62	79	68	Membrane-bound decoy
3167	74	88	45	69	123	56	72	39	56	72	85	78	56	OK	42	63	74	68	Membrane-bound decoy
3168	95	96	34	75	39	46	30	57	44	81	87	84	57	OK	40	60	80	68	Membrane-bound decoy
3169	64	86	49	66	182	62	56	58	59	72	68	80	51	OK	38	62	73	68	Membrane-bound decoy
3170	61	72	64	66	245	59	53	64	58	74	65	80	49	OK	39	62	73	68	Membrane-bound decoy
3171	85	85	38	63	291	47	54	49	50	91	88	89	66	OK	50	56	76	67	Membrane-bound decoy
3172	66	90	43	74	90	52	31	38	40	82	89	86	54	OK	52	57	80	67	Membrane-bound decoy
3173	81	89	43	71	124	59	51	42	51	80	81	81	48	OK	44	61	76	67	Membrane-bound decoy
3174	73	85	59	72	201	49	54	67	57	72	73	73	51	OK	41	64	72	67	Membrane-bound decoy
3175	90	91	46	76	72	38	52	29	40	83	86	85	50	OK	45	58	80	67	Membrane-bound decoy
3176	72	82	38	64	173	51	53	65	56	74	90	82	60	OK	39	60	73	67	Membrane-bound decoy
3177	57	70	46	58	334	66	62	27	52	93	90	91	54	OK	37	55	75	67	Membrane-bound decoy
3178	71	83	42	65	201	63	59	23	52	87	80	84	54	OK	33	58	74	67	Membrane-bound decoy
3179	51	77	49	59	314	63	60	49	57	82	87	84	55	OK	35	58	72	67	Membrane-bound decoy
3180	60	66	41	56	450	60	73	56	63	77	89	83	62	OK	33	59	69	67	Membrane-bound decoy
3181	91	93	40	75	81	39	53	63	52	76	72	74	38	OK	48	63	74	67	Membrane-bound decoy
3182	54	71	48	58	417	61	56	54	57	80	86	83	52	OK	47	57	70	66	Membrane-bound decoy
3183	28	64	19	37	436	73	78	76	76	81	87	84	57	OK	42	56	61	66	Membrane-bound decoy
3184	76	90	44	70	91	55	52	61	56	73	69	71	54	OK	44	63	70	66	Membrane-bound decoy
3185	81	88	38	69	144	49	69	46	55	76	74	76	49	OK	56	62	72	66	Membrane-bound decoy
3186	69	82	53	68	178	57	31	70	53	77	81	79	61	TT	53	60	73	66	Membrane-bound decoy
3187	90	94	46	77	104	40	35	64	46	79	72	75	42	OK	42	61	76	66	Membrane-bound decoy
3188	89	94	39	74	66	36	29	61	42	78	88	83	51	OK	50	58	78	66	Membrane-bound decoy
3189	68	80	42	63	216	57	66	18	47	85	91	88	59	OK	48	55	76	66	Membrane-bound decoy
3190	96	97	43	78	31	45	18	44	36	84	86	85	55	OK	41	57	82	66	Membrane-bound decoy
3191	51	73	49	58	474	35	59	74	56	83	87	85	49	OK	49	57	71	66	Membrane-bound decoy

FIG. 42I

SEQ ID NO:	MIT	CFD	Elevation	GUIDE	Offtarget #	Azimuth	DeepSpCas9	CrispScan	CFD	Lindel	InDelphi	Frameshift	Precision	Graf Motifs	Bioscore	Doench '16	Doench '14	MITBest	Interference Matrix Rows
3192	68	81	53	67	215	53	54	62	56	71	70	70	43	OK	33	62	69	65	Membrane-bound decoy
3193	81	87	50	79	75	16	6	64	29	60	81	85	57	TT	37	54	82	65	Membrane-bound decoy
3194	65	85	61	70	203	48	43	36	42	60	85	82	58	OK	50	56	76	65	Membrane-bound decoy
3195	49	75	34	53	303	51	47	69	56	86	87	87	45	OK	43	54	70	65	Membrane-bound decoy
3196	68	85	54	69	197	53	60	68	60	70	59	64	45	OK	46	65	67	65	Membrane-bound decoy
3197	75	88	38	67	225	48	50	55	51	69	83	76	64	OK	31	59	71	65	Membrane-bound decoy
3198	56	75	46	59	308	52	60	45	52	82	86	84	52	OK	47	56	71	65	Membrane-bound decoy
3199	55	74	50	60	350	53	44	65	54	78	83	81	58	OK	38	57	70	65	Membrane-bound decoy
3200	75	83	43	67	150	42	43	48	44	83	83	83	50	OK	49	56	75	65	Membrane-bound decoy
3201	70	86	44	67	137	52	36	48	45	87	81	84	47	OK	35	56	75	65	Membrane-bound decoy
3202	68	88	55	70	305	35	27	69	44	75	86	80	57	TT	62	57	75	65	Membrane-bound decoy
3203	61	82	35	59	216	58	45	69	64	73	70	71	46	OK	36	62	65	65	Membrane-bound decoy
3204	62	80	53	65	188	52	59	49	53	76	80	78	56	OK	62	59	71	65	Membrane-bound decoy
3205	57	76	53	62	257	55	36	21	37	82	92	90	57	OK	35	50	77	64	Membrane-bound decoy
3206	57	71	65	64	328	53	44	22	40	86	87	87	45	OK	49	52	76	64	Membrane-bound decoy
3207	62	76	37	58	265	76	59	42	57	72	84	78	63	OK	31	58	68	64	Membrane-bound decoy
3208	81	94	50	76	86	16	7	61	29	61	87	84	50	TT	40	53	81	64	Membrane-bound decoy
3209	89	95	37	74	38	47	33	31	37	79	86	82	45	OK	48	55	78	64	Membrane-bound decoy
3210	53	78	39	57	302	53	43	66	54	81	85	83	47	OK	32	55	70	64	Membrane-bound decoy
3211	89	95	34	73	50	72	63	28	54	63	67	65	56	OK	66	64	69	64	Membrane-bound decoy
3212	78	82	43	68	229	42	45	71	53	72	70	71	45	OK	41	60	69	64	Membrane-bound decoy
3213	65	83	34	61	167	56	33	67	52	79	82	81	45	OK	30	56	71	64	Membrane-bound decoy
3214	89	94	40	74	68	37	31	70	46	77	69	73	46	OK	49	60	74	64	Membrane-bound decoy
3215	83	91	42	72	79	40	33	69	47	69	76	72	44	OK	35	60	72	64	Membrane-bound decoy
3216	82	94	40	72	82	40	41	66	49	74	65	69	59	OK	37	61	71	64	Membrane-bound decoy
3217	91	93	40	75	67	49	21	54	41	75	80	77	50	OK	28	58	75	64	Membrane-bound decoy
3218	59	81	41	60	266	57	53	94	88	55	67	61	69	OK	26	64	61	63	Membrane-bound decoy
3219	91	94	41	75	65	35	48	20	34	79	81	80	43	OK	53	55	76	63	Membrane-bound decoy
3220	50	72	49	57	295	63	48	44	52	83	78	80	50	OK	56	54	69	63	Membrane-bound decoy
3221	28	67	22	39	485	52	58	77	62	87	90	89	67	OK	39	51	64	63	Membrane-bound decoy
3222	71	89	43	68	126	61	46	34	47	73	78	76	51	OK	55	57	72	63	Membrane-bound decoy
3223	89	95	38	74	67	24	33	90	49	70	64	67	48	OK	36	61	70	63	Membrane-bound decoy
3224	76	89	49	71	248	38	55	46	46	76	69	73	55	OK	32	59	72	63	Membrane-bound decoy
3225	77	83	39	66	188	32	39	41	37	85	85	85	50	OK	32	52	76	63	Membrane-bound decoy
3226	58	70	64	64	356	57	37	51	48	73	83	78	61	OK	45	56	71	63	Membrane-bound decoy
3227	72	80	57	70	206	42	39	61	47	67	79	73	71	TT	36	58	71	63	Membrane-bound decoy
3228	64	80	61	68	245	51	18	30	33	86	89	87	61	TT	52	51	78	63	Membrane-bound decoy
3229	70	88	48	69	386	46	45	55	49	67	76	72	47	OK	41	59	70	63	Membrane-bound decoy
3230	63	80	49	64	216	38	44	58	47	76	82	79	48	TT	32	55	72	63	Membrane-bound decoy
3231	75	86	40	67	179	33	20	75	43	79	82	81	45	OK	44	55	74	63	Membrane-bound decoy
3232	52	75	48	58	288	66	51	71	63	69	62	66	47	OK	30	61	62	62	Membrane-bound decoy
3233	46	65	43	51	323	51	60	54	55	79	78	78	67	OK	37	53	65	62	Membrane-bound decoy
3234	71	86	37	65	155	52	51	67	57	61	70	65	46	OK	47	61	65	62	Membrane-bound decoy
3235	65	78	53	65	226	62	49	51	54	67	67	67	46	OK	45	60	66	62	Membrane-bound decoy
3236	57	85	59	67	273	39	19	54	37	79	86	82	55	OK	51	52	75	62	Membrane-bound decoy
3237	48	69	59	59	282	47	46	45	46	78	82	80	56	OK	40	52	69	62	Membrane-bound decoy
3238	82	89	61	77	141	46	9	37	31	77	78	77	43	OK	56	54	77	62	Membrane-bound decoy
3239	55	78	52	62	286	40	39	67	49	74	77	75	50	OK	34	55	68	62	Membrane-bound decoy
3240	71	81	39	64	178	43	44	66	51	72	68	70	43	OK	40	57	67	62	Membrane-bound decoy
3241	36	76	32	45	402	63	67	73	66	75	71	73	44	OK	30	56	59	62	Membrane-bound decoy

FIG. 42J

SEQ ID NO:	MIT	CFD	Elevation	CT	OffAngel #	Azimuth	DeepSpCas9	CrispScan	CNN	Lindel	inDelphi	Frameshift	Precision	Graf Motifs	Bioscore	CNN_CRISPR	CNN_1D	CNN_2D	Membrane-bound / Membrane-free
3242	64	82	47	64	267	59	60	66	69	65	41	53	57	OK	25	66	59	62	Membrane-bound decoy
3243	47	71	47	55	390	51	50	50	50	71	84	78	57	OK	53	53	66	61	Membrane-bound decoy
3244	75	90	48	71	133	68	52	50	56	52	61	57	46	OK	49	64	54	61	Membrane-bound decoy
3245	55	79	38	57	418	38	30	66	51	77	69	73	42	OK	25	54	65	61	Membrane-bound decoy
3246	79	85	36	67	157	36	48	30	38	80	75	77	50	OK	32	52	72	61	Membrane-bound decoy
3247	56	78	40	58	311	39	57	45	47	75	76	78	46	TT	34	53	68	61	Membrane-bound decoy
3248	81	91	41	71	80	46	18	62	41	66	76	71	59	TT	41	56	71	61	Membrane-bound decoy
3249	48	75	37	53	419	46	61	58	55	79	73	76	58	OK	42	54	65	61	Membrane-bound decoy
3250	85	92	40	72	100	44	11	54	36	73	75	74	66	TT	29	54	73	61	Membrane-bound decoy
3251	62	81	46	63	204	35	21	30	29	86	84	90	64	TT	33	46	77	61	Membrane-bound decoy
3252	69	84	51	66	182	43	27	44	38	72	82	77	51	OK	43	53	72	61	Membrane-bound decoy
3253	93	96	39	76	50	49	39	21	36	71	73	72	45	OK	28	56	74	61	Membrane-bound decoy
3254	70	83	69	73	146	32	21	38	30	78	78	78	60	OK	66	51	75	60	Membrane-bound decoy
3255	53	74	49	58	338	59	67	58	51	50	71	60	58	OK	64	60	59	60	Membrane-bound decoy
3256	36	60	55	50	425	50	58	43	51	76	85	80	56	OK	42	50	65	60	Membrane-bound decoy
3257	64	74	48	62	230	43	48	31	41	79	77	78	48	OK	34	51	70	60	Membrane-bound decoy
3258	55	73	64	64	283	47	39	26	37	72	84	78	59	OK	44	51	71	60	Membrane-bound decoy
3259	76	86	59	74	135	43	53	19	38	68	76	67	59	OK	44	56	70	60	Membrane-bound decoy
3260	85	93	49	76	84	44	17	18	26	73	80	77	47	OK	33	51	76	60	Membrane-bound decoy
3261	77	85	48	70	180	43	24	39	35	80	67	74	70	OK	53	53	72	60	Membrane-bound decoy
3262	62	83	42	62	199	47	35	48	43	78	68	74	72	OK	39	53	68	60	Membrane-bound decoy
3263	53	67	40	53	397	49	60	23	44	61	81	81	47	OK	46	49	67	59	Membrane-bound decoy
3264	62	82	48	64	251	27	25	26	26	87	86	87	59	OK	34	45	75	59	Membrane-bound decoy
3265	64	81	61	69	241	55	46	46	49	63	58	61	49	OK	47	59	65	59	Membrane-bound decoy
3266	58	71	41	57	307	48	51	48	49	70	71	71	42	OK	41	53	64	59	Membrane-bound decoy
3267	79	90	38	69	181	37	29	58	41	85	69	67	43	OK	58	55	68	59	Membrane-bound decoy
3268	80	92	40	71	89	40	58	50	49	63	52	58	51	OK	37	60	64	59	Membrane-bound decoy
3269	83	87	38	69	160	45	49	42	45	62	63	63	46	OK	37	57	66	59	Membrane-bound decoy
3270	48	74	76	64	348	25	25	32	27	82	81	86	64	TT	31	46	75	59	Membrane-bound decoy
3271	43	64	50	52	398	62	20	36	39	86	87	87	56	OK	42	46	69	59	Membrane-bound decoy
3272	58	74	65	66	254	49	24	44	39	71	74	72	45	OK	35	52	69	59	Membrane-bound decoy
3273	75	85	34	65	145	37	29	60	42	70	71	70	66	OK	46	53	68	59	Membrane-bound decoy
3274	48	69	42	53	349	61	55	60	59	65	61	63	48	OK	67	56	58	58	Membrane-bound decoy
3275	13	44	29	29	[redacted]	35	45	97	59	97	98	98	56	OK	49	44	58	58	Membrane-bound decoy
3276	44	61	56	54	414	69	37	39	45	75	76	76	49	OK	49	50	65	58	Membrane-bound decoy
3277	45	71	31	49	428	49	47	52	49	69	81	75	60	GGC	28	49	62	58	Membrane-bound decoy
3278	47	69	38	51	480	49	55	46	50	67	75	71	49	OK	67	51	61	58	Membrane-bound decoy
3279	60	75	53	63	291	52	37	39	43	71	67	69	56	OK	64	53	66	58	Membrane-bound decoy
3280	38	64	34	45	540	32	43	76	50	79	80	80	47	OK	42	48	62	58	Membrane-bound decoy
3281	45	68	33	49	425	35	35	44	38	82	84	83	47	OK	31	43	66	57	Membrane-bound decoy
3282	79	89	36	68	199	35	32	73	47	61	49	55	58	OK	35	57	62	57	Membrane-bound decoy
3283	44	76	41	54	288	39	34	37	37	77	86	82	65	OK	39	45	68	57	Membrane-bound decoy
3284	74	83	52	70	176	26	41	40	36	76	55	66	55	OK	33	53	68	57	Membrane-bound decoy
3285	68	82	36	62	144	60	46	75	60	57	40	49	61	OK	52	61	55	57	Membrane-bound decoy
3286	65	84	37	62	209	39	37	56	44	73	59	66	60	OK	26	53	64	57	Membrane-bound decoy
3287	73	86	41	67	150	30	14	48	31	74	75	74	54	OK	44	49	70	57	Membrane-bound decoy
3288	61	80	41	61	213	50	36	15	34	79	74	76	60	GGC	35	47	69	57	Membrane-bound decoy
3289	48	75	35	53	321	29	23	63	38	74	77	76	43	OK	42	46	64	56	Membrane-bound decoy
3290	37	78	37	51	310	50	55	53	53	68	59	64	49	OK	44	52	57	56	Membrane-bound decoy
3291	75	86	36	66	201	45	32	25	34	70	66	68	46	OK	36	50	67	56	Membrane-bound decoy

FIG. 42K

SEQ ID NO:	MIT	CFD	Elevation	CFF	Offtarget #	Azimuth	DeepSpCas9	CrispScan	Ori	Lindel	InDelphi	Frameshift	Precision	Graf Motifs	Bioscore	Ori CFF	Ori CFD	Ori Bioscore	Interpretation predictions
3292	82	91	51	75	134	35	22	27	28	70	64	67	47	TT	37	51	71	56	Membrane-bound decoy
3293	33	60	38	40	916	62	45	47	51	75	79	77	47	OK	37	46	59	56	Membrane-bound decoy
3294	63	73	53	63	312	55	57	77	63	48	36	43	56	OK	42	63	53	56	Membrane-bound decoy
3295	63	66	47	59	300	45	22	59	42	62	73	68	56	OK	35	50	53	56	Membrane-bound decoy
3296	53	78	43	58	232	38	48	49	45	68	60	64	45	OK	26	52	61	56	Membrane-bound decoy
3297	54	75	37	57	302	26	45	98	56	55	45	51	59	OK	35	56	54	55	Membrane-bound decoy
3298	73	91	49	71	147	37	44	41	41	48	62	55	55	OK	33	56	63	55	Membrane-bound decoy
3299	75	80	38	64	283	45	39	11	32	68	70	69	46	OK	31	48	67	55	Membrane-bound decoy
3300	61	79	52	64	256	38	46	43	42	53	63	58	61	OK	48	53	61	55	Membrane-bound decoy
3301	52	64	48	55	360	42	46	53	47	72	53	63	62	OK	31	51	59	55	Membrane-bound decoy
3302	36	72	29	45	349	44	53	64	54	68	60	64	49	OK	57	49	54	54	Membrane-bound decoy
3303	71	87	46	66	182	25	36	14	25	76	63	70	52	OK	39	47	69	54	Membrane-bound decoy
3304	41	67	29	46	409	31	45	56	44	72	74	73	48	OK	42	45	59	54	Membrane-bound decoy
3305	33	62	27	41	630	28	44	67	46	77	75	76	39	OK	38	43	58	54	Membrane-bound decoy
3306	42	72	36	50	515	42	24	30	32	76	85	81	61	TT	37	41	65	54	Membrane-bound decoy
3307	39	66	27	44	406	39	50	51	47	64	75	69	48	OK	28	45	57	53	Membrane-bound decoy
3308	46	69	38	51	340	49	54	36	46	53	72	62	67	OK	48	49	57	53	Membrane-bound decoy
3309	72	85	39	65	131	40	40	36	39	61	48	54	54	OK	44	52	60	53	Membrane-bound decoy
3310	45	62	52	53	413	49	50	52	50	62	51	56	54	OK	52	52	55	53	Membrane-bound decoy
3311	68	76	34	59	252	38	27	12	26	75	65	70	45	OK	32	43	65	52	Membrane-bound decoy
3312	48	66	59	58	408	33	27	28	29	61	78	69	66	TT	38	44	63	52	Membrane-bound decoy
3313	49	62	34	48	340	43	36	65	48	69	50	59	62	OK	30	48	54	52	Membrane-bound decoy
3314	47	81	57	62	223	38	37	8	27	64	69	67	44	OK	42	44	64	52	Membrane-bound decoy
3315	43	62	42	49	418	41	36	56	44	64	60	62	52	OK	43	47	55	52	Membrane-bound decoy
3316	32	64	25	40	667	44	39	67	50	67	59	63	45	OK	41	45	52	51	Membrane-bound decoy
3317	56	71	43	57	263	38	31	44	38	60	47	54	53	OK	47	47	55	49	Membrane-bound decoy
3318	42	62	34	46	483	23	6	70	33	64	70	67	46	OK	28	40	56	49	Membrane-bound decoy
3319	50	68	34	51	458	40	42	49	44	45	59	51	45	OK	37	47	51	48	Membrane-bound decoy
3320	47	71	48	55	386	41	34	24	33	58	53	56	54	OK	48	44	55	48	Membrane-bound decoy
3321	55	70	63	63	342	17	15	15	16	48	48	46	58	TT	37	39	55	42	Membrane-bound decoy
3322	31	40	16	26	832	27	6	38	24	69	30	54	70	OK	30	25	40	35	Membrane-bound decoy
3323	86	91	49	75	46	66	64	58	63	81	82	82	51	OK	64	80	78	73	Soluble decoy receptor
3324	80	91	43	71	76	59	67	53	60	80	89	84	59	OK	49	66	78	72	Soluble decoy receptor
3325	91	93	52	70	130	48	33	45	42	86	87	86	57	OK	47	60	83	69	Soluble decoy receptor
3326	82	90	58	77	91	45	29	37	37	85	89	87	62	GGC	42	57	82	67	Soluble decoy receptor
3327	72	83	60	72	184	54	39	35	43	64	81	82	53	OK	42	57	77	66	Soluble decoy receptor
3328	59	78	60	66	350	62	41	39	47	65	87	86	55	OK	49	57	76	66	Soluble decoy receptor
3329	77	91	51	73	92	53	21	18	31	87	85	86	55	OK	48	52	80	63	Soluble decoy receptor
3330	52	72	67	64	367	37	26	28	30	86	90	88	53	OK	56	47	76	61	Soluble decoy receptor
3331	78	84	62	75	130	42	14	23	26	77	82	80	63	OK	29	51	77	60	Soluble decoy receptor
3332	60	73	48	60	359	55	50	63	55	85	86	86	44	OK	35	58	73	67	Wildtype-like
3333	84	89	37	70	112	42	33	54	43	77	79	78	41	GGC	8	56	74	64	Wildtype-like
3334	37	64	42	48	697	44	41	35	40	84	92	88	55	OK	35	44	68	59	Wildtype-like
3335	42	48	32	41	910	46	44	47	46	80	89	84	61	OK	29	43	63	57	Wildtype-like

FIG. 42L

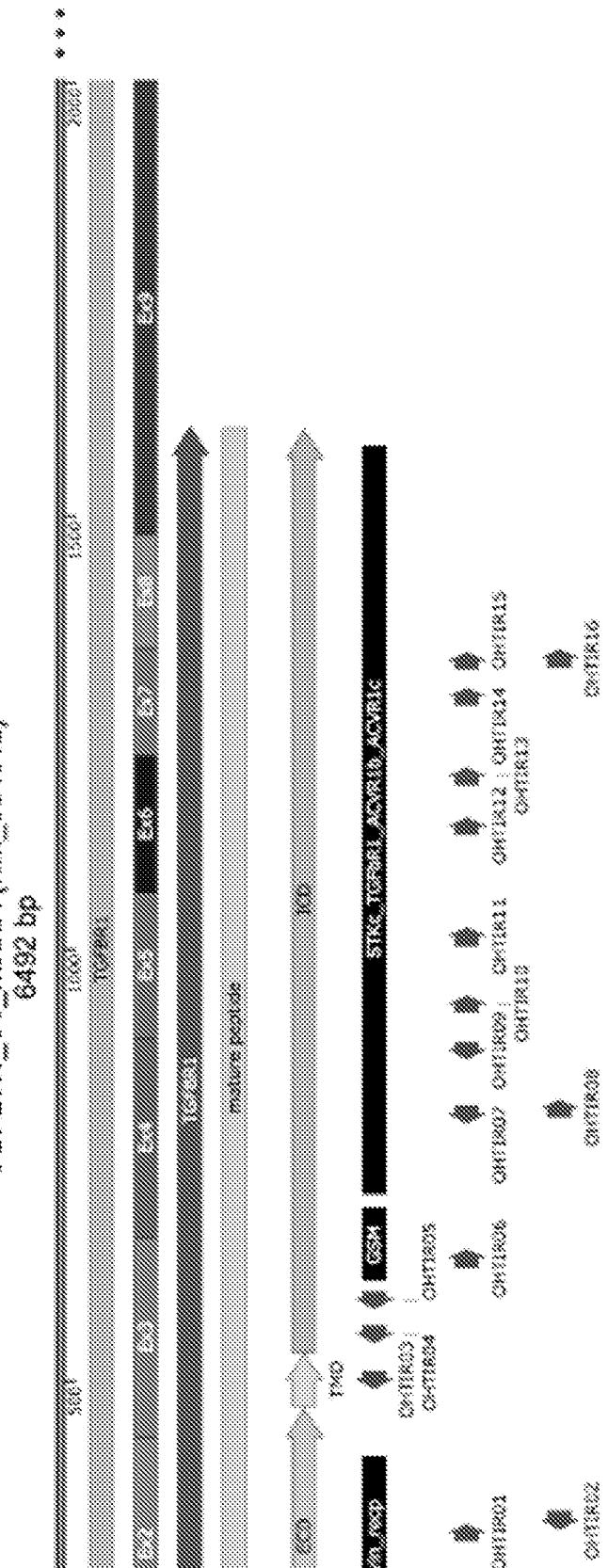

TGFBR1_V1_mRNA (NM_004612)
6492 bp
Start (1)
5'UTR
1,000
1,500
2,000
2,500
3,000
3,500
4,000
4,500
5,000
5,500
6,000
6,492
E1
E2
E3
E4
E5
E6
E7
E8
E9
TGFBR1
mature protein
signal peptide
ECD
TMD
GSM
Activin_recep
STKc_TGFBR1_ACVR1B_ACVR1C
OMTIR01
OMTIR02
OMTIR03
OMTIR04
OMTIR05
OMTIR06
OMTIR07
OMTIR08
OMTIR09
OMTIR10
OMTIR11
OMTIR12
OMTIR13
OMTIR14
OMTIR15
OMTIR16

FIG. 43A

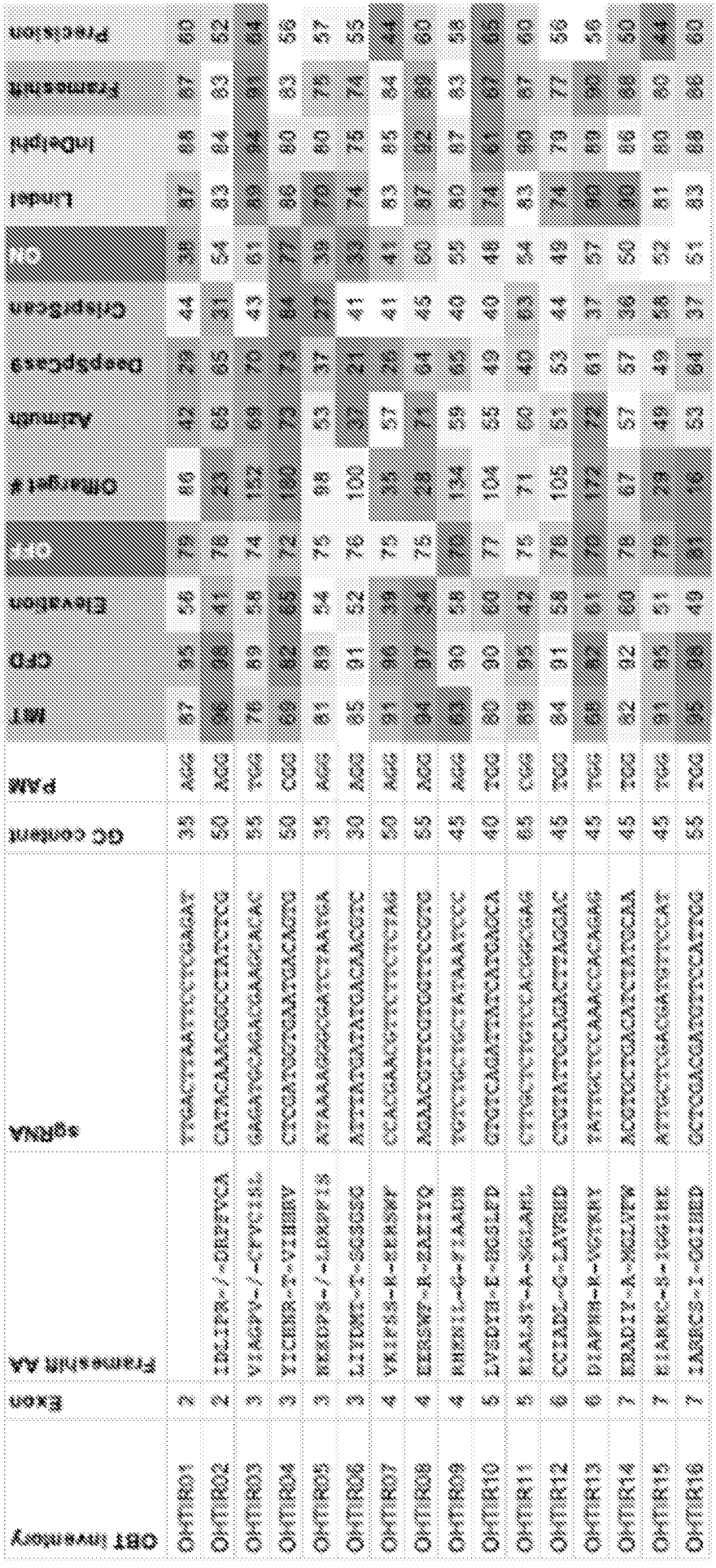

OBT inventory
Exon
Frameshift AA
sgRNA
GC content
PAM
MIT
CFD
Elevation
Off
CRISPRoff
Azimuth
DeepSpCas9
CHOPCHOP
Off
Lindel
inDelphi
Frameshift
Precision

FIG. 43B

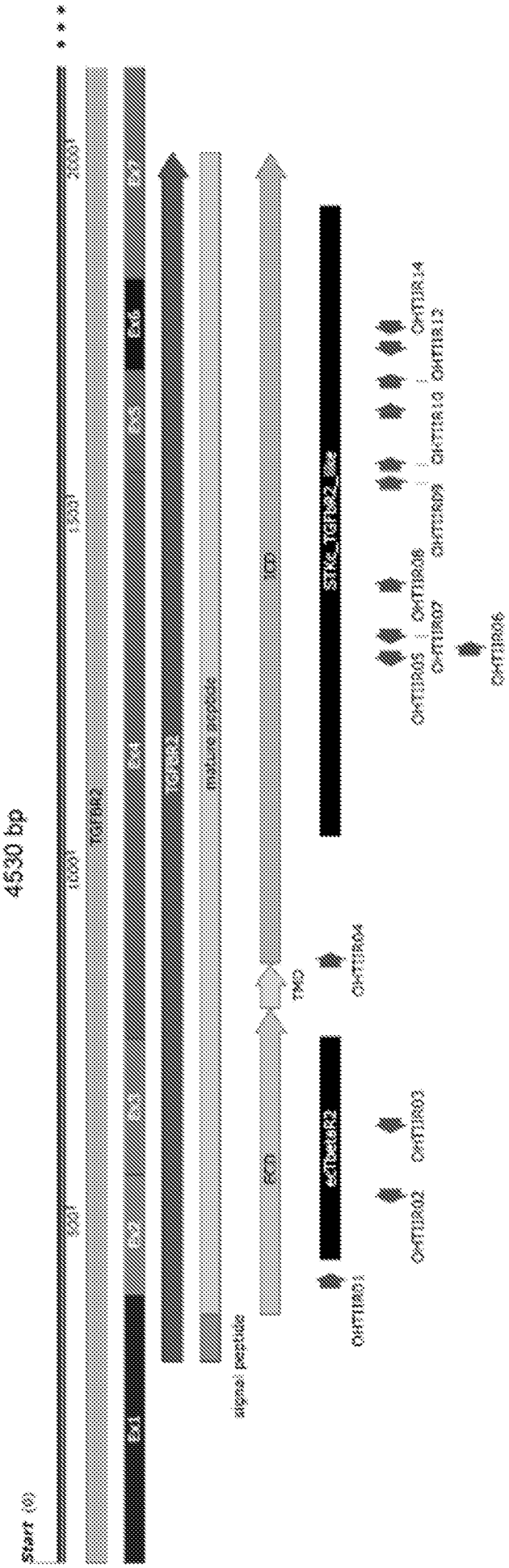

TGFBR1_V2_mRNA (NM_003242)
4530 bp
Start (0)
1000
2000
3000
4000
TGFBR2
E1
E2
E3
E4
E5
E6
E7
E8
E9
TGFBR1
signal peptide
ECD
TMD
ICD
SMAD_binding_2
OMTTIR01
OMTTIR02
OMTTIR03
OMTTIR04
OMTTIR05
OMTTIR06
OMTTIR07
OMTTIR08
OMTTIR09
OMTTIR10
OMTTIR11
OMTTIR12
OMTTIR13
OMTTIR14

FIG. 44A

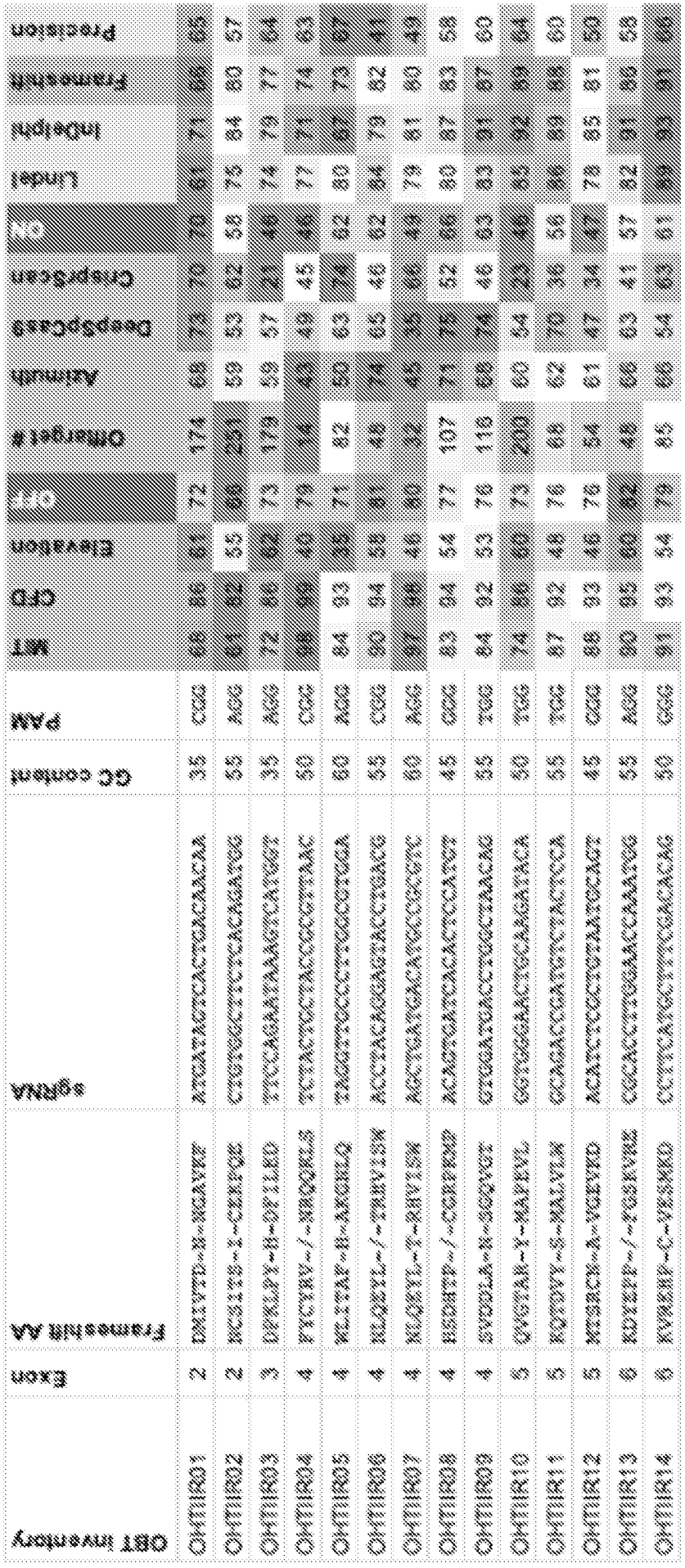

OBT inventory
Exon
Frameshift AA
sgRNA
GC content
PAM
MIT
CFD
Elevation
Off
Off-target #
Azimuth
DeepSpCas9
CrispScan
Doench
Lindel
inDelphi
Frameshift
Precision
OHTIIR01 2 DMIVTD-R-KGAVEF ATCATAGTCACTGACAACAA 35 CGG 68 86 61 72 174 68 72 70 80 71 71 65
OHTIIR02 2 KGSITS-I-CEMFQS CTGTGCCTTCTCACAGATGG 55 AGG 61 82 55 68 231 59 53 62 58 75 84 60 57
OHTIIR03 3 DPKLPY-R-GFILKD TTCCAGATAAAGTCATCGT 35 AGG 72 86 62 73 179 59 57 21 46 79 79 77 64
OHTIIR04 4 FTCTRV-/-KRQQKLS TCTACTCCTACCCCTTAAC 60 CGC 88 93 69 79 74 43 49 45 46 77 73 74 63
OHTIIR05 4 KLITAF-R-AKCKLQ TAGGTTCCCTTGCCTGGA 60 AGG 84 93 69 71 82 50 63 78 62 80 73 67
OHTIIR06 4 KLQITL-/-ZRVISK ACCTAGAGGAGTACCTGAAG 55 CGG 80 94 58 61 46 74 65 46 62 84 79 82 46
OHTIIR07 4 KLQITL-T-ZRVISK AGCTGATGACATGCCCGTC 60 AGG 97 96 60 60 32 49 35 66 49 79 81 80 49
OHTIIR08 4 RSDFTP-/-CGHFMP ACACTGATCAGACTCCATGT 45 GGC 83 94 54 77 107 71 75 52 66 80 87 83 58
OHTIIR09 4 SVDGLA-R-SGQVGT GTGGATGACCTGGCTAACAG 55 TGG 84 92 53 76 116 68 74 46 63 83 81 87 60
OHTIIR10 5 QVGTAR-Y-MAFEVL CGTGGGAACTGCAAGATACA 60 TGG 74 86 69 73 209 60 54 43 46 83 82 89 64
OHTIIR11 5 KQTDVT-S-MALVLK GCAGACCGATGTCTACTCCA 55 TGG 87 92 48 76 66 62 70 36 56 86 89 86 60
OHTIIR12 5 KTSACR-A-VGAVYD ACATCTCCTCTGTAATCCAGT 45 CGG 88 93 46 78 54 61 47 34 47 78 85 81 59
OHTIIR13 6 KDTERP-/-FGSAVK CGCACCTTGGAAGCAAAATG 55 AGG 80 95 60 82 48 66 63 41 57 82 91 80 58
OHTIIR14 6 KVMERP-C-YESMKD CCTTCATGCTTTTCGGACAG 50 GGG 91 93 54 79 85 60 54 63 61 89 93 91 69

FIG. 44B

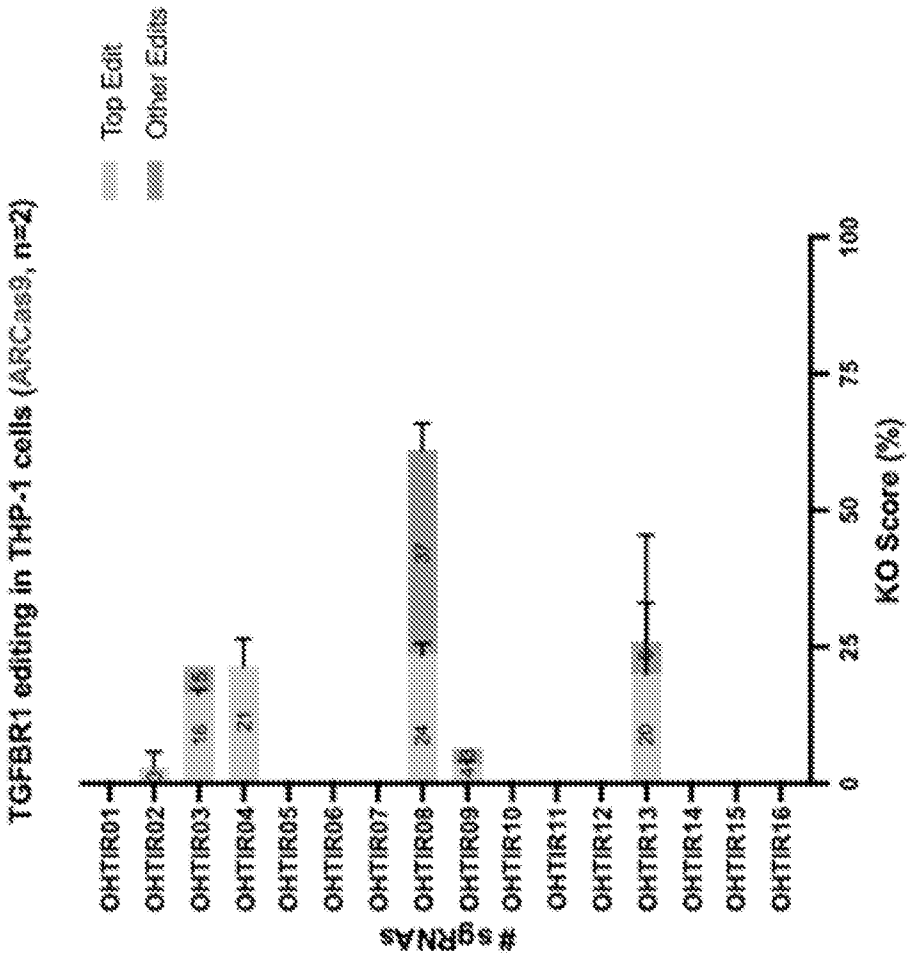


FIG. 45B

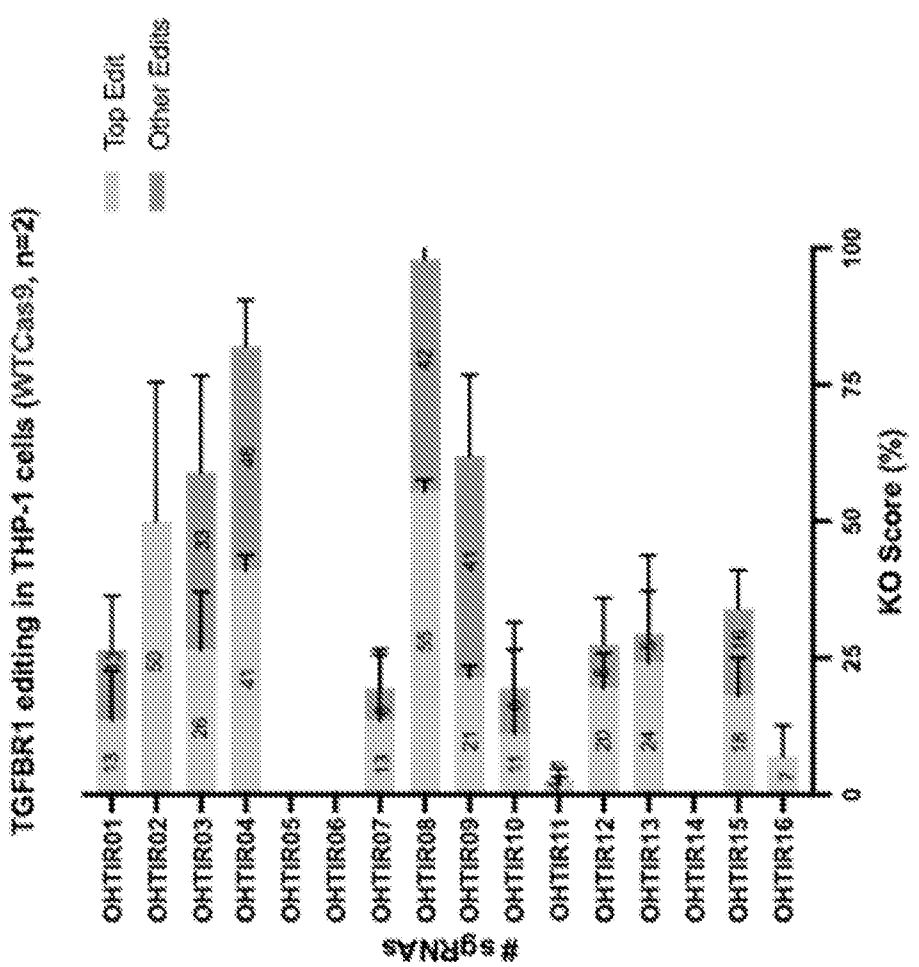


FIG. 45A

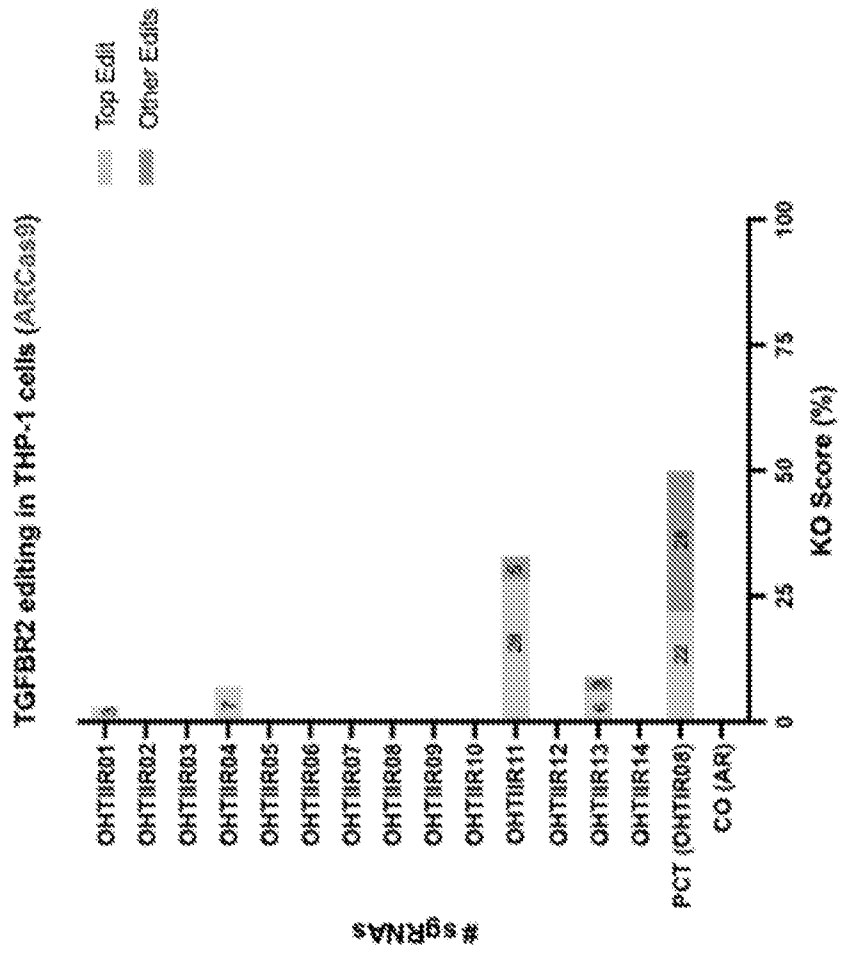


FIG. 46B

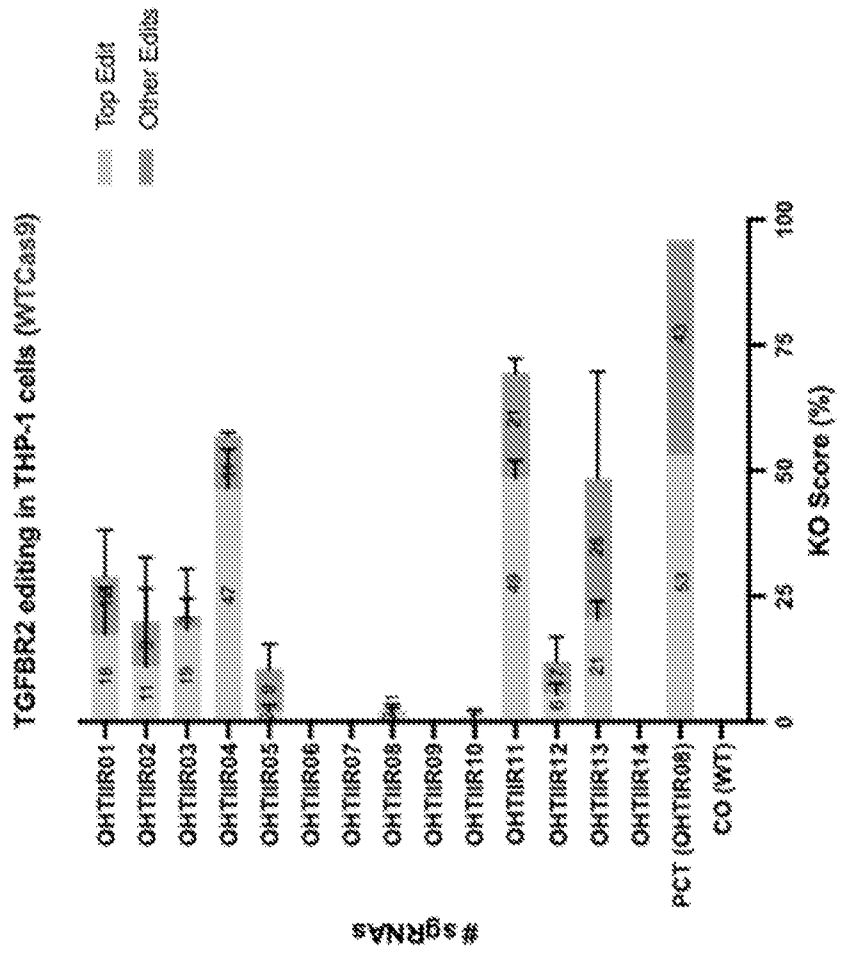


FIG. 46A

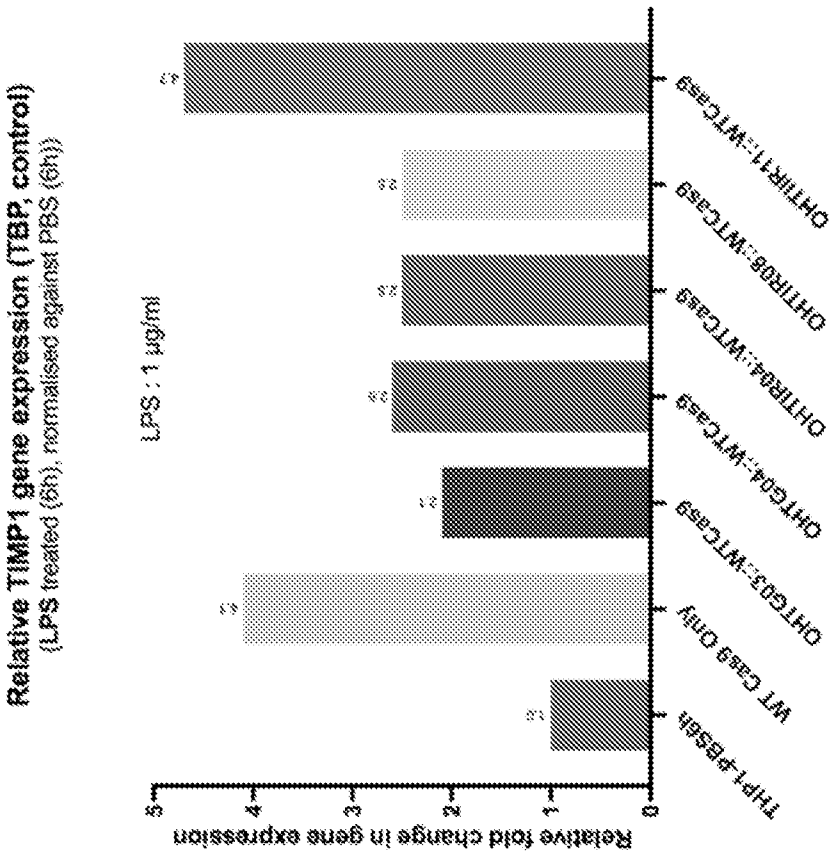


FIG. 47B

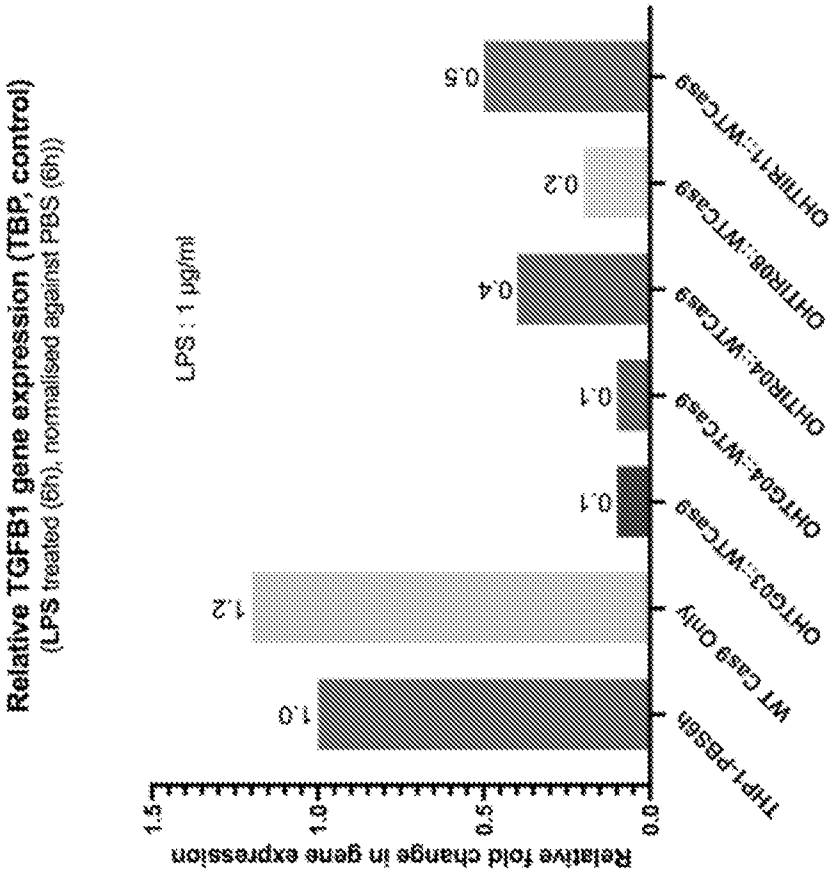


FIG. 47A

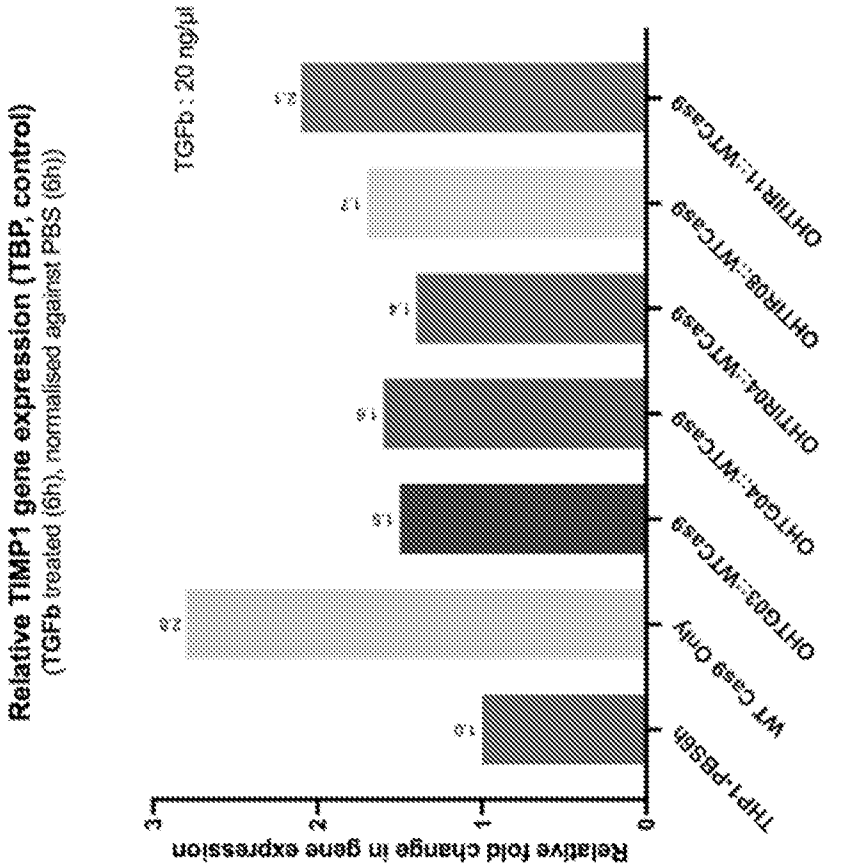


FIG. 47D

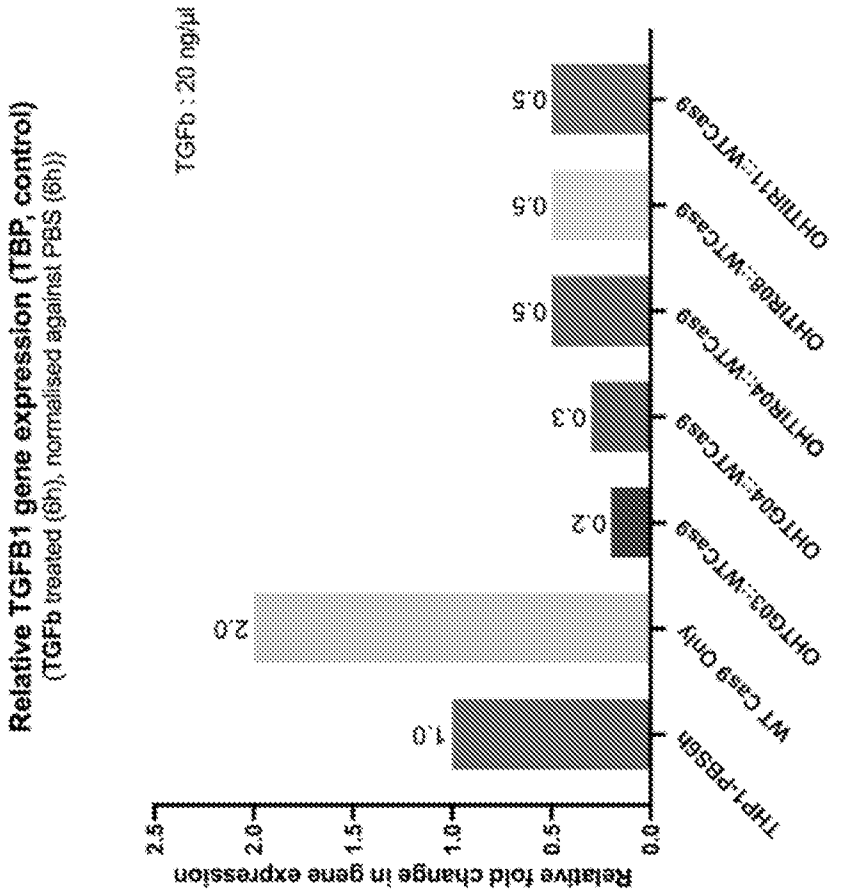


FIG. 47C

SEQ ID NO:	crRNA	interference predictions
3491	CUUAACCCAAAUGAACACAA	Knockout
3492	GAGGCUUGUUCUGUAGAUAC	Knockout
3493	AUGUGGCUGAAAAGCAUAGA	Knockout
3494	UUGGUUUGUUCCUGCUAAGG	Knockout
3495	UUCAGGACAUUACUAUUGCG	Knockout
3496	AAGCAGAAACUACCCGUUGC	Knockout
3497	UAGGCUCAUCGUGAUGAAUG	Knockout
3498	AAUGUGGCUGAAAAGCAUAG	Knockout
3499	CAUGCAUCCUACACAUACUU	Knockout
3500	GCAAGCAAUAUCCUAUUACC	Knockout
3501	CAAGCAAUAUCCUAUUACCC	Knockout
3502	GAGCCCAGCUAAUGAGACAA	Knockout
3503	AGCAAUGUCACUCAACUGGC	Knockout
3504	UAUAUCCAGUUAAUAUAUCC	Soluble decoy receptor
3505	UGGAAGGGAUGACUACGUUG	Membrane-bound decoy receptor
3506	AGGGAUGACUACGUUGGGGA	Membrane-bound decoy receptor
3507	ACAUCAGGCUUCAGCUGGCU	Membrane-bound decoy receptor
3508	CUGAACAAGAGCAUUAUACA	Membrane-bound decoy receptor
3509	GUGUAAAGUCCCCUGACCAG	Membrane-bound decoy receptor
3510	AUGGGGCUAUCCGCUGGUCA	Membrane-bound decoy receptor
3511	UGGGGCUAUCCGCUGGUCAG	Membrane-bound decoy receptor
3512	CUGGUCAGGGGACUUUACAC	Membrane-bound decoy receptor
3513	UGGUCAGGGGACUUUACACA	Membrane-bound decoy receptor

FIG. 48A

SEQ ID NO:	crRNA	interference predictions
3514	ACUGGGGACUAGACACCAUG	Knockout
3515	CAGCUGGCCUUACUCUGAUC	Knockout
3516	GAUCUGGUAUUGGACUAGGC	Knockout
3517	CCUUACUAAUGCGGUUCUCG	Knockout
3518	AUGCACUGGGAGUUUCAUGG	Knockout
3519	UAUGCACUGGGAGUUUCAUG	Knockout
3520	AUAUAGAAUAUGGCAUUCAG	Knockout
3521	AUAGUCGGUUUGACACUGGA	Knockout
3522	AGUGAUAGUCGGUUUGACAC	Knockout
3523	GAAACUCAAGUUCAUACCUU	Knockout
3524	GUGGUCUAUGAGAAAGAACC	Knockout
3525	GGAGCUACUCAUUCCCUGUA	Knockout
3526	AAACUAAAAAUAGACCGUACA	Knockout
3527	GAGGUUUGGUGGACCAUUGA	Knockout
3528	UUGAUGUCACCAUUAACGAA	Knockout
3529	GCUGCGCUUGAGAUCCUCAG	Knockout
3530	GCCAGCUCCAAGAUACACAG	Soluble decoy receptor
3531	UACACAGUGGAACUGGCUUG	Soluble decoy receptor
3532	AAUCACCACUAGCAGGACUG	Soluble decoy receptor
3533	UGUAUCCUAUGCAAGGAAUG	Membrane-bound decoy receptor
3534	UUUGUAUUACUGACCCUCCG	Membrane-bound decoy receptor
3535	AUUCUCCAAAACUCCACGGA	Membrane-bound decoy receptor
3536	CAUUCUCCAAAACUCCACGG	Membrane-bound decoy receptor
3537	UUGACCGAGACAGUCUGCCU	Membrane-bound decoy receptor
3538	UGACCGAGACAGUCUGCCUG	Membrane-bound decoy receptor
3539	GACCGAGACAGUCUGCCUGG	Membrane-bound decoy receptor
3540	UGGGGCUUAGAACAACCAGG	Membrane-bound decoy receptor
3541	AGCCCCAACUACGUGCUCCA	Membrane-bound decoy receptor
3542	CUAGAAAAUAUGGCCUCUCG	Membrane-bound decoy receptor
3543	GACGUUGAUGUUGCCCCGAG	Membrane-bound decoy receptor

FIG. 48B

SEQ ID NO:	crRNA	Interference predictions
3491	CUUAACCCAAAUGAACACAA	Knockout
3492	GAGGCUUGUUCUGUAGAUAC	Knockout
3493	AUGUGGCUGAAAAGCAUAGA	Knockout
3494	UUGGUUUGUUCCUGCUAAGG	Knockout
3495	UUCAGGACAUUACUAUUGCG	Knockout
3496	AAGCAGAAACUACCCGUUGC	Knockout
3497	UAGGCUCAUCGUGAUGAAUG	Knockout
3498	AAUGUGGCUGAAAAGCAUAG	Knockout
3499	CAUGCAUCCUACACAUACUU	Knockout
3500	GCAAGCAAUAUCCUAUUACC	Knockout
3501	CAAGCAAUAUCCUAUUACCC	Knockout
3502	GAGCCCAGCUAAUGAGACAA	Knockout
3503	AGCAAUGUCACUCAACUGGC	Knockout
3504	UAUAUCCAGUUAAUAUAUCC	Soluble decoy receptor
3505	UGGAAGGGAUGACUACGUUG	Membrane-bound decoy receptor
3506	AGGGAUGACUACGUUGGGGA	Membrane-bound decoy receptor
3507	ACAUCAGGCUUCAGCUGGCU	Membrane-bound decoy receptor
3508	CUGAACAAGAGCAUUAUACA	Membrane-bound decoy receptor
3509	GUGUAAAGUCCCCUGACCAG	Membrane-bound decoy receptor
3510	AUGGGGCUAUCCGCUGGUCA	Membrane-bound decoy receptor
3511	UGGGGCUAUCCGCUGGUCAG	Membrane-bound decoy receptor
3512	CUGGUCAGGGGACUUUACAC	Membrane-bound decoy receptor
3513	UGGUCAGGGGACUUUACACA	Membrane-bound decoy receptor

FIG. 48C

SEQ ID NO:	crRNA	Interference predictions
3514	ACUGGGGACUAGACACCAUG	Knockout
3515	CAGCUGGCCUUACUCUGAUC	Knockout
3516	GAUCUGGUAUUGGACUAGGC	Knockout
3517	CCUUACUAAUGCGGUUCUCG	Knockout
3518	AUGCACUGGGAGUUUCAUGG	Knockout
3519	UAUGCACUGGGAGUUUCAUG	Knockout
3520	AUAUAGAAUAUGGCAUUCAG	Knockout
3521	AUAGUCGGUUUGACACUGGA	Knockout
3522	AGUGAUAGUCGGUUUGACAC	Knockout
3523	GAAACUCAAGUUCAUACCUU	Knockout
3524	GUGGUCUAUGAGAAAGAACC	Knockout
3525	GGAGCUACUCAUUCCCUGUA	Knockout
3526	AAACUAAAAUAGACCGUACA	Knockout
3527	GAGGUUUGGUGGACCAUUGA	Knockout
3528	UUGAUGUCACCAUUAACGAA	Knockout
3529	GCUGCGCUUGAGAUCCUCAG	Knockout
3530	GCCAGCUCCAAGAUACACAG	Soluble decoy receptor
3531	UACACAGUGGAACUGGCUUG	Soluble decoy receptor
3532	AAUCACCACUAGCAGGACUG	Soluble decoy receptor
3533	UGUAUCCUAUGCAAGGAAUG	Membrane-bound decoy receptor
3534	UUUGUAUUACUGACCCUCCG	Membrane-bound decoy receptor
3535	AUUCUCCAAAACUCCACGGA	Membrane-bound decoy receptor
3536	CAUUCUCCAAAACUCCACGG	Membrane-bound decoy receptor
3537	UUGACCGAGACAGUCUGCCU	Membrane-bound decoy receptor
3538	UGACCGAGACAGUCUGCCUG	Membrane-bound decoy receptor
3539	GACCGAGACAGUCUGCCUGG	Membrane-bound decoy receptor
3540	UGGGGCUUAGAACAACCAGG	Membrane-bound decoy receptor
3541	AGCCCCAACUACGUGCUCCA	Membrane-bound decoy receptor
3542	CUAGAAAAUAUGGCCUCUCG	Membrane-bound decoy receptor
3543	GACGUUGAUGUUGCCCCGAG	Membrane-bound decoy receptor

FIG. 48D

SEQ ID NO:	crRNA	Interference predictions
3607	UUGGUGGGAAUAUACCCCUC	Knockout
3608	UGGUGGGAAUAUACCCCUCA	Knockout
3609	GGUGGGAAUAUACCCCUCAG	Knockout
3610	CCAGUCCAAUAACCCCUGAG	Knockout
3611	GACCAGUCCAAUAACCCCUG	Knockout
3612	UGGACUGGUCCCUCACCUAG	Knockout
3613	UGCUGUACCAAGUGCCACAA	Knockout
3614	UGGACAGUCAUUGUACAAGU	Knockout
3615	ACAAUGACUGUCCAGGCCCG	Knockout
3616	GGGGCAGGAUACGGACUGCA	Knockout
3617	CAGCUGCUCCAAAUGCCGAA	Knockout
3618	GGAGAUCUCUUCUUGCACAG	Knockout
3619	GUGGACCGGGACACCGUGUG	Knockout
3620	AGAGGUGCACGGUCCCAUUG	Knockout
3621	ACCGUGUGCACCUGCCAUGC	Knockout or soluble decoy receptor
3622	GACCAGGGGCAACAGCACUG	Soluble decoy receptor
3623	GUUUAAUGUAUCGCUACCAA	Membrane-bound receptor
3624	UAAUGUAUCGCUACCAACGG	Membrane-bound receptor
3625	AGAGCUUGGACUUCCACCGU	Membrane-bound receptor
3626	AGGAACUACUACUAAGCCCC	Membrane-bound receptor
3627	AAAGUUGGGACAGUCACCGG	Membrane-bound receptor
3628	CAAAGUUGGGACAGUCACCG	Membrane-bound receptor
3629	CUGCGGGGAGCCGCAAAGUU	Membrane-bound receptor
3630	CGGUGACUGUCCCAACUUUG	Membrane-bound receptor
3631	GGUGGUGCCACCUCUCUGCG	Membrane-bound receptor
3632	CUUUGCGGCUCCCCGCAGAG	Membrane-bound receptor
3633	GGGUCAGCCCCCUGAUAGGG	Membrane-bound receptor
3634	AGGUGGCACCACCCUAUCAG	Membrane-bound receptor
3635	GGUGGCACCACCCUAUCAGG	Membrane-bound receptor
3636	CCACGGCGUACAGCGUCGCG	Membrane-bound receptor
3637	CGCGACGCUGUACGCCGUGG	Membrane-bound receptor
3638	CGGGGGCACGUUCUCCACCA	Membrane-bound receptor
3639	AAUUCCUUCCAGCGCAACGG	Membrane-bound receptor
3640	GAAUUCCUUCCAGCGCAACG	Membrane-bound receptor
3641	ACGAAUUCCUUCCAGCGCAA	Membrane-bound receptor
3642	CGUGCCCCCGUUGCGCUGGA	Membrane-bound receptor
3643	UGCGCUGGAAGGAAUUCGUG	Membrane-bound receptor
3644	UGAGCGACCACGAGAUCGAU	Membrane-bound receptor
3645	AAUACAGCAUGCUGGCGACC	Membrane-bound receptor
3646	ACAGCAUGCUGGCGACCUGG	Membrane-bound receptor
3647	UCCAGCGUGGCCUCGCGCCG	Membrane-bound receptor

FIG. 48E

Inventory	SEQ ID NO:	crRNA	Interference predictions
OHT1B01	3648	CUCCAGUCCGACGGCCAGCG	Knockout
OHT1B02	3649	CUCCCGGGCUCCGGGGCGUA	Knockout
OHT1B03	3650	GGCAUUUACACCCUACGCCC	Knockout
OHT1B04	3651	GCAUGUGCUCCCGGGCUCCG	Knockout
OHT1B05	3652	CUGAGCCGGCAUGUGCUCCC	Knockout
OHT1B06	3653	GUGCUGCAGCAAAUGCUCGC	Knockout
OHT1B07	3654	GGAGUCACACACGGUGUCCG	Knockout
OHT1B08	3655	GUCCUCACAGGAGUCACACA	Knockout
OHT1B09	3656	CACCGUGUGUGACUCCUGUG	Knockout
OHT1B10	3657	GGUGUAUGUGCUGUCCUCAC	Knockout
OHT1B11	3658	GGGAACCCAGUUCCAGAGCU	Knockout
OHT1B12	3659	GGAAACUCAAGCCUGCACUC	Knockout
OHT1B13	3660	GCGGUUCUGUUCCCGAGUGC	Knockout
OHT1B14	3661	GUACUGCGCGCUGAGCAAGC	Knockout
OHT1B15	3662	UGCGCGCUGAGCAAGCAGGA	Knockout
OHT1B16	3663	CCCGGGCGGCACUUGCGCAG	Knockout
OHT1B17	3664	CCGCUGCGCAAGUGCCGCCC	Knockout or soluble receptor decoy
OHT1B18	3665	UGGCCACGCCGAAGCCCGGG	Knockout or soluble receptor decoy
OHT1B19	3666	AGGAACUGAAACAUCAGACG	Knockout or soluble receptor decoy
OHT1B20	3667	GAGAACGUCCCCGGGGCACA	Knockout or soluble receptor decoy
OHT1B21	3668	UGUGCAAGCCCUGUGCCCCG	Knockout or soluble receptor decoy
OHT1B22	3669	CGUGUUGGAGAACGUCCCCG	Knockout or soluble receptor decoy
OHT1B23	3670	GUCGUGUUGGAGAACGUCCC	Knockout or soluble receptor decoy
OHT1B24	3671	CUCCAACACGACUUCAUCCA	Knockout or soluble receptor decoy
OHT1B25	3672	GUGGGGCCUGCAAAUAUCCG	Knockout or soluble receptor decoy
OHT1B26	3673	GUAACGUGGUGGCCAUCCCU	Knockout or soluble receptor decoy
OHT1B27	3674	CUGGGGCCAUACUCCGGGUG	Soluble decoy receptor
OHT1B28	3675	CCUGGGGCCAUACUCCGGGU	Soluble decoy receptor
OHT1B29	3676	CCACCCGGAGUAUGGCCCCA	Soluble decoy receptor
OHT1B30	3677	CACCCGGAGUAUGGCCCCAG	Soluble decoy receptor
OHT1B31	3678	UGUUGGGAUCGUGUGGACAC	Soluble decoy receptor
OHT1B32	3679	CUGCGUGUGUUGGGAUCGUG	Soluble decoy receptor
OHT1B33	3680	UGGAGUUGGCUGCGUGUGUU	Soluble decoy receptor
OHT1B34	3681	GAACUGUGUCAUCAUGACCC	Membrane-bound receptor
OHT1B35	3682	UUGCCUGCCGAUAAGGCCCG	Membrane-bound receptor
OHT1B36	3683	CGAUAAGGCCCGGGGUACAC	Membrane-bound receptor
OHT1B37	3684	GAUAAGGCCCGGGGUACACA	Membrane-bound receptor
OHT1B38	3685	GCCUGUGGCUGGUUCCGAGU	Membrane-bound receptor
OHT1B39	3686	UGCCUGUGGCUGGUUCCGAG	Membrane-bound receptor
OHT1B40	3687	GAUGCAGGUGACAUUGACCU	Membrane-bound receptor
OHT1B41	3688	GCUACAGACGUUCACGAUGC	Membrane-bound receptor
OHT1B42	3689	CUCCCAAGCCAGCUCCACAA	Membrane-bound receptor
OHT1B43	3690	CGUCCUUCGGGGACUCCGAG	Membrane-bound receptor
OHT1B44	3691	GGGGACCUGCUCGUCCUUCG	Membrane-bound receptor
OHT1B45	3692	GCAGGUCCCCUUCUCCAAGG	Membrane-bound receptor

FIG. 48F

SEQ ID NO:	crRNA	Interference predictions
3693	UGGUUCUCCGACGCAUAUGG	Knockout
3694	GUCGGAGAACCAGACCUGCA	Knockout
3695	GGAGCAGCAGAUGCGGUGCU	Knockout
3696	GCUACAUUUAGCUGAGACAU	Knockout
3697	AUGUGGCACAAACUGUGUCC	Knockout
3698	UUGCCCCCUGCACAAGCAAA	Knockout
3699	GCUCGCAGUGUGUACACUCG	Knockout or soluble decoy receptor
3700	UGGAAGUGCCCGGCCUUGCA	Knockout or soluble decoy receptor
3701	GAGCUGCCUCCACCAGACCU	Knockout or soluble decoy receptor
3702	GUGUGAGAACCAAGGUCUGG	Knockout or soluble decoy receptor
3703	CAAUCCUGUAGCUGGAAGCU	Membrane-bound decoy receptor
3704	AAGUAUGGAUGGGCCUUCGG	Membrane-bound decoy receptor
3705	CAAGUCAGGGAAGUAUGGAU	Membrane-bound decoy receptor
3706	GCAGUGGCUGUACCAAGUCA	Membrane-bound decoy receptor
3707	CCUCCAAAACUGGGGCUGCG	Membrane-bound decoy receptor
3708	GAGUCCUCUGGACCUGACCA	Membrane-bound decoy receptor
3709	ACCAAUGGCAUUCAUGUCAC	Membrane-bound decoy receptor
3710	AGUGAUAGUCAUAGACCCGC	Membrane-bound decoy receptor
3711	UCUACAAUGGACCAGUACUG	Membrane-bound decoy receptor
3712	AAUGGGGUAUGGAGGUUCGG	Membrane-bound decoy receptor
3713	GAAUGGGGUAUGGAGGUUCG	Membrane-bound decoy receptor

FIG. 48G

SEQ ID NO:	crRNA	Interference predictions
3714	GCAGAGCCGCACACGGCCCG	Knockout
3715	GCUGGGCCGCGGGCCGUGUG	Knockout
3716	AGGAGGAGCAGAGCCGCACA	Knockout
3717	GACACAGUGGAGCCCCGUCA	Knockout
3718	GGUAGGUGUCCCCGACACAG	Knockout
3719	GACGGGGCUCCACUGUGUCG	Knockout
3720	CUGCAGCCGCUCCCAGAACA	Knockout
3721	AACACGGUGUGCCGUCCGUG	Knockout
3722	AGAAGCCCGGCCCGCACGGA	Knockout
3723	ACACGGUGUGCCGUCCGUGC	Knockout
3724	UUGUAGAAGCCCGGCCCGCA	Knockout
3725	CUGAGGUUACACCACGUGCA	Knockout
3726	UGAGCGGAAGCAGCUGUGCA	Knockout
3727	GCGGCAGACUGUGUCCUGUG	Knockout
3728	CCAGGCUUGUAGCUGUCCAG	Knockout
3729	UCCAGGCUUGUAGCUGUCCA	Knockout
3730	CUGGGGAGAAGUGCCCUGGA	Knockout or soluble decoy receptor
3731	GCAGGCCUGGUUGUCGCCUG	Knockout or soluble decoy receptor
3732	GCUAUUGCUGGCCGGCUGCA	Knockout or soluble decoy receptor
3733	GCGUCCGAGCUAUUGCUGGC	Knockout or soluble decoy receptor
3734	UAGCUCGGACGCAAUCUGUG	Knockout or soluble decoy receptor
3735	GGGGACCUCCACGGGCCGGG	Soluble decoy receptor
3736	CGGCCCGUGGAGGUCCCCGG	Soluble decoy receptor
3737	CCAGGAUGGCGGCAACCGCA	Soluble decoy receptor
3738	GUCCCUCCGGAGCAGGUACA	Membrane-bound decoy
3739	GGCCUGCUCCUCUUGGAUGG	Membrane-bound decoy
3740	UUUCCGGACCCCCAUCCAAG	Membrane-bound decoy

FIG. 48H

SEQ ID NO:	crRNA	Intervention predicted
3741	UGCUUCUCACUGGUACAUGG	Knockout
3742	UAAUGCUUCUCACUGGUACA	Knockout
3743	GAGAAGCAUUAUGAGCAUCU	Knockout
3744	AGCAUUAUGAGCAUCUGGGA	Knockout
3745	GGGCAGACAUACACUGUCAG	Knockout
3746	GACAGUGUAUGUCUGCCCUG	Knockout
3747	AAGUAUUCAUCCGGGCCACA	Knockout
3748	CGUGCACGCGCAGCGCCGGG	Knockout
3749	CCCCCGGCGCUGCGCGUGCA	Knockout or soluble decoy receptor
3750	GCGCGCACUCGGUGUUGCGG	Knockout or soluble decoy receptor
3751	CAUCAGAGAAGUAGCCUGCA	Knockout or soluble decoy receptor
3752	CCAGGGUCUGCAUUUGUCCG	Knockout or soluble decoy receptor
3753	UGGGACAGAGAAAUCCGAUG	Knockout or soluble decoy receptor
3754	AGAAGAACUGCAAACCGCAU	Knockout or soluble decoy receptor
3755	AAACCGGGCAAGUAAACAUG	Soluble decoy receptor
3756	UAAACCGGGCAAGUAAACAU	Soluble decoy receptor
3757	UUUGUGGCACUGGAUCAAUG	Membrane-bound decoy
3758	CACUGGAUCAAUGAGGCUUG	Membrane-bound decoy
3759	UGGCCGCCUAAGUGGAGAUA	Membrane-bound decoy
3760	ACUGACACAACUGUCACCUG	Membrane-bound decoy
3761	CAGUUGUGUCAGUACACACA	Membrane-bound decoy
3762	AGUACACACACGGCAAACUU	Membrane-bound decoy
3763	ACGGCAAACUUUGGUCAGCA	Membrane-bound decoy
3764	UGUCAGGGCACAUGUGUAGG	Membrane-bound decoy
3765	GGAGGUGGUCCCUACGCACA	Membrane-bound decoy
3766	ACGCACAAGGCGAAGAUGCC	Membrane-bound decoy
3767	GGUCAGCAAGACCGAGAUAG	Membrane-bound decoy
3768	GUUUAAGCCAGUGCUUCACG	Membrane-bound decoy
3769	GUCCAAUCAGUCCUGCACAG	Membrane-bound decoy
3770	UUGCAAAAAGAGGUGGACAG	Membrane-bound decoy
3771	CAGUGGCCAUUGCCCGCACU	Membrane-bound decoy
3772	GAGGACUGUGAACCCCUCGU	Membrane-bound decoy
3773	CGUUUUGGGGAACCCACGAG	Membrane-bound decoy
3774	ACGUUUUGGGGAACCCACGA	Membrane-bound decoy
3775	CACGUUUUGGGGAACCCACG	Membrane-bound decoy
3776	GGGCAAGGGUCCACGUUUUG	Membrane-bound decoy
3777	CUCGUGGGUUCCCCAAAACG	Membrane-bound decoy
3778	CCCAUGCCAUAGGCGCACUG	Membrane-bound decoy
3779	GAGGCUCCCAAGCUCAGCGA	Membrane-bound decoy
3780	CUACGUCAGCCAGACCUCGC	Membrane-bound decoy
3781	CGUCAGCCAGACCUCGCAGG	Membrane-bound decoy
3782	GUCAGCCAGACCUCGCAGGA	Membrane-bound decoy
3783	GAAGGAGUCUCGGCGCGCCA	Membrane-bound decoy
3784	GGCGCGCCGAGACUCCUUCG	Membrane-bound decoy
3785	CGCGCCGAGACUCCUUCGCG	Membrane-bound decoy
3786	GCGCGGGCCGUUCCCCGCGA	Membrane-bound decoy
3787	CCGCGCUUCCCCGGACCCGUG	Membrane-bound decoy
3788	ACCCGUGCGGCGGCCCCGAG	Membrane-bound decoy

FIG. 48I

SEQ ID NO:	crRNA	Interference predictions
3789	UUGACUUAAUUCCUCGAGAU	Knockout
3790	GUUGUGUAUAACUUUGUCUG	Knockout
3791	CAUACAAACGGCCUAUCUCG	Knockout
3792	GAGAUGCAGACGAAGCACAC	Soluble or membrane-bound decoy receptor
3793	CUCGAUGGUGAAUGACAGUG	Membrane-bound decoy receptor
3794	UAAAAGGGCGAUCUAAUGAA	Membrane-bound decoy receptor
3795	AUAAAAGGGCGAUCUAAUGA	Membrane-bound decoy receptor
3796	AUUUAUGAUAUGACAACGUC	Membrane-bound decoy receptor
3797	AAGGUCGAUUUGGAGAAGUU	Membrane-bound decoy receptor
3798	CCACGAACGUUCUUCUCUAG	Membrane-bound decoy receptor
3799	CCUCUAGAGAAGAACGUUCG	Membrane-bound decoy receptor
3800	AGAACGUUCGUGGUUCCGUG	Membrane-bound decoy receptor
3801	UGUCUGCUGCUAUAAAUCCC	Membrane-bound decoy receptor
3802	UACUUGGACUCAGCUCUGGU	Membrane-bound decoy receptor
3803	GUGUCAGAUUAUCAUGAGCA	Membrane-bound decoy receptor
3804	CUUGCUCUGUCCACGGCGAG	Membrane-bound decoy receptor
3805	CUGUAUUGCAGACUUAGGAC	Membrane-bound decoy receptor
3806	UAUUGCUCCAAACCACAGAG	Membrane-bound decoy receptor
3807	AUUGCUCCAAACCACAGAGU	Membrane-bound decoy receptor
3808	GGAAUCAUCGAGAACUUCAG	Membrane-bound decoy receptor
3809	ACGUGCUGACAUCUAUGCAA	Membrane-bound decoy receptor
3810	AUUGCUCGACGAUGUUCCAU	Membrane-bound decoy receptor
3811	GCUCGACGAUGUUCCAUUGG	Membrane-bound decoy receptor
3812	GGUAUGCCAAUGGAGCAGCU	Membrane-bound decoy receptor
3813	CAGCUAGGCUUACAGCAUUG	Membrane-bound decoy receptor

FIG. 48J

SEQ ID NO:	crRNA	Interference predictions
3814	AACGUGCGGUGGGAUCGUGC	Knockout
3815	CCGACUUCUGAACGUGCGGU	Knockout
3816	CCCGACUUCUGAACGUGCGG	Knockout
3817	AUGAUAGUCACUGACAACAA	Knockout
3818	CUGUGGCUUCUCACAGAUGG	Knockout
3819	UUCCAGAAUAAAGUCAUGGU	Knockout
3820	AAUAUGACUAGCAACAAGUC	Soluble decoy receptor
3821	GAUAUGGCAACUCCCAGUGG	Soluble or membrane-bound decoy receptor
3822	ACAGAUAUGGCAACUCCCAG	Soluble or membrane-bound decoy receptor
3823	GCUUCUGCUGCCGGUUAACG	Membrane-bound decoy receptor
3824	UCUACUGCUACCGCGUUAAC	Membrane-bound decoy receptor
3825	GCAGAAGCUGAGUUCAACCU	Membrane-bound decoy receptor
3826	CCUGGGAAACCGGCAAGACG	Membrane-bound decoy receptor
3827	CGGCAAGACGCGGAAGCUCA	Membrane-bound decoy receptor
3828	GCGGUCAUCUUCCAGGAUGA	Membrane-bound decoy receptor
3829	GUUGAUGUUGUUGGCACACG	Membrane-bound decoy receptor
3830	AUUGAGCUGGACACCCUGGU	Membrane-bound decoy receptor
3831	AAAGCGACCUUUCCCCACCA	Membrane-bound decoy receptor
3832	UUCAGAGCAGUUUGAGACAG	Membrane-bound decoy receptor
3833	AGUCAAGAUCUUUCCCUAUG	Membrane-bound decoy receptor
3834	UAGGUUGCCCUUGGCGUGGA	Membrane-bound decoy receptor
3835	AUCACCGCCUUCCACGCCAA	Membrane-bound decoy receptor
3836	ACCUACAGGAGUACCUGACG	Membrane-bound decoy receptor
3837	AGCUGAUGACAUGCCGCGUC	Membrane-bound decoy receptor
3838	GACGCGGCAUGUCAUCAGCU	Membrane-bound decoy receptor
3839	GCGGCAUGUCAUCAGCUGGG	Membrane-bound decoy receptor
3840	UGGGCAGCUCCCUCGCCCGG	Membrane-bound decoy receptor
3841	GUGGAGGUGAGCAAUCCCCC	Membrane-bound decoy receptor
3842	UGUGGAGGUGAGCAAUCCCC	Membrane-bound decoy receptor
3843	AUGGAGUGUGAUCACUGUGG	Membrane-bound decoy receptor
3844	CACAUGGAGUGUGAUCACUG	Membrane-bound decoy receptor
3845	ACAGUGAUCACACUCCAUGU	Membrane-bound decoy receptor
3846	GUGAUCACACUCCAUGUGGG	Membrane-bound decoy receptor
3847	GGGAAAGCCCAAAGUCACAC	Membrane-bound decoy receptor
3848	CAGAGUAGGGUCCAGACGCA	Membrane-bound decoy receptor
3849	UCUGGACCCUACUCUGUCUG	Membrane-bound decoy receptor
3850	GUGGAUGACCUGGCUAACAG	Membrane-bound decoy receptor
3851	UGGAUGACCUGGCUAACAGU	Membrane-bound decoy receptor
3852	GGUGGGAACUGCAAGAUACA	Membrane-bound decoy receptor
3853	CAGAGCCAUGGAGUAGACAU	Membrane-bound decoy receptor
3854	GCAGACCGAUGUCUACUCCA	Membrane-bound decoy receptor
3855	ACAUCUCGCUGUAAUGCAGU	Membrane-bound decoy receptor
3856	CGCACCUUGGAACCAAAUGG	Membrane-bound decoy receptor
3857	CCUUCAUGCUUUCGACACAG	Membrane-bound decoy receptor
3858	GUCCUUCAUGCUUUCGACAC	Membrane-bound decoy receptor
3859	CCCCUGUGUCGAAAGCAUGA	Membrane-bound decoy receptor
3860	ACAACGUGUUGAGAGAUCGA	Membrane-bound decoy receptor
3861	GUGAGACGUUGACUGAGUGC	Membrane-bound decoy receptor
3862	UGAGACGUUGACUGAGUGCU	Membrane-bound decoy receptor
3863	GUGCUGGGACCACGACCCAG	Membrane-bound decoy receptor
3864	CCGUCUCACAGCCCAGUGUG	Membrane-bound decoy receptor
3865	GAAGCGUUCUGCCACACACU	Membrane-bound decoy receptor

FIG. 48K