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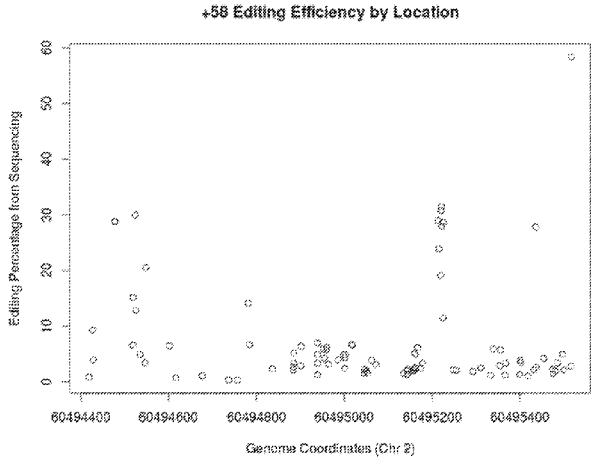
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(54) Title: COMPOSITIONS AND METHODS FOR THE TREATMENT OF HEMOGLOBINOPATHIES

Figure 1



(57) Abstract: The present invention is directed to genome editing systems, reagents and methods for the treatment of hemoglobinopathies.

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COMPOSITIONS AND METHODS FOR THE TREATMENT OF HEMOGLOBINOPATHIES

RELATED APPLICATIONS

This application claims priority to U.S. Provisional patent application number 62/271,968, filed December 28, 2015, and U.S. Provisional patent application number 62/347,484, filed June 8, 2016. The entire contents of these applications are incorporated herein by reference.

SEQUENCE LISTING

The instant application contains a Sequence Listing which has been submitted electronically in ASCII format and is hereby incorporated by reference in its entirety. Said ASCII copy, created on January 26, 2017, is named PAT057179-WO-PCT_SL.txt and is 1,115,217 bytes in size.

BACKGROUND

CRISPRs (Clustered Regularly Interspaced Short Palindromic Repeats) evolved in bacteria as an adaptive immune system to defend against viral attack. Upon exposure to a virus, short segments of viral DNA are integrated into the CRISPR locus of the bacterial genome. RNA is transcribed from a portion of the CRISPR locus that includes the viral sequence. That RNA, which contains sequence complimentary to the viral genome, mediates targeting of a Cas9 protein to the sequence in the viral genome. The Cas9 protein cleaves and thereby silences the viral target.

Recently, the CRISPR/Cas system has been adapted for genome editing in eukaryotic cells. The introduction of site-specific single (SSBs) or double strand breaks (DSBs) allows for target sequence alteration through, for example, non-homologous end-joining (NHEJ) or homology-directed repair (HDR).

SUMMARY OF THE INVENTION

Without being bound by theory, the invention is based in part on the discovery that CRISPR systems, e.g., Cas9 CRISPR systems, e.g., as described herein, can be used to modify cells (e.g., hematopoietic stem and progenitor cells (HSPCs)) to increase fetal hemoglobin (HbF) expression and/or decrease expression of beta globin (e.g., a beta globin

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gene having a disease-causing mutation), and that such cells may be used to treat hemoglobinopathies, e.g., sickle cell disease and beta thalassemia.

Thus, in an aspect, the invention provides CRISPR systems (e.g., Cas CRISPR systems, e.g., Cas9 CRISPR systems, e.g., *S. pyogenes* Cas9 CRISPR systems) comprising one or more, e.g., one,gRNA molecule as described herein. Any of the gRNA molecules described herein may be used in such systems, and in the methods and cells described herein.

In an aspect, the invention provides a gRNA molecule that includes a tracr and crRNA, wherein the crRNA includes a targeting domain that is complementary with a target sequence of the BCL11A gene, a BCL11a enhancer, or a HFPH region.

In another aspect, the invention provides a gRNA molecule that includes a targeting domain that is complementary with a target sequence of the BCL11A gene, e.g., is complementary with a target

In an aspect, the invention provides a gRNA molecule that includes a tracr and crRNA, wherein the crRNA includes a targeting domain that is complementary with a target sequence of the BCL11A gene, a BCL11a enhancer, or a HFPH region.

In another aspect, the invention provides a gRNA molecule that includes a targeting domain that is complementary with a target sequence of the BCL11A gene, e.g., is complementary with a target sequence within a BCL11a coding region (e.g., within a BCL11a exon, e.g., within BCL11a exon 2). In embodiments, the gRNA comprises a targeting domain that includes, e.g., consists of, any one of SEQ ID NO: 1 to SEQ ID NO: 85 or SEQ ID NO: 400 to SEQ ID NO: 1231.

In another aspect, the invention provides a gRNA molecule that includes a targeting domain that is complementary with a target sequence of a BCL11A enhancer.

In embodiments, the gRNA comprises a targeting domain that includes, e.g., consists of, any one of SEQ ID NO: 1232 to SEQ ID NO: 1499.

In embodiments, the gRNA to a target sequence of a BCL11a enhancer is to a target sequence within the +58 region of the BCL11a enhancer, and the targeting domain includes, e.g., consists of, any one of SEQ ID NO: 182 to SEQ ID NO: 277 or SEQ ID NO: 334 to SEQ ID NO: 341. In embodiments, the targeting domain includes, e.g., consists of, any one of SEQ ID NO: 341, SEQ ID NO: 246, SEQ ID NO: 248, SEQ ID NO: 247, SEQ ID NO: 245, SEQ ID NO: 249, SEQ ID NO: 244, SEQ ID NO: 199, SEQ ID NO: 251, SEQ ID NO: 250, SEQ ID NO: 334, SEQ ID NO: 185, SEQ ID NO: 186, SEQ ID NO: 336, or SEQ ID NO: 337. In embodiments, the targeting domain includes, e.g., consists of, SEQ ID NO: 248. In embodiments, the targeting domain includes, e.g., consists of, SEQ ID NO: 247. In embodiments, the targeting domain includes, e.g., consists of, SEQ ID NO: 245. In embodiments, the targeting domain includes, e.g., consists of, SEQ ID NO: 336. In embodiments, the targeting domain includes, e.g., consists of, SEQ ID NO: 337. In embodiments, the targeting domain includes, e.g., consists of, SEQ ID NO: 338. In embodiments, the targeting domain includes, e.g., consists of, SEQ ID NO: 335. In embodiments, the targeting domain includes, e.g., consists of, SEQ ID NO: 252. In an embodiment, the gRNA is a dgRNA that includes a crRNA that includes, e.g., consists of, e.g., from 5' to 3', SEQ ID NO: 248 – SEQ ID NO: 6607, and a tracr that includes, e.g., consists of, e.g., from 5' to 3', SEQ ID NO: 6660. In an embodiment, the gRNA is a dgRNA that includes a crRNA that includes, e.g., consists of, e.g., from 5' to 3', SEQ ID NO: 247 – SEQ ID NO: 6607, and a tracr that includes, e.g., consists of, e.g., from 5' to 3', SEQ ID NO: 6660. In an embodiment, the gRNA molecule is a sgRNA molecule and includes, e.g., consists of, e.g., from 5' to 3', SEQ ID NO: 338 – SEQ ID NO: 6604 – UUUU. In an embodiment, the gRNA molecule is a sgRNA molecule and includes, e.g., consists of, e.g., from 5' to 3', SEQ ID NO: 335 – SEQ ID NO: 6604 – UUUU. In an embodiment, the gRNA molecule is a sgRNA molecule and includes, e.g., consists of, e.g., from 5' to 3', SEQ ID NO: 336 – SEQ ID NO: 6604 – UUUU. In an embodiment, the gRNA molecule is a

sgRNA molecule and includes, e.g., consists of, e.g., from 5' to 3', SEQ ID NO: 245 – SEQ ID NO: 6604 – UUUU. In an embodiment, the gRNA molecule is a sgRNA molecule and includes, e.g., consists of, e.g., from 5' to 3', SEQ ID NO: 337 – SEQ ID NO: 6604 – UUUU. In an embodiment, the gRNA molecule is a sgRNA molecule and includes, e.g., consists of, e.g., from 5' to 3', SEQ ID NO: 252 – SEQ ID NO: 6604 – UUUU.

In embodiments, the gRNA to a target sequence of a BCL11a enhancer is to a target sequence within the +62 region of the BCL11a enhancer, and the targeting domain includes, e.g., consists of, any one of SEQ ID NO: 278 to SEQ ID NO: 333. In embodiments, the targeting domain includes, e.g., consists of, any one of SEQ ID NO: 318, SEQ ID NO: 312, SEQ ID NO: 313, SEQ ID NO: 294, SEQ ID NO: 310, SEQ ID NO: 319, SEQ ID NO: 298, SEQ ID NO: 322, SEQ ID NO: 311, SEQ ID NO: 315, SEQ ID NO: 290, SEQ ID NO: 317, SEQ ID NO: 309, SEQ ID NO: 289, or SEQ ID NO: 281. In embodiments, the targeting domain includes, e.g., consists of, SEQ ID NO: 318.

In embodiments, the gRNA to a target sequence of a BCL11a enhancer is to a target sequence within the +55 region of the BCL11a enhancer, and the targeting domain includes, e.g., consists of, any one of SEQ ID NO: 1596 to SEQ ID NO: 1691. In embodiments, the targeting domain includes, e.g., consists of, any one of SEQ ID NO: 1683, SEQ ID NO: 1638, SEQ ID NO: 1647, SEQ ID NO: 1609, SEQ ID NO: 1621, SEQ ID NO: 1617, SEQ ID NO: 1654, SEQ ID NO: 1631, SEQ ID NO: 1620, SEQ ID NO: 1637, SEQ ID NO: 1612, SEQ ID NO: 1656, SEQ ID NO: 1619, SEQ ID NO: 1675, SEQ ID NO: 1645, SEQ ID NO: 1598, SEQ ID NO: 1599, SEQ ID NO: 1663, SEQ ID NO: 1677, or SEQ ID NO: 1626.

In another aspect, the invention provides a gRNA molecule that includes a targeting domain that is complementary with a target sequence of a hereditary persistence of fetal hemoglobin (HPFH) region. In an embodiment, the HPFH region is the French HPFH region. In embodiments, the targeting domain includes, e.g., consists of, any one of SEQ ID NO: 86 to SEQ ID NO: 181 or SEQ ID NO: 1500 to SEQ ID NO: 1595. In embodiments, the targeting domain includes, e.g., consists of, any one of SEQ ID NO: 100, SEQ ID NO: 165, SEQ ID NO: 113, SEQ ID NO: 99, SEQ ID NO: 112, SEQ ID NO: 98, SEQ ID NO: 1580, SEQ ID NO: 106, SEQ ID NO: 1503, SEQ ID NO: 1589, SEQ ID NO: 160, SEQ ID NO: 1537, SEQ ID NO: 159, SEQ ID NO: 101, SEQ ID NO: 162, SEQ ID NO: 104, SEQ ID NO: 138, SEQ ID NO: 1536, SEQ ID NO: 1539, SEQ ID NO: 1585. In embodiments, the targeting domain includes, e.g., consists of, SEQ ID NO: 100. In embodiments, the targeting domain includes, e.g., consists of, SEQ ID NO: 165. In embodiments, the targeting domain includes, e.g., consists of, SEQ ID NO: 113.

In any of the aforementioned embodiments, the gRNA molecule may further have regions and/or properties described herein. In an aspect, the gRNA molecule (e.g., of any of the aforementioned aspects or embodiments) includes a targeting domain that includes, e.g., consists of, 17, 18, 19, 20,

21, 22, 23, or 24 consecutive nucleic acids of any one of the recited targeting domain sequences. In embodiments, the 17, 18, 19, 20, 21, 22, 23, or 24 consecutive nucleic acids of any one of the recited targeting domain sequences are the 17, 18, 19, 20, 21, 22, 23, or 24 consecutive nucleic acids disposed at the 3' end of the recited targeting domain sequence. In embodiments, the 17, 18, 19, 20, 21, 22, 23, or 24 consecutive nucleic acids of any one of the recited targeting domain sequences are the 17, 18, 19, 20, 21, 22, 23, or 24 consecutive nucleic acids disposed at the 5' end of the recited targeting domain sequence. In embodiments, the 17, 18, 19, 20, 21, 22, 23, or 24 consecutive nucleic acids of any one of the recited targeting domain sequences do not include either the 5' or 3' nucleic acid of the recited targeting domain sequence. In any of the aforementioned aspects or embodiments, the targeting domain may consist of the recited targeting domain sequence.

In embodiments of the gRNA molecule, including in any of the aforementioned aspects and embodiments, the targeting domain includes 17, 18, 19, 20, 21 (if present in the reference sequence), 22 (if present in the reference sequence), 23 (if present in the reference sequence), 24 (if present in the reference sequence), or 25 (if present in the reference sequence) consecutive nucleic acids of any one of the recited targeting domain sequences. In other embodiments of the gRNA molecule, including in any of the aforementioned aspects and embodiments, the targeting domain consists of 17, 18, 19, 20, 21 (if present in the reference sequence), 22 (if present in the reference sequence), 23 (if present in the reference sequence), or 24 (if present in the reference sequence), or 25 (if present in the reference sequence) consecutive nucleic acids of any one of the recited targeting domain sequences. In embodiments of the gRNA molecule, including in any of the aforementioned aspects and embodiments, the 17, 18, 19, 20, 21 (if present in the reference sequence), 22 (if present in the reference sequence), 23 (if present in the reference sequence), or 24 (if present in the reference sequence), or 25 (if present in the reference sequence) consecutive nucleic acids of any one of the recited targeting domain sequences are the 17, 18, 19, 20, 21 (if present in the reference sequence), 22 (if present in the reference sequence), 23 (if present in the reference sequence), or 24 (if present in the reference sequence), or 25 (if present in the reference sequence) consecutive nucleic acids disposed at the 3' end of the recited targeting domain sequence. In other embodiments of the gRNA molecule, including in any of the aforementioned aspects and embodiments, the 17, 18, 19, 20, 21 (if present in the reference sequence), 22 (if present in the reference sequence), 23 (if present in the reference sequence), or 24 (if present in the reference sequence), or 25 (if present in the reference sequence) consecutive nucleic acids of any one of the recited targeting domain sequences are the 17, 18, 19, 20, 21 (if present in the reference sequence), 22 (if present in the reference sequence), 23 (if present in the reference sequence), or 24 (if present in the reference sequence), or 25 (if present in the reference sequence) consecutive nucleic acids disposed at the 5' end of the recited targeting domain sequence. In other embodiments of the gRNA molecule, including in any of the aforementioned aspects and embodiments, the 17, 18, 19, 20, 21 (if present in the reference sequence), 22 (if present in the

reference sequence), 23 (if present in the reference sequence), or 24 (if present in the reference sequence), or 25 (if present in the reference sequence) consecutive nucleic acids of any one of the recited targeting domain sequences do not include either the 5' or 3' nucleic acid of the recited targeting domain sequence.

In an aspect, including in any of the aforementioned aspects or embodiments, the gRNA molecule includes a portion of the crRNA and a portion of the tracr that hybridize to form a flagpole, that includes SEQ ID NO: 6584 or 6585. In embodiments, the flagpole further includes a first flagpole extension, located 3' to the crRNA portion of the flagpole, wherein said first flagpole extension includes SEQ ID NO: 6586. In embodiments, the flagpole further includes a second flagpole extension located 3' to the crRNA portion of the flagpole and, if present, the first flagpole extension, wherein said second flagpole extension includes SEQ ID NO: 6587.

In an aspect, including in any of the aforementioned aspects or embodiments, the invention provides a gRNA molecule that includes a tracr that includes, e.g., consists of, SEQ ID NO: 6660 or SEQ ID NO: 6661. In embodiments, the crRNA portion of the flagpole includes SEQ ID NO: 6607 or SEQ ID NO: 6608.

In an aspect, including in any of the aforementioned aspects or embodiments, the invention provides a gRNA molecule that includes a tracr that includes SEQ ID NO: 6589 or 6590, and optionally, if a first flagpole extension is present, a first tracr extension, disposed 5' to SEQ ID NO: 6589 or 6590, said first tracr extension including SEQ ID NO: 6591.

In an aspect, including in any of the aforementioned aspects or embodiments, the invention provides a gRNA molecule wherein the targeting domain and the tracr are disposed on separate nucleic acid molecules (e.g., a dgRNA molecule).

In an aspect, including in any of the aforementioned aspects or embodiments, the invention provides a gRNA molecule wherein the targeting domain and the tracr are disposed on a single nucleic acid molecule (e.g., a sgRNA molecule), and wherein the tracr is disposed 3' to the targeting domain. In embodiments, the sgRNA molecule includes a loop, disposed 3' to the targeting domain and 5' to the tracr, e.g., a loop including, e.g., consisting of, SEQ ID NO: 6588.

In an aspect, including in any of the aforementioned aspects or embodiments, the invention provides a gRNA molecule including, from 5' to 3', [targeting domain]-:

(a) SEQ ID NO: 6601;

(b) SEQ ID NO: 6602;

(c) SEQ ID NO: 6603;

(d) SEQ ID NO: 6604; or

(e) any of (a) to (d), above, further including, at the 3' end, 1, 2, 3, 4, 5, 6 or 7 uracil (U) nucleotides, e.g., 4 uracil nucleotides. In embodiments, there are no intervening nucleotides between the targeting domain and the sequence of any of (a)-(e).

In another aspect, the invention provides CRISPR systems, e.g., Cas CRISPR systems, e.g., Cas9 CRISPR systems, e.g., *S. pyogenes* Cas9 CRISPR systems, the include one or more, e.g., one, gRNA molecule of any of the aforementioned aspects and embodiments. In an aspect, the invention provides a composition including a first gRNA molecule of any of the aforementioned aspects and embodiments, further including a Cas9 molecule. In embodiments, the Cas9 molecule is an active or inactive *s. pyogenes* Cas9. In embodiments, the first gRNA molecule and Cas9 molecule are present in a ribonuclear protein complex (RNP).

In another aspect, the invention provides compositions that include more than one gRNA, e.g., more than one gRNA molecule as described herein, e.g., more than one gRNA molecule of any of the aforementioned gRNA molecule aspects or embodiments. Thus, in a further aspect, the invention provides a composition of any of the aforementioned composition aspects and embodiments, further including a second gRNA molecule; a second gRNA molecule and a third gRNA molecule; or a second gRNA molecule, a third gRNA molecule, and a fourth gRNA molecule, wherein the second gRNA molecule, the third gRNA molecule (if present), and the fourth gRNA molecule (if present) are a gRNA molecule as described herein, e.g., a gRNA molecule of any of the aforementioned gRNA molecule aspects or embodiments. In an embodiment, each gRNA molecule of the composition is complementary to a different target sequence. In an embodiment, each gRNA molecule is complementary to target sequences within the same gene or region. In an aspect, the first gRNA molecule, the second gRNA molecule, the third gRNA molecule (if present), and the fourth gRNA molecule (if present) are complementary to target sequences not more than 20000 nucleotides, not more than 10000 nucleotides, not more than 6000, not more than 5000 nucleotides, not more than 4000, not more than 1000 nucleotides, not more than 500 nucleotides, not more than 400 nucleotides, not more than 300 nucleotides, not more than 200 nucleotides, not more than 100 nucleotides, not more than 90 nucleotides, not more than 80 nucleotides, not more than 70 nucleotides, not more than 60 nucleotides, not more than 50 nucleotides, not more than 40 nucleotides, not more than 30 nucleotides, not more than 20 nucleotides or not more than 10 nucleotides apart. In another aspect, each gRNA molecule of the composition is complementary to target sequence within a different gene or region.

Specific and preferred combinations of more than one gRNA molecule of the invention are described herein. In an aspect, the composition includes a first gRNA molecule and a second gRNA molecule,

wherein the first gRNA molecule and second gRNA molecule are complementary to different target sequences, and are:

(a) independently selected from the gRNA molecules described herein (e.g., above) to the BCL11a gene;

(b) independently selected from the gRNA molecules described herein (e.g., above) to the +58 BCL11a enhancer;

(c) independently selected from the gRNA molecules described herein (e.g., above) to the +62 BCL11a enhancer;

(d) independently selected from the gRNA molecules described herein (e.g., above) to the +55 BCL11a enhancer; or

(e) independently selected from the gRNA molecules described herein (e.g., above) to a HPFH region.

In an aspect, the composition includes a first gRNA molecule and a second gRNA molecule, wherein the first gRNA molecule and second gRNA molecule are complementary to different target sequences, and:

(a) the first gRNA molecule is selected from the gRNA molecules described herein (e.g., above) to the BCL11a gene, and the second gRNA molecule is selected from the gRNA molecules described herein (e.g., above) to the +58 BCL11a enhancer;

(b) the first gRNA molecule is selected from the gRNA molecules described herein (e.g., above) to the BCL11a gene, and the second gRNA molecule is selected from the gRNA molecules described herein (e.g., above) to the +62 BCL11a enhancer;

(c) the first gRNA molecule is selected from the gRNA molecules described herein (e.g., above) to the BCL11a gene, and the second gRNA molecule is selected from the gRNA molecules described herein (e.g., above) to the +55 BCL11a enhancer;

(d) the first gRNA molecule is selected from the gRNA molecules described herein (e.g., above) to the BCL11a gene, and the second gRNA molecule is selected from the gRNA molecules described herein (e.g., above) to a HPFH region;

(e) the first gRNA molecule is selected from the gRNA molecules described herein (e.g., above) to the +58 BCL11a enhancer, and the second gRNA molecule is selected from the gRNA molecules described herein (e.g., above) to the +62 BCL11a enhancer;

(f) the first gRNA molecule is selected from the gRNA molecules described herein (e.g., above) to the +58 BCL11a enhancer, and the second gRNA molecule is selected from the gRNA molecules described herein (e.g., above) to the +55 BCL11a enhancer;

(g) the first gRNA molecule is selected from the gRNA molecules described herein (e.g., above) to the +58 BCL11a enhancer, and the second gRNA molecule is selected from the gRNA molecules described herein (e.g., above) to a HPFH region;

(h) the first gRNA molecule is selected from the gRNA molecules described herein (e.g., above) to the +62 BCL11a enhancer, and the second gRNA molecule is selected from the gRNA molecules described herein (e.g., above) to the +55 BCL11a enhancer;

(i) the first gRNA molecule is selected from the gRNA molecules described herein (e.g., above) to the +62 BCL11a enhancer, and the second gRNA molecule is selected from the gRNA molecules described herein (e.g., above) to a HPFH region;

(j) the first gRNA molecule is selected from the gRNA molecules described herein (e.g., above) to the +55 BCL11a enhancer, and the second gRNA molecule is selected from the gRNA molecules described herein (e.g., above) to a HPFH region;

In another aspect, the composition that includes a first gRNA molecule and a second gRNA molecule, includes:

(a) a first gRNA molecule that is selected from the gRNA molecules described herein (e.g., above) to a HPFH region, and a second gRNA molecule includes a targeting domain that is complementary to a target sequence of the beta globin gene; or

(b) a first gRNA molecule that is selected from the gRNA molecules described herein (e.g., above) to a BCL11a enhancer, e.g., a +58 BCL11a enhancer, a +55 BCL11a enhancer or a +62 BCL11a enhancer, and a second gRNA molecule includes a targeting domain that is complementary to a target sequence of the beta globin gene.

In any of the aforementioned composition aspects and embodiments, the composition may consist of, with respect to the gRNA components of the composition, a first gRNA molecule and a second gRNA molecule.

In any of the aforementioned composition aspects and embodiments, the compositions may be formulated in a medium suitable for electroporation.

In another aspect, the invention provides nucleic acids encoding the gRNA molecule(s) and/or Cas molecules of the CRISPR systems. Without being bound by theory, it is believed that delivering such

nucleic acids to cells will lead to the expression of the CRISPR system within the cell. In an aspect, the invention provides a nucleic acid sequence that encodes one or more gRNA molecules of any of the previous gRNA aspects and embodiments. In embodiments, the nucleic acid includes a promoter operably linked to the sequence that encodes the one or more gRNA molecules. In embodiments, the promoter is a promoter recognized by an RNA polymerase II or RNA polymerase III. In embodiments, the promoter is a U6 promoter or an HI promoter.

In further aspects, the nucleic acid further comprises sequence encoding a Cas9 molecule. In embodiments, the nucleic acid includes a promoter operably linked to the sequence that encodes a Cas9 molecule. In embodiments, the promoter is an EF-1 promoter, a CMV IE gene promoter, an EF-1α promoter, an ubiquitin C promoter, or a phosphoglycerate kinase (PGK) promoter.

In an aspect the invention provides a vector that includes the nucleic acid of any of the previous nucleic acid aspects and embodiments. In embodiments, the vector is selected from the group consisting of a lentiviral vector, an adenoviral vector, an adeno-associated viral (AAV) vector, a herpes simplex virus (HSV) vector, a plasmid, a minicircle, a nanoplasmid, and an RNA vector.

In another aspect, the invention provides a composition including one or more gRNA molecules, e.g., as described herein, e.g., in any of the previous gRNA molecule aspects and embodiments, and nucleic acid encoding a Cas9 molecule.

In another aspect, the invention provides a composition including nucleic acid encoding one or more gRNA molecules (e.g., as described herein, e.g., of any of the previous gRNA molecule aspects and embodiments), and a Cas9 molecule.

In another aspect, the invention provides a composition, e.g., a composition of any of the aforementioned composition aspects and embodiments, further including a template nucleic acid. In another aspect, the invention provides a composition, e.g., a composition of any of the aforementioned composition aspects and embodiments, further including nucleic acid sequence encoding a template nucleic acid. In embodiments, the template nucleic acid includes a nucleotide that corresponds to a nucleotide of a target sequence of the gRNA molecule. In embodiments, the template nucleic acid includes nucleic acid encoding human beta globin, e.g., human beta globin including one or more of the mutations G16D, E22A and T87Q. In embodiments, the template nucleic acid includes nucleic acid encoding human gamma globin.

In another aspect, the invention provides cells that include (or at any time included) a gRNA molecule, CRISPR system, composition or nucleic acid (e.g., as described herein, e.g., as in any of the aforementioned aspects and embodiments). In such aspects, the invention provides cells that have been modified by such inclusion.

Thus, in an aspect, the invention provides a method of altering e.g., altering the structure, e.g., sequence, of a target sequence within nucleic acid of a cell, including contacting said cell with:

1) one or more gRNA molecules of any of the aforementioned gRNA molecule aspects and embodiments, and a Cas9 molecule (e.g., as described herein);

2) one or more gRNA molecules of any of the aforementioned gRNA molecule aspects and embodiments, and nucleic acid encoding a Cas9 molecule (e.g., as described herein);

3) nucleic acid encoding one or more gRNA molecules of any of the aforementioned gRNA molecule aspects and embodiments, and a Cas9 molecule (e.g., as described herein);

4) nucleic acid encoding one or more gRNA molecules of the aforementioned gRNA molecule aspects and embodiments, and nucleic acid encoding a Cas9 molecule (e.g., as described herein); or

5) any of 1) to 4), above, and a template nucleic acid (e.g., as described herein);

6) any of 1) to 4) above, and nucleic acid including sequence encoding a template nucleic acid (e.g., as described herein);

7) a composition as described herein (e.g., of any of the aforementioned composition aspects and embodiments); or

8) the vector of any of the aforementioned vector aspects and embodiments.

In embodiments, the gRNA molecule or nucleic acid encoding the gRNA molecule, and the Cas9 molecule or nucleic acid encoding the Cas9 molecule, are formulated in a single composition. In other embodiments, the gRNA molecule or nucleic acid encoding the gRNA molecule, and the Cas9 molecule or nucleic acid encoding the Cas9 molecule, are formulated in more than one composition. In embodiments, the more than one composition are delivered simultaneously or sequentially.

In embodiments, the cell is an animal cell. In embodiments, the cell the cell is a mammalian, primate, or human cell. In embodiments, the cell is a hempatopoietic stem or progenitor cell (HSPC) (e.g., a population of HSPCs). In embodiments, the cell is a CD34+ cell. In embodiments, the cell is a CD34+/CD38-/CD90+/CD45RA- cell. In embodiments, the cell is a CD34+/CD90+/CD49f+ cell. In embodiments, the cell is a CD34+/CD38-/CD90+/CD45RA-/CD49f+ cell. In embodiments, the method includes a population of cells that has been enriched for HSPCs, e.g., for CD34+ cells.

In embodiments, the cell (e.g. population of cells) has been isolated from bone marrow. In embodiments, the cell (e.g. population of cells) has been isolated from mobilized peripheral blood. In embodiments, the cell (e.g. population of cells) has been isolated from umbilical cord blood.

In embodiments, the cell (e.g. population of cells) is autologous with respect to a patient to be administered said cell (e.g. population of cells). In embodiments, the cell (e.g. population of cells) is allogeneic with respect to a patient to be administered said cell (e.g. population of cells).

In embodiments, of the methods described herein, the altering results in an increase of fetal hemoglobin expression in the cell. In embodiments, of the methods described herein, the altering results in a reduction of fetal hemoglobin expression in the cell.

In another aspect, the invention provides a cell, altered by the method of any of the aforementioned method aspects and embodiments. In another aspect, the invention provides a cell, including a first gRNA molecule (e.g., as described herein), or a composition (e.g., as described herein), or a nucleic acid encoding the first gRNA molecule (e.g., as described herein), of any of the previous aspects and embodiments. In embodiments, the cell is an animal cell. In embodiments, the cell the cell is a mammalian, primate, or human cell. In embodiments, the cell is a hematopoietic stem or progenitor cell (HSPC) (e.g., a population of HSPCs). In embodiments, the cell is a CD34+ cell. In embodiments, the cell is a CD34+/CD38-/CD90+/CD45RA- cell. In embodiments, the cell is a CD34+/CD90+/CD49f+ cell. In embodiments, the method includes a population of cells that has been enriched for HSPCs, e.g., for CD34+ cells.

In embodiments, the cell (e.g. population of cells) has been isolated from bone marrow. In embodiments, the cell (e.g. population of cells) has been isolated from mobilized peripheral blood. In embodiments, the cell (e.g. population of cells) has been isolated from umbilical cord blood.

In embodiments, the cell (e.g. population of cells) is autologous with respect to a patient to be administered said cell (e.g. population of cells). In embodiments, the cell (e.g. population of cells) is allogeneic with respect to a patient to be administered said cell (e.g. population of cells).

In embodiments, the cell includes, has included, or will include a second gRNA molecule, e.g., as described herein, e.g., of any of the previous gRNA molecule aspects and embodiments, or a nucleic acid encoding the second gRNA molecule, wherein the first gRNA molecule and second gRNA molecule include nonidentical targeting domains.

In embodiments, expression of fetal hemoglobin is increased in the cell, e.g., relative to a cell of the same cell type that has not been modified to include a gRNA molecule (e.g., as described herein). In embodiments, expression of beta globin is decreased in the cell, e.g., relative to a cell of the same cell type that has not been modified to include a gRNA molecule (e.g., as described herein). In embodiments, expression of fetal hemoglobin is increased and expression of beta globin is decreased in the cell, e.g., relative to a cell of the same cell type that has not been modified to include a gRNA molecule (e.g., as described herein).

In an aspect, the cells of the invention (or methods comprising a cell) have been contacted with a stem cell expander, e.g., as described herein, e.g., compound 1, compound 2, compound 3 or compound 4. In an aspect, the cells of the invention (or methods comprising a cell) have been contacted with a stem cell expander, e.g., as described herein, e.g., compound 1, compound 2, compound 3, compound 4 or a combination thereof (e.g., compound 1 and compound 4). In an embodiment, the stem cell expander is compound 4. In an embodiment, the stem cell expander is a combination of compound 1 and compound 4. In embodiments, the contacting is ex vivo.

In another aspect, the invention provides methods of treatment, e.g., methods of treatment of hemoglobinopathies. In an aspect, the invention provides a method of treating a hemoglobinopathy, that includes administering to a patient a cell (e.g., a population of cells) of any of the previous cell or method aspects and embodiments.

In another aspect, the invention provides a method of increasing fetal hemoglobin expression in a mammal, including administering to a patient a cell of any of the previous cell or method aspects and embodiments. In an embodiment, the hemoglobinopathy is beta-thalassemia or sickle cell disease.

In another aspect, the invention provides a guide RNA molecule, e.g., as described herein, for use as a medicament, e.g., for use in the treatment of a disease. In embodiments, the disease is a hemoglobinopathy, e.g., beta-thalassemia or sickle cell disease.

In another aspect, the invention provides a gRNA molecule, e.g., as described herein, e.g., as described in any of the aforementioned gRNA molecule aspects and embodiments, wherein when a CRISPR system including the gRNA is introduced into a cell (e.g., a CD34+ cell, e.g., an HSC), at least about 15% of the indels produced include (a) a frameshift mutation; or (b) a large deletion, relative to unmodified target DNA, as measured by NGS. In embodiments, at least about 25% of the indels produced include (a) a frameshift mutation; or (b) a large deletion, relative to unmodified target DNA, as measured by NGS. In embodiments, at least about 40%, at least about 50%, at least about 60%, at least about 70% at least about 80%, at least about 90%, at least about 95%, at least about 96%, at least about 97%, at least about 98%, or at least about 99% of the indels produced include (a) a frameshift mutation; or (b) a large deletion, relative to unmodified target DNA, as measured by NGS.

In another aspect, the invention provides methods for the ex vivo expansion and modification of HSPCs (e.g., CD34+ cells). In an aspect, the invention provides a method of modifying cells (e.g., a population of cells) including:

(a) providing a population of cells;

(b) expanding said cells ex vivo in the presence of a stem cell expander; and

(c) introducing into said cells a first gRNA molecule (e.g., as described herein, e.g., of any of the aforementioned gRNA molecule aspects and embodiments), a nucleic acid molecule encoding the first gRNA molecule, or a composition (e.g., as described herein, e.g., of any of the aforementioned composition aspects and embodiments);

such that hemoglobin, e.g., fetal hemoglobin, expression is increased in said cells relative to the same cell type which have not been subjected to step (c).

In embodiments, the cells are introduced into a subject in need thereof, e.g., a subject that has a hemoglobinopathy, e.g., sickle cell disease or beta thalassemia.

In embodiments, the cells are or comprise CD34+ cells. In embodiments, the cells are or comprise HSPCs. In embodiments, the cells are isolated from bone marrow, mobilized peripheral blood or umbilical cord blood. In a preferred embodiment, the cells are isolated from bone marrow. In other embodiments, the cells are isolated from mobilized peripheral blood. In aspects, the moblized peripheral blood is isolated from a subject who has been administered a G-CSF. In aspects, the moblized peripheral blood is isolated from a subject who has been administered a moblization agent other than G-CSF, for example, Plerixafor® (AMD3100). In embodiments, the cells are an enriched population of cells.

In embodiments, the stem cell expander is compound 1, compound 2, compound 3, or compound 4, e.g., compound 4. In embodiments, the stem cell expander is compound 1, compound 2, compound 3, compound 4, or a combination thereof (e.g., a combination of compound 1 and compound 4). In embodiments, the cells are contacted with compound 4 at a concentration of from about 1 to about 200 micromolar (uM). In an embodiment, the concentration of compound 4 is about 75 micromolar (uM). In embodiments, the expanding said cells ex vivo in the presence of a stem cell expander occurs for a period of about 1-10 days, e.g., about 1-5 days, e.g., about 2-5 days, e.g., about 4 days.

In embodiments, the cells are autologous to a patient intended to be administered said cells. In embodiments, the cells are allogeneic to a patient intended to be administered said cells.

In embodiments, the expanding of step (b) is further in the presence of thrombopoietin (Tpo), Flt3 ligand (Flt-3L), human stem cell factor (SCF) and human interleukin-6 (IL-6). In embodiments, the thrombopoietin (Tpo), Flt3 ligand (Flt-3L), human stem cell factor (SCF) and human interleukin-6 (IL-6) are each at a concentration of about 50 ng/mL. In embodiments, the thrombopoietin (Tpo), Flt3 ligand (Flt-3L), human stem cell factor (SCF) and human interleukin-6 (IL-6) are each at a concentration of 50 ng/mL.

Additional aspects and embodiments are described below.

In an aspect, the invention provides a gRNA molecule that includes a tracr and crRNA, wherein the crRNA includes a targeting domain that is complementary with a target sequence of a BCL11A gene (e.g., a human BCL11a gene), a BCL11a enhancer (e.g., a human BCL11a enhancer), or a HFPH region (e.g., a human HPFH region).

In embodiments, the target sequence is of the BCL11A gene, and the targeting domain includes, e.g., consists of, any one of SEQ ID NO: 1 to SEQ ID NO: 85 or SEQ ID NO: 400 to SEQ ID NO: 1231. These embodiments are referred to herein as gRNA molecule embodiment 2.

In other embodiments, the target sequence is of a BCL11a enhancer, and the targeting domain includes, e.g., consists of, any one of SEQ ID NO: 1232 to SEQ ID NO: 1499. These embodiments are referred to herein as gRNA molecule embodiment 3. In preferred embodiments, the target sequence is of a BCL11a enhancer, and the targeting domain includes, e.g., consists of, any one of SEQ ID NO: 182 to SEQ ID NO: 277 or SEQ ID NO: 334 to SEQ ID NO: 341. These embodiments are referred to herein as gRNA molecule embodiment 4. In more preferred embodiments, the targeting domain includes, e.g., consists of, any one of SEQ ID NO: 341, SEQ ID NO: 246, SEQ ID NO: 248, SEQ ID NO: 247, SEQ ID NO: 245, SEQ ID NO: 249, SEQ ID NO: 244, SEQ ID NO: 199, SEQ ID NO: 251, SEQ ID NO: 250, SEQ ID NO: 334, SEQ ID NO: 185, SEQ ID NO: 186, SEQ ID NO: 336, or SEQ ID NO: 337. These embodiments are referred to herein as gRNA molecule embodiment 5. In still more preferred embodiments, the targeting domain includes, e.g., consists of, any one of SEQ ID NO: 247, SEQ ID NO: 248, SEQ ID NO: 335, SEQ ID NO: 336, SEQ ID NO: 337, or SEQ ID NO: 338 (referred to herein as gRNA molecule embodiment 6), for example, includes, e.g., consists of, any one of SEQ ID NO: 248 or SEQ ID NO: 338 (referred to herein as gRNA molecule embodiment 7). In embodiments, the targeting domain includes, e.g., consists of, SEQ ID NO: 248 (referred to herein as gRNA molecule embodiment 8). In embodiments, the targeting domain includes, e.g., consists of, SEQ ID NO: 338 (referred to herein as gRNA molecule embodiment 9).

In other embodiments, the target sequence is of a BCL11a enhancer, and the targeting domain includes, e.g., consists of, any one of SEQ ID NO: 278 to SEQ ID NO: 333 (referred to herein as gRNA molecule embodiment 10). In preferred embodiments, the targeting domain includes, e.g., consists of, any one of SEQ ID NO: 318, SEQ ID NO: 312, SEQ ID NO: 313, SEQ ID NO: 294, SEQ ID NO: 310, SEQ ID NO: 319, SEQ ID NO: 298, SEQ ID NO: 322, SEQ ID NO: 311, SEQ ID NO: 315, SEQ ID NO: 290, SEQ ID NO: 317, SEQ ID NO: 309, SEQ ID NO: 289, or SEQ ID NO: 281 (referred to herein as gRNA molecule embodiment 11). In one preferred embodiment, the targeting domain includes, e.g., consists of, SEQ ID NO: 318 (referred to herein as gRNA molecule embodiment 12).

In other embodiments, the target sequence is of a BCL11a enhancer, and the targeting domain includes, e.g., consists of, any one of SEQ ID NO: 1596 to SEQ ID NO: 1691 (referred to herein as gRNA molecule embodiment 13). In preferred embodiments, the targeting domain includes, e.g., consists of, any one of SEQ ID NO: 1683, SEQ ID NO: 1638, SEQ ID NO: 1647, SEQ ID NO: 1609, SEQ ID NO: 1621, SEQ ID NO: 1617, SEQ ID NO: 1654, SEQ ID NO: 1631, SEQ ID NO: 1620, SEQ ID NO: 1637, SEQ ID NO: 1612, SEQ ID NO: 1656, SEQ ID NO: 1619, SEQ ID NO: 1675, SEQ ID NO: 1645, SEQ ID NO: 1598, SEQ ID NO: 1599, SEQ ID NO: 1663, SEQ ID NO: 1677, or SEQ ID NO: 1626 (referred to herein as gRNA molecule embodiment 14).

In other embodiments, the target sequence is of a HFPH region (e.g., a French HPFH region), and the targeting domain includes, e.g., consists of, any one of SEQ ID NO: 86 to SEQ ID NO: 181, SEQ ID NO: 1500 to SEQ ID NO: 1595, or SEQ ID NO: 1692 to SEQ ID NO: 1761 (referred to herein as gRNA molecule embodiment 15). In preferred embodiments, the targeting domain includes, e.g., consists of, any one of SEQ ID NO: 100, SEQ ID NO: 165, SEQ ID NO: 113, SEQ ID NO: 99, SEQ ID NO: 112, SEQ ID NO: 98, SEQ ID NO: 1580, SEQ ID NO: 106, SEQ ID NO: 1503, SEQ ID NO: 1589, SEQ ID NO: 160, SEQ ID NO: 1537, SEQ ID NO: 159, SEQ ID NO: 101, SEQ ID NO: 162, SEQ ID NO: 104, SEQ ID NO: 138, SEQ ID NO: 1536, SEQ ID NO: 1539, SEQ ID NO: 1585 (referred to herein as gRNA molecule embodiment 16). In still more preferred embodiments, the targeting domain includes, e.g., consists of, any one of SEQ ID NO: 98, SEQ ID NO: 100, SEQ ID NO: 1505, SEQ ID NO: 1589, SEQ ID NO: 1700, or SEQ ID NO: 1750 (referred to herein as gRNA molecule embodiment 17). In other preferred embodiments, the targeting domain includes, e.g., consists of, any one of SEQ ID NO: 100, SEQ ID NO: 165, or SEQ ID NO: 113 (referred to herein as gRNA molecule embodiment 18).

In embodiments, the gRNA molecule includes a targeting domain that includes, e.g., consists of, 17, 18, 19, 20, 21, 22, 23, or 24, preferably 20, consecutive nucleic acids of any targeting domain sequence described herein, for example a targeting domain sequence of Table 1 or Table 2. In embodiments, the 17, 18, 19, 20, 21, 22, 23, or 24, preferably 20, consecutive nucleic acids of any one of targeting domain sequences described herein, for example a targeting domain sequence of Table 1 or Table 2, are the 17, 18, 19, 20, 21, 22, 23, or 24, preferably 20, consecutive nucleic acids disposed at the 3' end of the recited targeting domain sequence. In other embodiments, the 17, 18, 19, 20, 21, 22, 23, or 24, preferably 20, consecutive nucleic acids of any one of the targeting domain sequences described herein, for example a targeting domain sequence of Table 1 or Table 2, are the 17, 18, 19, 20, 21, 22, 23, or 24, preferably 20, consecutive nucleic acids disposed at the 5' end of the recited targeting domain sequence. In other embodiments, the 17, 18, 19, 20, 21, 22, 23, or 24, preferably 20, consecutive nucleic acids of any one of the targeting domain sequences described herein, for example a targeting domain sequence of Table 1 or Table 2, do not include either the 5' or 3' nucleic acid of the recited targeting domain sequence.

In embodiments, the gRNA molecule includes a targeting domain that includes, e.g., consists of, 17, 18, 19, or 20, preferably 20, consecutive nucleic acids of any targeting domain sequence described herein, for example a targeting domain sequence of Table 5, Table 6, Table 7, Table 8 or Table 9. In embodiments, the 17, 18, 19, or 20, preferably 20, consecutive nucleic acids of any one of targeting domain sequences described herein, for example a targeting domain sequence of Table 5, Table 6, Table 7, Table 8 or Table 9, are the 17, 18, 19, or 20, preferably 20, consecutive nucleic acids disposed at the 3' end of the recited targeting domain sequence. In other embodiments, the 17, 18, 19, or 20, preferably 20, consecutive nucleic acids of any one of the targeting domain sequences described herein, for example a targeting domain sequence of Table 5, Table 6, Table 7, Table 8 or Table 9, are the 17, 18, 19, or 20, preferably 20, consecutive nucleic acids disposed at the 5' end of the recited targeting domain sequence. In other embodiments, the 17, 18, 19, or 20, preferably 20, consecutive nucleic acids of any one of the targeting domain sequences described herein, for example a targeting domain sequence of Table 5, Table 6, Table 7, Table 8 or Table 9, do not include either the 5' or 3' nucleic acid of the recited targeting domain sequence.

The following aspects describe features of the gRNA molecule that may be combined with any of the aforementioned aspects and embodiments. In embodiments, the gRNA molecule, including the gRNA molecule of any of the aforementioned aspects and embodiments, include a portion of the crRNA and a portion of the tracr that hybridize to form a flagpole that includes SEQ ID NO: 6584 or 6585. In embodiments, the flagpole further includes a first flagpole extension, located 3' to the crRNA portion of the flagpole, wherein said first flagpole extension includes SEQ ID NO: 6586. In embodiments, the flagpole further includes (in addition to or in alternative to the first flagpole extension) a second flagpole extension located 3' to the crRNA portion of the flagpole and, if present, the first flagpole extension, wherein said second flagpole extension includes SEQ ID NO: 6587.

In embodiments, including in any of the aforementioned aspects and embodiments, the tracr includes SEQ ID NO: 6660 or SEQ ID NO: 6661. In embodiments, the tracr includes SEQ ID NO: 7812, optionally further including, at the 3' end, an additional 1, 2, 3, 4, 5, 6, or 7 uracil (U) nucleotides. In embodiments, the crRNA includes, from 5' to 3', [targeting domain]-: a) SEQ ID NO: 6584; b) SEQ ID NO: 6585; c) SEQ ID NO: 6605; d) SEQ ID NO: 6606; e) SEQ ID NO: 6607; f) SEQ ID NO: 6608; or g) SEQ ID NO: 7806.

In embodiments, including in any of the aforementioned aspects and embodiments, the tracr includes, from 5' to 3': a) SEQ ID NO: 6589; b) SEQ ID NO: 6590; c) SEQ ID NO: 6609; d) SEQ ID NO: 6610; e) SEQ ID NO: 6660; f) SEQ ID NO: 6661; g) SEQ ID NO: 7812; h) SEQ ID NO: 7807; i) SEQ ID NO: 7808; j) SEQ ID NO: 7809; k) any of a) to j), above, further including, at the 3' end, at least 1, 2, 3, 4, 5, 6 or 7 uracil (U) nucleotides, e.g., 1, 2, 3, 4, 5, 6, or 7 uracil (U) nucleotides; l) any of a) to k), above, further including, at the 3' end, at least 1, 2, 3, 4, 5, 6 or 7 adenine (A) nucleotides,

e.g., 1, 2, 3, 4, 5, 6, or 7 adenine (A) nucleotides; or m) any of a) to l), above, further including, at the 5' end (e.g., at the 5' terminus), at least 1, 2, 3, 4, 5, 6 or 7 adenine (A) nucleotides, e.g., 1, 2, 3, 4, 5, 6, or 7 adenine (A) nucleotides.

In embodiments, the targeting domain and the tracr are disposed on separate nucleic acids molecules. In embodiments of such gRNA molecules, the nucleic acid molecule including the targeting domain includes SEQ ID NO: 6607, optionally disposed immediately 3' to the targeting domain, and the nucleic acid molecule including the tracr includes, e.g., consists of, SEQ ID NO: 6660.

In embodiments, the crRNA portion of the flagpole includes SEQ ID NO: 6607 or SEQ ID NO: 6608.

In embodiments, the tracr includes SEQ ID NO: 6589 or 6590, and optionally, if a first flagpole extension is present, a first tracr extension, disposed 5' to SEQ ID NO: 6589 or 6590, said first tracr extension including SEQ ID NO: 6591.

In embodiments, including in embodiments of any of the aforementioned aspects and embodiments, the targeting domain and the tracr are disposed on separate nucleic acid molecules. In other embodiments, including in embodiments of any of the aforementioned aspects and embodiments, the targeting domain and the tracr are disposed on a single nucleic acid molecule, for example, the tracr is disposed 3' to the targeting domain.

In embodiments, when the targeting domain and the tracr are disposed on a single nucleic acid molecule, the gRNA molecule further includes a loop, disposed 3' to the targeting domain and 5' to the tracr. In embodiments, the loop includes, e.g., consists of, SEQ ID NO: 6588.

In embodiments, when the targeting domain and the tracr are disposed on a single nucleic acid molecule, the gRNA molecule includes, from 5' to 3', [targeting domain]-: (a) SEQ ID NO: 6601; (b) SEQ ID NO: 6602; (c) SEQ ID NO: 6603; (d) SEQ ID NO: 6604; (e) SEQ ID NO: 7811; or (f) any of (a) to (e), above, further including, at the 3' end, 1, 2, 3, 4, 5, 6 or 7 uracil (U) nucleotides. In embodiments, the gRNA molecule includes, e.g., consists of, said targeting domain and SEQ ID NO: 7811, optionally disposed immediately 3' to said targeting domain.

In embodiments, including in any of the aforementioned aspects and embodiments, each of the nucleic acid residues of the gRNA molecule is an unmodified A, U, G or C nucleic acid residue and unmodified phosphate bonds between each residue of the nucleic acid molecule(s). In other embodiments, including in any of the aforementioned aspects and embodiments, one, or optionally more than one, of the nucleic acid molecules that make up the gRNA molecule includes: a) one or more, e.g., three, phosphorothioate modifications at the 3' end of said nucleic acid molecule or molecules; b) one or more, e.g., three, phosphorothioate modifications at the 5' end of said nucleic acid molecule or molecules; c) one or more, e.g., three, 2'-O-methyl modifications at the 3' end of

said nucleic acid molecule or molecules; d) one or more, e.g., three, 2'-O-methyl modifications at the 5' end of said nucleic acid molecule or molecules; e) a 2' O-methyl modification at each of the 4th-to-terminal, 3rd-to-terminal, and 2nd-to-terminal 3' residues of said nucleic acid molecule or molecules; f) a 2' O-methyl modification at each of the 4th-to-terminal, 3rd-to-terminal, and 2nd-to-terminal 5' residues of said nucleic acid molecule or molecules; or f) any combination thereof.

In preferred embodiments, the invention provides a gRNA molecule (e.g., that is a sgRNA molecule) including, e.g., consisting of, the sequence: (a) SEQ ID NO: 342; (b) SEQ ID NO: 343; or (c) SEQ ID NO: 1762 (referred to in this summary of invention as gRNA molecule embodiment 41).

In other preferred embodiments, the invention provides gRNA molecule (e.g., that is a dual gRNA molecule) including, e.g., consisting of: (a) a crRNA including, e.g., consisting of, SEQ ID NO: 344, and a tracr including, e.g., consisting of, SEQ ID NO: 6660; (b) a crRNA including, e.g., consisting of, SEQ ID NO: 344, and a tracr including, e.g., consisting of, SEQ ID NO: 346; (c) a crRNA including, e.g., consisting of, SEQ ID NO: 345, and a tracr including, e.g., consisting of, SEQ ID NO: 6660; or (d) a crRNA including, e.g., consisting of, SEQ ID NO: 345, and a tracr including, e.g., consisting of, SEQ ID NO: 346 (referred to in this summary of invention as gRNA molecule embodiment 42).

In other preferred embodiments, the invention provides a gRNA molecule (e.g., that is a sgRNA molecule) including, e.g., consisting of, the sequence: (a) SEQ ID NO: 347; (b) SEQ ID NO: 348; or (c) SEQ ID NO: 1763 (referred to in this summary of invention as gRNA molecule embodiment 43).

In other preferred embodiments, the invention provides gRNA molecule (e.g., that is a dual gRNA molecule) including, e.g., consisting of: (a) a crRNA including, e.g., consisting of, SEQ ID NO: 349, and a tracr including, e.g., consisting of, SEQ ID NO: 6660; (b) a crRNA including, e.g., consisting of, SEQ ID NO: 349, and a tracr including, e.g., consisting of, SEQ ID NO: 346; (c) a crRNA including, e.g., consisting of, SEQ ID NO: 350, and a tracr including, e.g., consisting of, SEQ ID NO: 6660; or (d) a crRNA including, e.g., consisting of, SEQ ID NO: 350, and a tracr including, e.g., consisting of, SEQ ID NO: 346 (referred to in this summary of invention as gRNA molecule embodiment 44).

In other preferred embodiments, the invention provides a gRNA molecule (e.g., that is a sgRNA molecule) including, e.g., consisting of, the sequence: (a) SEQ ID NO: 351; (b) SEQ ID NO: 352; or (c) SEQ ID NO: 1764 (referred to in this summary of invention as gRNA molecule embodiment 45).

In other preferred embodiments, the invention provides gRNA molecule (e.g., that is a dual gRNA molecule) including, e.g., consisting of: (a) a crRNA including, e.g., consisting of, SEQ ID NO: 353, and a tracr including, e.g., consisting of, SEQ ID NO: 6660; (b) a crRNA including, e.g., consisting

of, SEQ ID NO: 353, and a tracr including, e.g., consisting of, SEQ ID NO: 346; (c) a crRNA including, e.g., consisting of, SEQ ID NO: 354, and a tracr including, e.g., consisting of, SEQ ID NO: 6660; or (d) a crRNA including, e.g., consisting of, SEQ ID NO: 354, and a tracr including, e.g., consisting of, SEQ ID NO: 346 (referred to in this summary of invention as gRNA molecule embodiment 46).

In other preferred embodiments, the invention provides a gRNA molecule (e.g., that is a sgRNA molecule) including, e.g., consisting of, the sequence: (a) SEQ ID NO: 355; (b) SEQ ID NO: 356; or (c) SEQ ID NO: 1765 (referred to in this summary of invention as gRNA molecule embodiment 47).

In other preferred embodiments, the invention provides gRNA molecule (e.g., that is a dual gRNA molecule) including, e.g., consisting of: (a) a crRNA including, e.g., consisting of, SEQ ID NO: 357, and a tracr including, e.g., consisting of, SEQ ID NO: 6660; (b) a crRNA including, e.g., consisting of, SEQ ID NO: 357, and a tracr including, e.g., consisting of, SEQ ID NO: 346; (c) a crRNA including, e.g., consisting of, SEQ ID NO: 358, and a tracr including, e.g., consisting of, SEQ ID NO: 6660; or (d) a crRNA including, e.g., consisting of, SEQ ID NO: 358, and a tracr including, e.g., consisting of, SEQ ID NO: 346 (referred to in this summary of invention as gRNA molecule embodiment 48).

In other preferred embodiments, the invention provides a gRNA molecule (e.g., that is a sgRNA molecule) including, e.g., consisting of, the sequence: (a) SEQ ID NO: 359; (b) SEQ ID NO: 360; or (c) SEQ ID NO: 1766 (referred to in this summary of invention as gRNA molecule embodiment 49).

In other preferred embodiments, the invention provides gRNA molecule (e.g., that is a dual gRNA molecule) including, e.g., consisting of: (a) a crRNA including, e.g., consisting of, SEQ ID NO: 361, and a tracr including, e.g., consisting of, SEQ ID NO: 6660; (b) a crRNA including, e.g., consisting of, SEQ ID NO: 361, and a tracr including, e.g., consisting of, SEQ ID NO: 346; (c) a crRNA including, e.g., consisting of, SEQ ID NO: 362, and a tracr including, e.g., consisting of, SEQ ID NO: 6660; or (d) a crRNA including, e.g., consisting of, SEQ ID NO: 362, and a tracr including, e.g., consisting of, SEQ ID NO: 346 (referred to in this summary of invention as gRNA molecule embodiment 50).

In other preferred embodiments, the invention provides a gRNA molecule (e.g., that is a sgRNA molecule) including, e.g., consisting of, the sequence: (a) SEQ ID NO: 363; (b) SEQ ID NO: 364; or (c) SEQ ID NO: 1767 (referred to in this summary of invention as gRNA molecule embodiment 51).

In other preferred embodiments, the invention provides gRNA molecule (e.g., that is a dual gRNA molecule) including, e.g., consisting of: (a) a crRNA including, e.g., consisting of, SEQ ID NO: 365, and a tracr including, e.g., consisting of, SEQ ID NO: 6660; (b) a crRNA including, e.g., consisting

of, SEQ ID NO: 365, and a tracr including, e.g., consisting of, SEQ ID NO: 346; (c) a crRNA including, e.g., consisting of, SEQ ID NO: 366, and a tracr including, e.g., consisting of, SEQ ID NO: 6660; or (d) a crRNA including, e.g., consisting of, SEQ ID NO: 366, and a tracr including, e.g., consisting of, SEQ ID NO: 346 (referred to in this summary of invention as gRNA molecule embodiment 52).

In other preferred embodiments, the invention provides a gRNA molecule (e.g., that is a sgRNA molecule) including, e.g., consisting of, the sequence: (a) SEQ ID NO: 367; (b) SEQ ID NO: 368; or (c) SEQ ID NO: 1768 (referred to in this summary of invention as gRNA molecule embodiment 53).

In other preferred embodiments, the invention provides gRNA molecule (e.g., that is a dual gRNA molecule) including, e.g., consisting of: (a) a crRNA including, e.g., consisting of, SEQ ID NO: 369, and a tracr including, e.g., consisting of, SEQ ID NO: 6660; (b) a crRNA including, e.g., consisting of, SEQ ID NO: 369, and a tracr including, e.g., consisting of, SEQ ID NO: 346; (c) a crRNA including, e.g., consisting of, SEQ ID NO: 370, and a tracr including, e.g., consisting of, SEQ ID NO: 6660; or (d) a crRNA including, e.g., consisting of, SEQ ID NO: 370, and a tracr including, e.g., consisting of, SEQ ID NO: 346 (referred to in this summary of invention as gRNA molecule embodiment 54).

In other preferred embodiments, the invention provides a gRNA molecule (e.g., that is a sgRNA molecule) including, e.g., consisting of, the sequence: (a) SEQ ID NO: 371; (b) SEQ ID NO: 372; or (c) SEQ ID NO: 1769 (referred to in this summary of invention as gRNA molecule embodiment 55).

In other preferred embodiments, the invention provides gRNA molecule (e.g., that is a dual gRNA molecule) including, e.g., consisting of: (a) a crRNA including, e.g., consisting of, SEQ ID NO: 373, and a tracr including, e.g., consisting of, SEQ ID NO: 6660; (b) a crRNA including, e.g., consisting of, SEQ ID NO: 373, and a tracr including, e.g., consisting of, SEQ ID NO: 346; (c) a crRNA including, e.g., consisting of, SEQ ID NO: 374, and a tracr including, e.g., consisting of, SEQ ID NO: 6660; or (d) a crRNA including, e.g., consisting of, SEQ ID NO: 374, and a tracr including, e.g., consisting of, SEQ ID NO: 346 (referred to in this summary of invention as gRNA molecule embodiment 56).

In other preferred embodiments, the invention provides a gRNA molecule (e.g., that is a sgRNA molecule) including, e.g., consisting of, the sequence: (a) SEQ ID NO: 375; (b) SEQ ID NO: 376; or (c) SEQ ID NO: 1770 (referred to in this summary of invention as gRNA molecule embodiment 57).

In other preferred embodiments, the invention provides gRNA molecule (e.g., that is a dual gRNA molecule) including, e.g., consisting of: (a) a crRNA including, e.g., consisting of, SEQ ID NO: 377, and a tracr including, e.g., consisting of, SEQ ID NO: 6660; (b) a crRNA including, e.g., consisting

of, SEQ ID NO: 377, and a tracr including, e.g., consisting of, SEQ ID NO: 346; (c) a crRNA including, e.g., consisting of, SEQ ID NO: 378, and a tracr including, e.g., consisting of, SEQ ID NO: 6660; or (d) a crRNA including, e.g., consisting of, SEQ ID NO: 378, and a tracr including, e.g., consisting of, SEQ ID NO: 346 (referred to in this summary of invention as gRNA molecule embodiment 58).

In other preferred embodiments, the invention provides a gRNA molecule (e.g., that is a sgRNA molecule) including, e.g., consisting of, the sequence: (a) SEQ ID NO: 379; (b) SEQ ID NO: 380; or (c) SEQ ID NO: 1771 (referred to in this summary of invention as gRNA molecule embodiment 59).

In other preferred embodiments, the invention provides gRNA molecule (e.g., that is a dual gRNA molecule) including, e.g., consisting of: (a) a crRNA including, e.g., consisting of, SEQ ID NO: 381, and a tracr including, e.g., consisting of, SEQ ID NO: 6660; (b) a crRNA including, e.g., consisting of, SEQ ID NO: 381, and a tracr including, e.g., consisting of, SEQ ID NO: 346; (c) a crRNA including, e.g., consisting of, SEQ ID NO: 382, and a tracr including, e.g., consisting of, SEQ ID NO: 6660; or (d) a crRNA including, e.g., consisting of, SEQ ID NO: 382, and a tracr including, e.g., consisting of, SEQ ID NO: 346 (referred to in this summary of invention as gRNA molecule embodiment 60).

In other preferred embodiments, the invention provides a gRNA molecule (e.g., that is a sgRNA molecule) including, e.g., consisting of, the sequence: (a) SEQ ID NO: 383; (b) SEQ ID NO: 384; or (c) SEQ ID NO: 1772 (referred to in this summary of invention as gRNA molecule embodiment 61).

In other preferred embodiments, the invention provides gRNA molecule (e.g., that is a dual gRNA molecule) including, e.g., consisting of: (a) a crRNA including, e.g., consisting of, SEQ ID NO: 385, and a tracr including, e.g., consisting of, SEQ ID NO: 6660; (b) a crRNA including, e.g., consisting of, SEQ ID NO: 385, and a tracr including, e.g., consisting of, SEQ ID NO: 346; (c) a crRNA including, e.g., consisting of, SEQ ID NO: 386, and a tracr including, e.g., consisting of, SEQ ID NO: 6660; or (d) a crRNA including, e.g., consisting of, SEQ ID NO: 386, and a tracr including, e.g., consisting of, SEQ ID NO: 346 (referred to in this summary of invention as gRNA molecule embodiment 62).

In other preferred embodiments, the invention provides a gRNA molecule (e.g., that is a sgRNA molecule) including, e.g., consisting of, the sequence: (a) SEQ ID NO: 387; (b) SEQ ID NO: 388; or (c) SEQ ID NO: 1773 (referred to in this summary of invention as gRNA molecule embodiment 63).

In other preferred embodiments, the invention provides gRNA molecule (e.g., that is a dual gRNA molecule) including, e.g., consisting of: (a) a crRNA including, e.g., consisting of, SEQ ID NO: 389, and a tracr including, e.g., consisting of, SEQ ID NO: 6660; (b) a crRNA including, e.g., consisting

of, SEQ ID NO: 389, and a tracr including, e.g., consisting of, SEQ ID NO: 346; (c) a crRNA including, e.g., consisting of, SEQ ID NO: 390, and a tracr including, e.g., consisting of, SEQ ID NO: 6660; or (d) a crRNA including, e.g., consisting of, SEQ ID NO: 390, and a tracr including, e.g., consisting of, SEQ ID NO: 346 (referred to in this summary of invention as gRNA molecule embodiment 64).

In other preferred embodiments, the invention provides a gRNA molecule (e.g., that is a sgRNA molecule) including, e.g., consisting of, the sequence: (a) SEQ ID NO: 391; (b) SEQ ID NO: 392; or (c) SEQ ID NO: 1774 (referred to in this summary of invention as gRNA molecule embodiment 65).

In other preferred embodiments, the invention provides gRNA molecule (e.g., that is a dual gRNA molecule) including, e.g., consisting of: (a) a crRNA including, e.g., consisting of, SEQ ID NO: 393, and a tracr including, e.g., consisting of, SEQ ID NO: 6660; (b) a crRNA including, e.g., consisting of, SEQ ID NO: 393, and a tracr including, e.g., consisting of, SEQ ID NO: 346; (c) a crRNA including, e.g., consisting of, SEQ ID NO: 394, and a tracr including, e.g., consisting of, SEQ ID NO: 6660; or (d) a crRNA including, e.g., consisting of, SEQ ID NO: 394, and a tracr including, e.g., consisting of, SEQ ID NO: 346 (referred to in this summary of invention as gRNA molecule embodiment 66).

In other preferred embodiments, the invention provides a gRNA molecule (e.g., that is a sgRNA molecule) including, e.g., consisting of, the sequence: (a) SEQ ID NO: 395; (b) SEQ ID NO: 396; or (c) SEQ ID NO: 1775 (referred to in this summary of invention as gRNA molecule embodiment 67).

In other preferred embodiments, the invention provides gRNA molecule (e.g., that is a dual gRNA molecule) including, e.g., consisting of: (a) a crRNA including, e.g., consisting of, SEQ ID NO: 397, and a tracr including, e.g., consisting of, SEQ ID NO: 6660; (b) a crRNA including, e.g., consisting of, SEQ ID NO: 397, and a tracr including, e.g., consisting of, SEQ ID NO: 346; (c) a crRNA including, e.g., consisting of, SEQ ID NO: 398, and a tracr including, e.g., consisting of, SEQ ID NO: 6660; or (d) a crRNA including, e.g., consisting of, SEQ ID NO: 398, and a tracr including, e.g., consisting of, SEQ ID NO: 346 (referred to in this summary of invention as gRNA molecule embodiment 68).

In embodiments, including in any of the aforementioned aspects and embodiments, the invention provides a gRNA molecule, wherein when a CRISPR system (e.g., an RNP as described herein) including the gRNA molecule is introduced into a cell, an indel is formed at or near the target sequence complementary to the targeting domain of the gRNA molecule. In embodiments, including in embodiments comprising a targeting domain complementary to a target sequence of a +58 Enhancer region, the indel does not include a nucleotide of a GATA-1 and/or TAL-1 binding site. In embodiments, the indel does not interfere with the binding of GATA-1 and/or TAL-1 to their binding

sites. In embodiments, including in any of the aforementioned aspects and embodiments, the invention provides a gRNA molecule, wherein when a CRISPR system (e.g., an RNP as described herein) including the gRNA molecule is introduced into a population of cells, an indel is formed at or near the target sequence complementary to the targeting domain of the gRNA molecule in at least about 40%, e.g., at least about 50%, e.g., at least about 60%, e.g., at least about 70%, e.g., at least about 80%, e.g., at least about 90%, e.g., at least about 95%, e.g., at least about 96%, e.g., at least about 97%, e.g., at least about 98%, e.g., at least about 99%, of the cells of the population. In embodiments, including in any of the aforementioned aspects and embodiments, the invention provides a gRNA molecule, wherein when a CRISPR system (e.g., an RNP as described herein) including the gRNA molecule is introduced into a population of cells, an indel that does not include a nucleotide of a GATA-1 and/or TAL-1 binding site is formed at or near the target sequence complementary to the targeting domain of the gRNA molecule in at least about 20%, e.g., at least about 30%, e.g., at least about 35%, e.g., at least about 40%, e.g., at least about 45%, e.g., at least about 50%, e.g., at least about 55%, e.g., at least about 60%, e.g., at least about 65%, e.g., at least about 70%, e.g., at least about 75%, e.g., at least about 80%, e.g., at least about 85%, e.g., at least about 90%, e.g., at least about 95%, e.g., at least about 99%, of the cells of the population. In embodiments, including in any of the aforementioned aspects and embodiments, the indel is an indel listed in any of Figure 25, Table 15, Table 26, Table 27 or Table 37. In embodiments, in at least about 30%, e.g., least about 40%, e.g., at least about 50%, e.g., at least about 60%, e.g., at least about 70%, e.g., at least about 80%, e.g., at least about 90%, e.g., at least about 95%, e.g., at least about 96%, e.g., at least about 97%, e.g., at least about 98%, e.g., at least about 99%, of the cells of the population, the indel is an indel listed in any of Figure 25, Table 15, Table 26, Table 27 or Table 37. In embodiments, the three most frequently detected indels in said population of cells include the indels associated with any gRNA molecule listed in any of Figure 25, Table 15, Table 26, Table 27 or Table 37. In embodiments, the indel (or pattern of top indels) is as measured by next generation sequencing (NGS), e.g., as described in the art. In embodiments, including in any of the aforementioned aspects and embodiments, the invention provides a gRNA molecule, wherein when a CRISPR system (e.g., an RNP as described herein) including the gRNA molecule is introduced into a cell, no off-target indels are formed in said cell, e.g., as detectible by next generation sequencing and/or a nucleotide insertional assay, e.g., assayed in an HPCS cell, e.g., a CD34+ cell. In embodiments, including in any of the aforementioned aspects and embodiments, the invention provides a gRNA molecule, wherein when a CRISPR system (e.g., an RNP as described herein) including the gRNA molecule is introduced into a population of cells, no off-target indel is detected in more than about 5%, e.g., more than about 1%, e.g., more than about 0.1%, e.g., more than about 0.01%, of the cells of the population of cells, e.g., as detectible by next generation sequencing and/or a nucleotide insertional assay, e.g., assayed in a population of HPSC cells, e.g., a population of CD34+ cells.

In embodiments, including in any of the aforementioned aspects and embodiments, the invention provides a gRNA molecule, wherein when a CRISPR system (e.g., an RNP as described herein) including the gRNA molecule is introduced into a cell, expression of fetal hemoglobin is increased in said cell or its progeny, e.g., its erythroid progeny, e.g., its red blood cell progeny. In embodiments, expression of fetal hemoglobin is increased in said cell or its progeny, e.g., its erythroid progeny, e.g., its red blood cell progeny, by at least about 20%, e.g., at least about 30%, e.g., at least about 40%, e.g., at least about 50%, e.g., at least about 60%, e.g., at least about 70%, e.g., at least about 80%, e.g., at least about 90%, e.g., at least about 95%, e.g., at least about 96%, e.g., at least about 97%, e.g., at least about 98%, e.g., at least about 99%. In embodiments, said cell or its progeny, e.g., its erythroid progeny, e.g., its red blood cell progeny, produces at least about 6 picograms (e.g., at least about 7 picograms, at least about 8 picograms, at least about 9 picograms, at least about 10 picograms, or from about 8 to about 9 picograms, or from about 9 to about 10 picograms) fetal hemoglobin per cell. In embodiments, including in any of the aforementioned aspects and embodiments, the invention provides a gRNA molecule, wherein when a CRISPR system (e.g., an RNP as described herein) including the gRNA molecule is introduced into a cell, levels of fetal hemoglobin (e.g., gamma globin) mRNA are increased in said cell or its progeny, e.g., its erythroid progeny, e.g., its red blood cell progeny. In embodiments, including in any of the aforementioned aspects and embodiments, the invention provides a gRNA molecule, wherein when a CRISPR system (e.g., an RNP as described herein) including the gRNA molecule is introduced into a cell, expression of BCL11a mRNA is decreased in said cell or its progeny, e.g., its erythroid progeny, e.g., its red blood cell progeny. In embodiments, including in any of the aforementioned aspects and embodiments, the invention provides a gRNA molecule, wherein when a CRISPR system (e.g., an RNP as described herein) including the gRNA molecule is introduced into a cell, levels of BCL11a mRNA are decreased in said cell or its progeny, e.g., its erythroid progeny, e.g., its red blood cell progeny.

In any of the aforementioned aspects and embodiments that mention a cell, the cell is (or population of cells includes) a mammalian, primate, or human cell, e.g., is a human cell or population of human cells. In embodiments, the cell is (or population of cells includes) an HSPC, for example, is CD34+, for example, is CD34+CD90+. In embodiments, the cell (or population of cells) is autologous with respect to a patient to be administered said cell. In other embodiments, the cell (or population of cells) is allogeneic with respect to a patient to be administered said cell.

In another aspect, the invention provides a composition including: 1) one or more gRNA molecules (including a first gRNA molecule) described herein, for example, one or more gRNA molecules of any of the previous aspects and embodiments, and a Cas9 molecule, for example, as described herein; 2) one or more gRNA molecules (including a first gRNA molecule) described herein, for example, one or more gRNA molecules of any of the previous aspects and embodiments, and nucleic acid encoding a Cas9 molecule (described herein); 3) nucleic acid encoding one or more gRNA molecules

(including a first gRNA molecule) described herein, for example, one or more gRNA molecules of any of the previous aspects and embodiments, and a Cas9 molecule (described herein); 4) nucleic acid encoding one or more gRNA molecules (including a first gRNA molecule) described herein, for example, one or more gRNA molecules of any of the previous aspects and embodiments, and nucleic acid encoding a Cas9 molecule (described herein); or 5) any of 1) to 4), above, and a template nucleic acid; or 6) any of 1) to 4) above, and nucleic acid including sequence encoding a template nucleic acid.

In preferred embodiments, the invention provides a composition including a first gRNA molecule (e.g., described herein, e.g., a first gRNA molecule of any of the previous gRNA molecule aspects and embodiments), further including a Cas9 molecule (described herein).

In embodiments, the Cas9 molecule is an active or inactive *s. pyogenes* Cas9. In embodiments, the Cas9 molecule includes SEQ ID NO: 6611. In embodiments, the Cas9 molecule includes, e.g., consists of: (a) SEQ ID NO: 7821; (b) SEQ ID NO: 7822; (c) SEQ ID NO: 7823; (d) SEQ ID NO: 7824; (e) SEQ ID NO: 7825; (f) SEQ ID NO: 7826; (g) SEQ ID NO: 7827; (h) SEQ ID NO: 7828; (i) SEQ ID NO: 7829; (j) SEQ ID NO: 7830; or (k) SEQ ID NO: 7831.

In preferred embodiments, the first gRNA molecule and Cas9 molecule are present in a ribonuclear protein complex (RNP).

In embodiments, the invention provides a composition, e.g., a composition of any of the previous aspects and embodiments, further including a second gRNA molecule; a second gRNA molecule and a third gRNA molecule; or a second gRNA molecule, optionally, a third gRNA molecule, and, optionally, a fourth gRNA molecule, wherein the second gRNA molecule, the optional third gRNA molecule, and the optional fourth gRNA molecule are a gRNA molecule of a gRNA molecule described herein, e.g., a gRNA molecule of any of the previous gRNA molecule aspects and embodiments, and wherein each gRNA molecule of the composition is complementary to a different target sequence.

In embodiments, two or more of the first gRNA molecule, the second gRNA molecule, the optional third gRNA molecule, and the optional fourth gRNA molecule are complementary to target sequences within the same gene or region. In embodiments, the first gRNA molecule, the second gRNA molecule, the optional third gRNA molecule, and the optional fourth gRNA molecule are complementary to target sequences not more than 20000 nucleotides, not more than 10000 nucleotides, not more than 6000, not more than 5000 nucleotides, not more than 4000, not more than 1000 nucleotides, not more than 500 nucleotides, not more than 400 nucleotides, not more than 300 nucleotides, not more than 200 nucleotides, not more than 100 nucleotides, not more than 90 nucleotides, not more than 80 nucleotides, not more than 70 nucleotides, not more than 60

nucleotides, not more than 50 nucleotides, not more than 40 nucleotides, not more than 30 nucleotides, not more than 20 nucleotides or not more than 10 nucleotides apart.

In other embodiments, two or more of the first gRNA molecule, the second gRNA molecule, the optional third gRNA molecule, and the optional fourth gRNA molecule are complementary to target sequence within different genes or regions.

In embodiments, including in any of the aforementioned composition aspects and embodiments, the invention provides a composition including a first gRNA molecule and a second gRNA molecule, wherein the first gRNA molecule and second gRNA molecule are:

(a) independently selected from the gRNA molecules of gRNA molecule embodiment 4, and are complementary to different target sequences;

(b) independently selected from the gRNA molecules of gRNA molecule embodiment 5, and are complementary to different target sequences;

c) independently selected from the gRNA molecules of gRNA molecule embodiment 6, and are complementary to different target sequences; or

(d) independently selected from the gRNA molecules of gRNA molecule embodiment 7, and are complementary to different target sequences; or

(e) independently selected from the gRNA molecules of any of gRNA molecule embodiments 41-56, and are complementary to different target sequences.

In embodiments, including in any of the aforementioned composition aspects and embodiments, the invention provides a composition including a first gRNA molecule and a second gRNA molecule, wherein the first gRNA molecule and second gRNA molecule are:

(a) independently selected from the gRNA molecules of gRNA molecule embodiment 10, and are complementary to different target sequences; or

(b) independently selected from the gRNA molecules of gRNA molecule embodiment 11, and are complementary to different target sequences.

In embodiments, including in any of the aforementioned composition aspects and embodiments, the invention provides a composition, including a first gRNA molecule and a second gRNA molecule, wherein the first gRNA molecule and second gRNA molecule are:

(a) independently selected from the gRNA molecules of gRNA molecule embodiment 13, and are complementary to different target sequences; or

(b) independently selected from the gRNA molecules of gRNA molecule embodiment 14, and are complementary to different target sequences.

In embodiments, including in any of the aforementioned composition aspects and embodiments, the invention provides a composition, including a first gRNA molecule and a second gRNA molecule, wherein the first gRNA molecule and second gRNA molecule are:

(a) independently selected from the gRNA molecules of gRNA molecule embodiment 16, and are complementary to different target sequences;

(b) independently selected from the gRNA molecules of gRNA molecule embodiment 17, and are complementary to different target sequences;

(c) independently selected from the gRNA molecules of gRNA molecule embodiment 18, and are complementary to different target sequences; or

(d) independently selected from the gRNA molecules of any of gRNA molecule embodiments 57-68, and are complementary to different target sequences.

In embodiments, including in any of the aforementioned composition aspects and embodiments, the invention provides a composition, including a first gRNA molecule and a second gRNA molecule, wherein:

(1) the first gRNA molecule is: (a) selected from the gRNA molecules of gRNA molecule embodiment 4, (b) selected from the gRNA molecules of gRNA molecule embodiment 5, (c) selected from the gRNA molecules of gRNA molecule embodiment 6, (d) selected from the gRNA molecules of gRNA molecule embodiment 7, or (e) selected from the gRNA molecules of any of gRNA molecule embodiments 41-56; and

(2) the second gRNA molecule is: (a) selected from the gRNA molecules of gRNA molecule embodiment 10, or (b) selected from the gRNA molecules of gRNA molecule embodiment 11.

In embodiments, including in any of the aforementioned composition aspects and embodiments, the invention provides a composition, including a first gRNA molecule and a second gRNA molecule, wherein:

(1) the first gRNA molecule is: (a) selected from the gRNA molecules of gRNA molecule embodiment 4, (b) selected from the gRNA molecules of gRNA molecule embodiment 5, (c) selected from the gRNA molecules of gRNA molecule embodiment 6, (d) selected from the gRNA molecules of gRNA molecule embodiment 7, or (e) selected from the gRNA molecules of any of gRNA molecule embodiments 41-56; and

(2) the second gRNA molecule is: (a) selected from the gRNA molecules of gRNA molecule embodiment 13, (b) selected from the gRNA molecules of gRNA molecule embodiment 14.

In embodiments, including in any of the aforementioned composition aspects and embodiments, the invention provides a composition, including a first gRNA molecule and a second gRNA molecule, wherein:

(1) the first gRNA molecule is: (a) selected from the gRNA molecules of gRNA molecule embodiment 4, (b) selected from the gRNA molecules of gRNA molecule embodiment 5, (c) selected from the gRNA molecules of gRNA molecule embodiment 6, (d) selected from the gRNA molecules of gRNA molecule embodiment 7, or (e) selected from the gRNA molecules of any of gRNA molecule embodiments 41-56; and

(2) the second gRNA molecule is: (a) selected from the gRNA molecules of gRNA molecule embodiment 16, (b) selected from the gRNA molecules of gRNA molecule embodiment 17, (c) selected from the gRNA molecules of gRNA molecule embodiment 18, or (d) selected from the gRNA molecules of any of gRNA molecule embodiments 57-68.

In embodiments, including in any of the aforementioned composition aspects and embodiments, the invention provides a composition, including a first gRNA molecule and a second gRNA molecule, wherein:

(1) the first gRNA molecule is: (a) selected from the gRNA molecules of gRNA molecule embodiment 10, or (b) selected from the gRNA molecules of gRNA molecule embodiment 11; and

(2) the second gRNA molecule is: (a) selected from the gRNA molecules of gRNA molecule embodiment 13, (b) selected from the gRNA molecules of gRNA molecule embodiment 14.

In embodiments, including in any of the aforementioned composition aspects and embodiments, the invention provides a composition, including a first gRNA molecule and a second gRNA molecule, wherein:

(1) the first gRNA molecule is: (a) selected from the gRNA molecules of gRNA molecule embodiment 10, or (b) selected from the gRNA molecules of gRNA molecule embodiment 11; and

(2) the second gRNA molecule is: (a) selected from the gRNA molecules of gRNA molecule embodiment 16, (b) selected from the gRNA molecules of gRNA molecule embodiment 17, (c) selected from the gRNA molecules of gRNA molecule embodiment 18, or (d) selected from the gRNA molecules of any of gRNA molecule embodiments 57-68.

In embodiments, including in any of the aforementioned composition aspects and embodiments, the invention provides a composition, including a first gRNA molecule and a second gRNA molecule, wherein:

(1) the first gRNA molecule is: (a) selected from the gRNA molecules of gRNA molecule embodiment 13, (b) selected from the gRNA molecules of gRNA molecule embodiment 14; and

(2) the second gRNA molecule is: (a) selected from the gRNA molecules of gRNA molecule embodiment 16, (b) selected from the gRNA molecules of gRNA molecule embodiment 17, (c) selected from the gRNA molecules of gRNA molecule embodiment 18, or (d) selected from the gRNA molecules of any of gRNA molecule embodiments 57-68.

In embodiments, including in any of the aforementioned composition aspects and embodiments, the invention provides a composition, including a first gRNA molecule and a second gRNA molecule, wherein:

(1) the first gRNA molecule is: (a) selected from the gRNA molecules of gRNA molecule embodiment 16, (b) selected from the gRNA molecules of gRNA molecule embodiment 17, (c) selected from the gRNA molecules of gRNA molecule embodiment 18, or (d) selected from the gRNA molecules of any of gRNA molecule embodiments 57-68; and (2) the second gRNA molecule includes a targeting domain that is complementary to a target sequence of the beta globin gene; or

(1) the first gRNA molecule is: (a) selected from the gRNA molecules of gRNA molecule embodiment 4, (b) selected from the gRNA molecules of gRNA molecule embodiment 5, (c) selected from the gRNA molecules of gRNA molecule embodiment 6, (d) selected from the gRNA molecules of gRNA molecule embodiment 7, (e) selected from the gRNA molecules of any of gRNA molecule embodiments 41-56, (f) selected from the gRNA molecules of gRNA molecule embodiment 10, (g) selected from the gRNA molecules of gRNA molecule embodiment 11, (h) selected from the gRNA molecules of gRNA molecule embodiment 13, or (i) selected from the gRNA molecules of gRNA molecule embodiment 14; and (2) the second gRNA molecule includes a targeting domain that is complementary to a target sequence of the beta globin gene.

In embodiments, including in any of the aforementioned composition aspects and embodiments, the invention provides a composition, wherein the first gRNA molecule and the second gRNA molecule are independently selected from the gRNA molecules of any of gRNA molecule embodiments 41-68.

In embodiments of the composition, with respect to the gRNA molecule components of the composition, the composition consists of a first gRNA molecule and a second gRNA molecule.

In embodiments of the composition, each of said gRNA molecules is in a ribonuclear protein complex (RNP) with a Cas9 molecule described herein.

In embodiments, including in any of the aforementioned composition aspects and embodiments, the invention provides a composition, further including a template nucleic acid, wherein the template nucleic acid includes a nucleotide that corresponds to a nucleotide at or near the target sequence of the first gRNA molecule. In embodiments, the template nucleic acid includes nucleic acid encoding: (a) human beta globin, e.g., human beta globin including one or more of the mutations G16D, E22A and T87Q, or fragment thereof; or (b) human gamma globin, or fragment thereof.

In embodiments, including in any of the aforementioned composition aspects and embodiments, the composition is formulated in a medium suitable for electroporation, for example, suitable for electroporation into HSPC cells. In embodiments of the composition which include one or more gRNA molecules, each of said gRNA molecules is in a RNP with a Cas9 molecule described herein, and wherein each of said RNP is at a concentration of less than about 10uM, e.g., less than about 3uM, e.g., less than about 1uM, e.g., less than about 0.5uM, e.g., less than about 0.3uM, e.g., less than about 0.1uM.

In another aspect, the invention provides a nucleic acid sequence that encodes one or more gRNA molecules described herein, for example, a gRNA molecule of any of the previous aspects and embodiments. In embodiments, the nucleic acid includes a promoter operably linked to the sequence that encodes the one or more gRNA molecules, for example, a promoter recognized by an RNA polymerase II or RNA polymerase III, for example, a U6 promoter or an HI promoter. In embodiments, the nucleic acid further encodes a Cas9 molecule, for example, described herein, for example, a Cas9 molecule that includes (e.g., consists of) any of SEQ ID NO: 6611, SEQ ID NO: 7821, SEQ ID NO: 7822, SEQ ID NO: 7823, SEQ ID NO: 7824, SEQ ID NO: 7825, SEQ ID NO: 7826, SEQ ID NO: 7827, SEQ ID NO: 7828, SEQ ID NO: 7829, SEQ ID NO: 7830, or SEQ ID NO: 7831. In embodiments, the nucleic acid includes a promoter operably linked to the sequence that encodes a Cas9 molecule, for example, an EF-1 promoter, a CMV IE gene promoter, an EF-1α promoter, an ubiquitin C promoter, or a phosphoglycerate kinase (PGK) promoter.

In another aspect, the invention provides a vector including the nucleic acid of any of the previous nucleic acid aspects and embodiments. In embodiments, the vector is selected from the group consisting of a lentiviral vector, an adenoviral vector, an adeno-associated viral (AAV) vector, a herpes simplex virus (HSV) vector, a plasmid, a minicircle, a nanoplasmid, and an RNA vector.

In another aspect, the invention provides a method of altering a cell (e.g., a population of cells), (e.g., altering the structure (e.g., sequence) of nucleic acid) at or near a target sequence within said cell, including contacting (e.g., introducing into) said cell (e.g., population of cells) with: 1) one or more

gRNA molecules of any of the previous gRNA molecule aspects and embodiments and a Cas9 molecule (e.g., described herein); 2) one or more gRNA molecules of any of the previous gRNA molecule aspects and embodiments and nucleic acid encoding a Cas9 molecule (e.g., described herein); 3) nucleic acid encoding one or more gRNA molecules of any of the previous gRNA molecule aspects and embodiments and a Cas9 molecule (e.g., described herein); 4) nucleic acid encoding one or more gRNA molecules of any of the previous gRNA molecule aspects and embodiments and nucleic acid encoding a Cas9 molecule (e.g., described herein); 5) any of 1) to 4), above, and a template nucleic acid; 6) any of 1) to 4) above, and nucleic acid including sequence encoding a template nucleic acid; 7) the composition of any of the previous composition aspects and embodiments; or 8) the vector of any of the previous vector aspects and embodiments. In embodiments, the gRNA molecule or nucleic acid encoding the gRNA molecule, and the Cas9 molecule or nucleic acid encoding the Cas9 molecule, are formulated in a single composition. In other embodiments, the gRNA molecule or nucleic acid encoding the gRNA molecule, and the Cas9 molecule or nucleic acid encoding the Cas9 molecule, are formulated in more than one composition. In embodiments that include more than one composition, the more than one composition are delivered simultaneously or sequentially. In embodiments, the cell is an animal cell, for example, a mammalian, primate, or human cell. In embodiments, the cell, is a hematopoietic stem or progenitor cell (HSPC) (e.g., a population of HSPCs), for example, the cell is a CD34+ cell, for example, the cell is a CD34+CD90+ cell. In embodiments, the cell is disposed in a composition including a population of cells that has been enriched for CD34+ cells. In embodiments, the cell (e.g. population of cells) has been isolated from bone marrow, mobilized peripheral blood, or umbilical cord blood. In embodiments, the cell is autologous with respect to a patient to be administered said cell. In other embodiments, the cell is allogeneic with respect to a patient to be administered said cell. In embodiments, the method results in an indel at or near a genomic DNA sequence complementary to the targeting domain of the one or more gRNA molecules, for example, an indel shown on Figure 25, Table 15, Table 26, Table 27 or Table 37, for example an indel associated with the targeting domain of the gRNA molecule as shown in Figure 25, Table 15, Table 26, Table 27 or Table 37. In embodiments, the indel is an insertion or deletion of less than about 40 nucleotides, e.g., less than 30 nucleotides, e.g., less than 20 nucleotides, e.g., less than 10 nucleotides, for example, is a single nucleotide deletion. In embodiments, the method results in a population of cells wherein at least about 50%, e.g., at least about 60%, e.g., at least about 70%, e.g., at least about 80%, e.g., at least about 90% (e.g., at least about 95%, at least about 96%, at least about 97%, at least about 98%, or at least about 99%) of the cells of the population have been altered, e.g., include an indel. In embodiments, the method (e.g., the method performed on a population of cells, e.g., described herein) results in a cell (e.g., population of cells) that is capable of differentiating into a differentiated cell of an erythroid lineage (e.g., a red blood cell), and wherein said differentiated cell exhibits an increased level of fetal hemoglobin, e.g., relative to an unaltered cell (e.g., population of cells). In

embodiments, the method results in a population of cells that is capable of differentiating into a population of differentiated cells, e.g., a population of cells of an erythroid lineage (e.g., a population of red blood cells), and wherein said population of differentiated cells has an increased fraction of F cells (e.g., at least about 15%, at least about 20% , at least about 25%, at least about 30%, or at least about 40% higher) e.g., relative to a population of unaltered cells. In embodiments, the method results in a cell that is capable of differentiating into a differentiated cell, e.g., a cell of an erythroid lineage (e.g., a red blood cell), and wherein said differentiated cell produces at least about 6 picograms (e.g., at least about 7 picograms, at least about 8 picograms, at least about 9 picograms, at least about 10 picograms, or from about 8 to about 9 picograms, or from about 9 to about 10 picograms) fetal hemoglobin per cell. In embodiments, the method is performed ex vivo. In other embodiments, the method is performed in vivo.

In another aspect, the invention provides a cell, altered by the method of altering a cell of any of the previous method aspects and embodiments.

In another aspect, the invention provides a cell, obtainable the method of altering a cell of any of the previous method aspects and embodiments.

In another aspect, the invention provides a cell, including a first gRNA molecule, e.g., described herein, e.g., of any of the previous gRNA molecule aspects and embodiments, or a composition, e.g., described herein, e.g., of any of the previous composition aspects and embodiments, a nucleic acid, e.g., described herein, e.g., of any of the previous nucleic acid aspects and embodiments, or a vector , e.g., described herein, e.g., of any of the previous vector aspects and embodiments. In embodiments, the cell further includes a Cas9 molecule, e.g., described herein, for example, a Cas9 molecule that includes, e.g., consists of, any of SEQ ID NO: 6611, SEQ ID NO: 7821, SEQ ID NO: 7822, SEQ ID NO: 7823, SEQ ID NO: 7824, SEQ ID NO: 7825, SEQ ID NO: 7826, SEQ ID NO: 7827, SEQ ID NO: 7828, SEQ ID NO: 7829, SEQ ID NO: 7830, or SEQ ID NO: 7831. In embodiments, the cell includes, has included, or will include a second gRNA molecule, e.g., described herein, e.g., of any of the previous gRNA molecule aspects and embodiments, or a nucleic acid encoding a second gRNA molecule, e.g., described herein, e.g., of any of the previous gRNA molecule aspects and embodiments, wherein the first gRNA molecule and second gRNA molecule include nonidentical targeting domains. In embodiments, expression of fetal hemoglobin is increased in said cell or its progeny (e.g., its erythroid progeny, e.g., its red blood cell progeny) relative to a cell or its progeny of the same cell type that has not been modified to include a gRNA molecule. In embodiments, the cell is capable of differentiating into a differentiated cell, e.g., a cell of an erythroid lineage (e.g., a red blood cell), and wherein said differentiated cell exhibits an increased level of fetal hemoglobin, e.g., relative to a cell of the same type that has not been modified to include a gRNA molecule. In embodiments, the differentiated cell (e.g., cell of an erythroid lineage, e.g., red blood cell) produces at

least about 6 picograms (e.g., at least about 7 picograms, at least about 8 picograms, at least about 9 picograms, at least about 10 picograms, or from about 8 to about 9 picograms, or from about 9 to about 10 picograms) fetal hemoglobin, e.g., relative to a cell of the same type that has not been modified to include a gRNA molecule. In embodiments, the cell has been contacted, e.g., contacted ex vivo, with a stem cell expander, e.g., described herein, e.g., a stem cell expander that is compound 1, compound 2, compound 3, compound 4, or a combination thereof (e.g., compound 1 and compound 4), for example, a stem cell expander that is compound 4. In embodiments, including in any of the aforementioned aspects and embodiments, the cell includes an indel at or near a genomic DNA sequence complementary to the targeting domain of the gRNA molecule (as described herein, e.g., a gRNA molecule of any of the aforementioned aspects and embodiments) introduced therein, for example, an indel shown on Figure 25, Table 15, Table 26, Table 27 or Table 37, for example an indel shown on Figure 25, Table 15, Table 26, Table 27 or Table 37 that is associated with the gRNA molecule (as described herein, e.g., a gRNA molecule of any of the aforementioned aspects and embodiments) introduced therein. In embodiments, the indel is an insertion or deletion of less than about 40 nucleotides, e.g., less than 30 nucleotides, e.g., less than 20 nucleotides, e.g., less than 10 nucleotides, for example, the indel is a single nucleotide deletion. In embodiments, including in any of the aforementioned cell aspects and embodiments, the cell is an animal cell, for example, the cell is a mammalian, a primate, or a human cell. In embodiments, including in any of the aforementioned cell aspects and embodiments, the cell is a hematopoietic stem or progenitor cell (HSPC) (e.g., a population of HSPCs), for example, the cell is a CD34+ cell, for example, the cell is a CD34+CD90+ cell. In embodiments, including in any of the aforementioned cell aspects and embodiments, the cell (e.g. population of cells) has been isolated from bone marrow, mobilized peripheral blood, or umbilical cord blood. In embodiments, including in any of the aforementioned cell aspects and embodiments, the cell is autologous with respect to a patient to be administered said cell. In embodiments, the cell is allogeneic with respect to a patient to be administered said cell.

In another aspect, the invention provides a population of cells including the cell of any of the previous cell aspects and embodiments. In embodiments, at least about 50%, e.g., at least about 60%, e.g., at least about 70%, e.g., at least about 80%, e.g., at least about 90% (e.g., at least about 95%, at least about 96%, at least about 97%, at least about 98%, or at least about 99%) of the cells of the population are a cell according to any of the previous cell aspects and embodiments. In embodiments, the population of cells is capable of differentiating into a population of differentiated cells, e.g., a population of cells of an erythroid lineage (e.g., a population of red blood cells), and wherein said population of differentiated cells has an increased fraction of F cells (e.g., at least about 15%, at least about 20% , at least about 25%, at least about 30%, or at least about 40% higher) e.g., relative to a population of unmodified cells of the same type. In embodiments, the F cells of the population of differentiated cells produce an average of at least about 6 picograms (e.g., at least about 7 picograms,

at least about 8 picograms, at least about 9 picograms, at least about 10 picograms, or from about 8 to about 9 picograms, or from about 9 to about 10 picograms) fetal hemoglobin per cell. In embodiments, the population includes: 1) at least 1e6 CD34+ cells/kg body weight of the patient to whom the cells are to be administered; 2) at least 2e6 CD34+ cells/kg body weight of the patient to whom the cells are to be administered; 3) at least 3e6 CD34+ cells/kg body weight of the patient to whom the cells are to be administered; 4) at least 4e6 CD34+ cells/kg body weight of the patient to whom the cells are to be administered; or 5) from 2e6 to 10e6 CD34+ cells/kg body weight of the patient to whom the cells are to be administered. In embodiments, at least about 40%, e.g., at least about 50%, (e.g., at least about 60%, at least about 70%, at least about 80%, or at least about 90%) of the cells of the population are CD34+ cells. In embodiments, at least about 10%, e.g., at least about 15%, e.g., at least about 20%, e.g., at least about 30% of the cells of the population are CD34+CD90+ cells. In embodiments, the population of cells is derived from bone marrow, peripheral blood (e.g., mobilized peripheral blood), umbilical cord blood, or induced pluripotent stem cells (iPSCs). In a preferred embodiment, the population of cells is derived from bone marrow. In embodiments, the population of cells includes, e.g., consists of, mammalian cells, e.g., human cells. In embodiments, the population of cells is autologous relative to a patient to which it is to be administered. In other embodiments, the population of cells is allogeneic relative to a patient to which it is to be administered.

In another aspect, the invention provides a composition including a cell of any of the previous cell aspects and embodiments, or the population of cells of any of previous population of cell aspects and embodiments. In embodiments, the composition includes a pharmaceutically acceptable medium, e.g., a pharmaceutically acceptable medium suitable for cryopreservation.

In another aspect, the invention provides a method of treating a hemoglobinopathy, including administering to a patient a cell of any of the previous cell aspects and embodiments, a population of cells of any of previous population of cell aspects and embodiments, or a composition of any of the previous composition aspects and embodiments. In embodiments, the hemoglobinopathy is a thalassemia, for example, beta-thalassemia, or sickle cell disease.

In another aspect, the invention provides a method of increasing fetal hemoglobin expression in a mammal, including administering to a patient a cell of any of the previous cell aspects and embodiments, a population of cells of any of previous population of cell aspects and embodiments, or a composition of any of the previous composition aspects and embodiments.

In another aspect, the invention provides a method of preparing a cell (e.g., a population of cells) including: (a) providing a cell (e.g., a population of cells) (e.g., a HSPC (e.g., a population of HSPCs)); (b) culturing said cell (e.g., said population of cells) ex vivo in a cell culture medium including a stem cell expander; and (c) introducing into said cell a first gRNA molecule (e.g.,

described herein, for example, a gRNA molecule of any of the previous gRNA molecule aspects and embodiments), a nucleic acid molecule encoding a first gRNA molecule (e.g., described herein, for example, a gRNA molecule of any of the previous gRNA molecule aspects and embodiments), a composition (e.g., described herein, for example, a composition of any of the previous composition aspects and embodiments), a nucleic acid (e.g., described herein, for example, a nucleic acid of any of the previous nucleic acid aspects and embodiments), or a vector (e.g., described herein, for example, a vector of any of the previous vector aspects and embodiments). In embodiments of said method, after said introducing of step (c), said cell (e.g., population of cells) is capable of differentiating into a differentiated cell (e.g., population of differentiated cells), e.g., a cell of an erythroid lineage (e.g., population of cells of an erythroid lineage), e.g., a red blood cell (e.g., a population of red blood cells), and wherein said differentiated cell (e.g., population of differentiated cells) produces increased fetal hemoglobin, e.g., relative to the same cells which have not been subjected to step (c). In embodiments, including in any of the aforementioned method aspects and embodiments, the stem cell expander is compound 1, compound 2, compound 3, compound 4 or a combination thereof (e.g., compound 1 and compound 4), for example, is compound 4. In embodiments, including in any of the aforementioned method aspects and embodiments, the cell culture medium includes thrombopoietin (Tpo), Flt3 ligand (Flt-3L), and human stem cell factor (SCF). In embodiments, including in any of the aforementioned method aspects and embodiments, the cell culture medium further includes human interleukin-6 (IL-6). In embodiments, including in any of the aforementioned method aspects and embodiments, the cell culture medium includes thrombopoietin (Tpo), Flt3 ligand (Flt-3L), and human stem cell factor (SCF) each at a concentration ranging from about 10 ng/mL to about 1000 ng/mL, for example, each at a concentration of about 50 ng/mL, e.g., at a concentration of 50 ng/mL. In embodiments, including in any of the aforementioned method aspects and embodiments, the cell culture medium includes human interleukin-6 (IL-6) at a concentration ranging from about 10 ng/mL to about 1000 ng/mL, for example, at a concentration of about 50 ng/mL, e.g., at a concentration of 50 ng/mL. In embodiments, including in any of the aforementioned method aspects and embodiments, the cell culture medium includes a stem cell expander at a concentration ranging from about 1 nM to about 1 mM, for example, at a concentration ranging from about 1 uM to about 100 uM, for example, .at a concentration ranging from about 50 uM to about 75 uM, for example, at a concentration of about 50 uM, e.g., at a concentration of 50 uM, or at a concentration of about 75 uM, e.g., at a concentration of 75 uM. In embodiments, including in any of the aforementioned method aspects and embodiments, the culturing of step (b) includes a period of culturing before the introducing of step (c), for example, the period of culturing before the introducing of step (c) is at least 12 hours, e.g., is for a period of about 1 day to about 3 days, e.g., is for a period of about 1 day to about 2 days, e.g., is for a period of about 2 days. In embodiments, including in any of the aforementioned method aspects and embodiments, the culturing of step (b) includes a period of culturing after the introducing of step (c), for example, the period of culturing after the introducing of step (c) is at least 12 hours, e.g., is for

a period of about 1 day to about 10 days, e.g., is for a period of about 1 day to about 5 days, e.g., is for a period of about 2 days to about 4 days, e.g., is for a period of about 2 days or is for a period of about 3 days or is for a period of about 4 days. In embodiments, including in any of the aforementioned method aspects and embodiments, the population of cells is expanded at least 4-fold, e.g., at least 5-fold, e.g., at least 10-fold, e.g., relative to cells which are not cultured according to step (b). In embodiments, including in any of the aforementioned method aspects and embodiments, the introducing of step (c) includes an electroporation, for example, an electroporation that includes 1 to 5 pulses, e.g., 1 pulse, and wherein each pulse is at a pulse voltage ranging from 700 volts to 2000 volts and has a pulse duration ranging from 10 ms to 100 ms. In embodiments, including in any of the aforementioned method aspects and embodiments, the electroporation includes, for example, consists of, 1 pulse. In embodiments, including in any of the aforementioned method aspects and embodiments, the pulse voltage ranges from 1500 to 1900 volts, e.g., is 1700 volts. In embodiments, including in any of the aforementioned method aspects and embodiments, the pulse duration ranges from 10 ms to 40 ms, e.g., is 20 ms. In embodiments, including in any of the aforementioned method aspects and embodiments, the cell (e.g., population of cells) provided in step (a) is a human cell (e.g., a population of human cells). In embodiments, including in any of the aforementioned method aspects and embodiments, the cell (e.g., population of cells) provided in step (a) is isolated from bone marrow, peripheral blood (e.g., mobilized peripheral blood), umbilical cord blood, or induced pluripotent stem cells (iPSCs), preferably bone marrow. In embodiments, including in any of the aforementioned method aspects and embodiments, the cell (e.g., population of cells) provided in step (a) is isolated from bone marrow, e.g., is isolated from bone marrow of a patient suffering from a hemoglobinopathy. In embodiments, including in any of the aforementioned method aspects and embodiments, the population of cells provided in step (a) is enriched for HSPCs, e.g., CD34+ cells. In embodiments, including in any of the aforementioned method aspects and embodiments, subsequent to the introducing of step (c), the cell (e.g., population of cells) is cryopreserved. In embodiments, including in any of the aforementioned method aspects and embodiments, subsequent to the introducing of step (c), the cell (e.g., population of cells) includes an indel at or near a genomic DNA sequence complementary to the targeting domain of the first gRNA molecule, for example, an indel shown on Figure 25, Table 15, Table 26, Table 27 or Table 37, for example an indel shown in Figure 25, Table 15, Table 26, Table 27 or Table 37 as associated with the first gRNA molecule. In embodiments, including in any of the aforementioned method aspects and embodiments, after the introducing of step (c), at least about 50%, at least about 60%, at least about 70%, at least about 80%, at least about 90%, at least about 95%, at least about 96%, at least about 97%, at least about 98% or at least about 99% of the cells of the population of cells include an indel at or near a genomic DNA sequence complementary to the targeting domain of the first gRNA molecule, for example, an indel shown on Figure 25, Table 15, Table 26, Table 27 or Table 37, for example an indel shown in Figure 25, Table 15, Table 26, Table 27 or Table 37 as associated with the first gRNA molecule.

In another aspect, the invention provides a cell (e.g., population of cells), obtainable by the method of preparing a cell of any of the previous aspects and embodiments. In another aspect, the invention provides a method of treating a hemoglobinopathy (for example a thalassemia (e.g., beta-thalassemia) or sickle cell disease), including administering to a human patient a composition including said cell (e.g., population of cells). In another aspect, the invention provides a method of increasing fetal hemoglobin expression in a human patient, including administering to said human patient a composition including said cell (e.g., population of cells). In embodiments, the human patient is administered a composition including at least about 1e6 cells (e.g., CD34+ cells, e.g., cells obtainable by a method of preparing a cell of any of the previous aspects and embodiments) per kg body weight of the human patient, e.g., at least about 1e6 CD34+ cells obtainable by a method of preparing a cell of any of the previous aspects and embodiments per kg body weight of the human patient. In embodiments, the human patient is administered a composition including at least about 2e6 cells (e.g., CD34+ cells, e.g., cells obtainable by a method of preparing a cell of any of the previous aspects and embodiments) per kg body weight of the human patient, e.g., at least about 2e6 CD34+ cells obtainable by a method of preparing a cell of any of the previous aspects and embodiments per kg body weight of the human patient. In embodiments, the human patient is administered a composition including from about 2e6 to about 10e6cells (e.g., CD34+ cells, e.g., cells obtainable by a method of preparing a cell of any of the previous aspects and embodiments) per kg body weight of the human patient, e.g., at least about 2e6 to about 10e6 CD34+ cells obtainable by a method of preparing a cell of any of the previous aspects and embodiments per kg body weight of the human patient.

In another aspect, the invention provides a gRNA molecule described herein, for example, a gRNA molecule of any of the previous gRNA molecule aspects and embodiments, a composition described herein, for example, a composition of any of the previous composition aspects and embodiments, a nucleic acid described herein, for example, a nucleic acid of any of the previous nucleic acid aspects and embodiments, a vector described herein, for example, a vector of any of the previous vector aspects and embodiments, a cell described herein, for example, a cell of any of the previous cell aspects and embodiments, or a population of cells described herein, for example, a population of cells of any of the previous population of cell aspects and embodiments, for use as a medicament.

In another aspect, the invention provides a gRNA molecule described herein, for example, a gRNA molecule of any of the previous gRNA molecule aspects and embodiments, a composition described herein, for example, a composition of any of the previous composition aspects and embodiments, a nucleic acid described herein, for example, a nucleic acid of any of the previous nucleic acid aspects and embodiments, a vector described herein, for example, a vector of any of the previous vector aspects and embodiments, a cell described herein, for example, a cell of any of the previous cell aspects and embodiments, or a population of cells described herein, for example, a population of cells

of any of the previous population of cell aspects and embodiments, for use in the manufacture of a medicament.

In another aspect, the invention provides a gRNA molecule described herein, for example, a gRNA molecule of any of the previous gRNA molecule aspects and embodiments, a composition described herein, for example, a composition of any of the previous composition aspects and embodiments, a nucleic acid described herein, for example, a nucleic acid of any of the previous nucleic acid aspects and embodiments, a vector described herein, for example, a vector of any of the previous vector aspects and embodiments, a cell described herein, for example, a cell of any of the previous cell aspects and embodiments, or a population of cells described herein, for example, a population of cells of any of the previous population of cell aspects and embodiments, for use in the treatment of a disease.

In another aspect, the invention provides a gRNA molecule described herein, for example, a gRNA molecule of any of the previous gRNA molecule aspects and embodiments, a composition described herein, for example, a composition of any of the previous composition aspects and embodiments, a nucleic acid described herein, for example, a nucleic acid of any of the previous nucleic acid aspects and embodiments, a vector described herein, for example, a vector of any of the previous vector aspects and embodiments, a cell described herein, for example, a cell of any of the previous cell aspects and embodiments, or a population of cells described herein, for example, a population of cells of any of the previous population of cell aspects and embodiments, for use in the treatment of a disease, wherein the disease is a hemoglobinopathy, for example a thalassemia (e.g., beta-thalassemia) or sickle cell disease.

BRIEF DESCRIPTION OF THE DRAWINGS

Figure 1: Cas9 editing of the Bcl11a +58 erythroid enhancer region. Fraction of editing detected by NGS in HEK-293 Cas9GFP 24h post-delivery of crRNA targeting the +58 enhancer region and trRNA by lipofection. Each dot indicates a different crRNA, the trRNA was held constant. Genomic coordinates indicate location on Chromosome 2, e.g., in reference to hg38. (n=1)

Figure 2: Cas9 editing of the Bcl11a +62 erythroid enhancer region. Fraction of editing detected by NGS in HEK-293 Cas9GFP 24h post-delivery of crRNA targeting the +62 enhancer region and trRNA by lipofection. Each dot indicates a different crRNA, the trRNA was held constant. Genomic coordinates indicate location on Chromosome 2, e.g., in reference to hg38. (n=1)

Figure 3. Gating strategy for selection of cells after introduction of the Cas9 editing system.

Figure 4. Agarose gel electrophoresis of gene fragments from Cas9 editing system-treated CD34+ cells (shown are both CD34+CD90+ and CD34+CD90- cell populations, together with reference

unsorted cells). The upper band represents uncleaved homoduplex DNA and the lower bands indicate cleavage products resulting from heteroduplex DNA. The far left lane is a DNA ladder. Band intensity was calculated by peak integration of unprocessed images by ImageJ software. % gene modification (indel) was calculated as follows: % gene modification = 100 x (1 – (1- fraction cleaved)$^{1/2}$), and is indicated below each corresponding lane of the gel.

Figure 5. Erythroid enhancer region showing the sites of genomic DNA targeted by sgRNA molecules comprising targeting domains complimentary to the underlined nucleotides. Figure discloses SEQ ID NO: 2841.

Figure 6A/6B. NGS results for indel formation by sgEH1 (CR00276) (A) or sgEH2 (CR00275) (B) in CD34+ HSC cells. Insertions are in uppercase. Deletions are indicated by a dashed line. Regions of microhomology near the cutting site are highlighted in bold underline. Figure 6A discloses SEQ ID NOS 2842-2854 and Figure 6B discloses SEQ ID NOS 2855-2867, all respectively, in order of appearance.

Figure 6C/6D. NGS results for indel formation by sgEH8 (CR00273) (C) or sgEH9 (CR00277) (D) in CD34+ HSC cells. Insertions are in uppercase. Deletions are indicated by a dashed line. Regions of microhomology near the cutting site are highlighted in bold underline. Figure 6C discloses SEQ ID NOS 2868-2880 and Figure 6D discloses SEQ ID NOS 2881-2893, all respectively, in order of appearance.

Figure 7. NGS results and indel pattern formation across multiple donors for g7, g8 and g2. The sequences of the top 3 indels from two biological replicate experiments using g7 and g8 were identical, and the sequence of the top 3 indels using g2 were identical to those from a previous experiment. Figure discloses SEQ ID NOS 2894-2911, respectively, in order of appearance.

Figure 8. NGS results and indel pattern formation using a modified gRNA scaffold (BC). The sequences of the top 3 indels from these experiments are identical to those formed when using the standard gRNA scaffold. Figure discloses SEQ ID NOS 2912-2921, respectively, in order of appearance.

Figure 9. Comparison of indel pattern across different delivery methods. AVG % refers to the % of NGS reads exhibiting the indel indicated (Average of 2 experiments). Figure discloses SEQ ID NOS 2922-2946, respectively, in order of appearance.

Figure 10. Indel formation by co-introduction of g7 gRNA and g8 gRNA with either a non-extended flagpole region ("reg") or with a first flagpole extension and first tracr extension ("BC"). PAM sequences for the two gRNAs are boxed. Figure discloses SEQ ID NOS 2947-2955, respectively, in order of appearance.

Figure 11: Top gRNA sequences directed to +58 enhancer region of BCL11a gene in CD34+ cells, as measured by NGS (n=3).

Figure 12: Top gRNA sequences directed to +62 enhancer region of BCL11a gene in CD34+ cells, as measured by NGS (n=3).

Figure 13: Predicted excision sizes when 2 gRNA molecules targeting the BCL11a +62 enhancer locus are introduced into HEK293_Cas9 cells, when either CR00187 (light grey bars) or CR00202 (dark grey bars) is held constant and co-inserted into the cells with a second gRNA molecule including the targeting domain of the gRNA indicated.

Figure 14: Excision of genomic DNA within the +62 enhancer of BCL11a by addition of gRNA molecules including the targeting domain of CR00187 and the second gRNA molecule indicated in the graph. Stars (*) indicate excision observed at a frequency greater than 30%; Carats (^) indicate excision observed at a lower frequency (<30%). Those predicted excision products resulting in a fragment less than 50 nt could not be distinguished.

Figure 15: Excision of genomic DNA within the +62 enhancer of BCL11a by addition of gRNA molecules including the targeting domain of CR00202 and the second gRNA molecule indicated in the graph. Stars (*) indicate excision observed at a frequency greater than 30%; Carats (^) indicate excision observed at lower frequency (<30%).

Figure 16: % indel formation by 192 gRNA molecules targeted to the French HPFH region (*Sankaran VG et al. A functional element necessary for fetal hemoglobin silencing. NEJM (2011) 365:807-814.*)

Figure 17. Experimental scheme of Cas9:gRNA ribonucleoprotein (Cas9-RNP) delivery to primary human CD34+ HSPC for genome editing, followed by genetic and phenotypic characterization.

Figure 18. Cell viability following mock electroporation or electroporation of Cas9-RNP complexes into CD34+ HSPC. The HSPC were expanded *in vitro* for 48 hours after electroporation of RNP complexes and the cell viability monitored and percent viability determined. The names of gRNAs used to make RNP complexes are shown on x- axis and the corresponding cell viabilities on y-axis. The CRxxxx identifier indicates the targeting domain of the gRNA molecule.

Figure 19. Mismatch detection using T7 endonuclease assay. Human HSC were electroporated to deliver RNP complexes to introduce indels into +58 DHS region of BCL11A erythroid enhancer by NHEJ. PCR amplicons spanning the target region was subjected to the T7E1 assay and the resulting fragments analyzed by 2% agarose gel electrophoresis. Regions of +58 erythroid enhancer BCL11A were disrupted by both guide RNA formats (dual guide RNA – black; single guide RNA –gray (bottom graph and g7BCL11a-BC(1) and g7BCL11A-BC(2) from top graph)). The intensities of

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Figure 21. Colony forming cell (CFC) unit assay showing colony number and types of colonies observed for five select gRNAs. The HSPCs genome edited at the +58 erythroid enhancer were plated in methylcellulose and clonal colonies classified and counted based on the number and types of mature cells using morphological and phenotypic criteria using STEMvision. The colonies were classified into colony forming unit-erythroid (CFU-E), burst forming unit-erythroid (BFU-E), colony-forming unit - granulocyte/macrophage (CFU-GM) and colony-forming unit - granulocyte/erythrocyte/macrophage/megakaryocyte (CFU-GEMM).

Figure 22. Kinetics of cell division during erythroid differentiation. Total number of cells determined on day 0, 7, 14 and 21 during erythroid differentiation and the fold cell expansion calculated.

Figure 23. BCL11A, gamma and beta- globin mRNA levels in genome edited and erythroid differentiated HSC. Relative mRNA expression of BCL11A, gamma- and beta-globin chains in unilineage erythroid cultures were quantified by real time PCR. Transcript levels were normalized against human GAPDH transcript levels.

Figure 24A. Efficient editing of HSC obtained with dual gRNA/cas9 system for disruption of BCL11a enhancer (+58) resulted in high levels of induction of HbF. The HSC 48 hours after electroporation were subjected to *in vitro* erythroid differentiation and HbF expression was measured. The percent of HbF positive cells (F-cells) was monitored by FACS analysis at days 7, 14 and 21. Data shown in this figure was generated with dgRNA systems where the dgRNA included the indicated targeting domain.

Figure 24B. Efficient editing of HSC obtained with sgRNA/cas9 system for disruption of BCL11a enhancer (+58) resulted in high levels of induction of HbF. The HSC 48 hours after electroporation were subjected to *in vitro* erythroid differentiation and HbF expression was measured. The percent of HbF positive cells (F-cells) was monitored by FACS analysis at days 7, 14 and 21. Data shown in this figure was generated with sgRNA systems where the sgRNA included the indicated targeting domain.

Figure 25: Indel pattern produced in HSPCs by gRNAs including the indicated targeting domain. Figure discloses SEQ ID NOS 2956-2968, respectively, in order of appearance.

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Figure 26A: Phenotyping of edited and unedited cultures in CD34+ cell expansion medium by cell surface marker staining. All gRNA molecules were tested in the dgRNA format. The Tracr used was SEQ ID NO: 7808, and the crRNA had the following format and sequence with 2'O-Methyl (m) and Phosphorothioate Bond (*) modifications indicated: mN*mN*mN*rNrNrNrNrNrNrNrNrNrNrNrNrNrNrNrGrUrUrUrUrArGrArGrCrUrArU*mG*mC*mU (SEQ ID NO: 2003), where N's are the residues of the indicated targeting domain. Shown are representative dot plots showing the fluorescence of cells stained with each antibody panel or corresponding isotype controls as described in Materials and Methods. Cells shown were pre-gated on the viable cell

Figure 26A: Phenotyping of edited and unedited cultures in CD34+ cell expansion medium by cell surface marker staining. All gRNA molecules were tested in the dgRNA format. The Tracr used was SEQ ID NO: 7808, and the crRNA had the following format and sequence with 2'O-Methyl (m) and Phosphorothioate Bond (*) modifications indicated:
mN*mN*mN*rNrNrNrNrNrNrNrNrNrNrNrNrNrNrNrGrUrUrUrUrArGrArGrCrUrArU*mG*mC*mU (SEQ ID NO: 2003), where N's are the residues of the indicated targeting domain. Shown are representative dot plots showing the fluorescence of cells stained with each antibody panel or corresponding isotype controls as described in Materials and Methods. Cells shown were pre-gated on the viable cell population by forward and side scatter properties and DAPI (4',6-Diamidino-2-Phenylindole) discrimination. The percentage of each cell population named at the top of the plot was determined by the gate indicated by the bold lined box.

Figure 26B: Phenotyping of edited and unedited cultures in CD34+ cell expansion medium by cell surface marker staining. All gRNA molecules were tested in the dgRNA format. The Tracr used was SEQ ID NO: 7808, and the crRNA had the following format and sequence with 2'O-Methyl (m) and Phosphorothioate Bond (*) modifications indicated:
mN*mN*mN*rNrNrNrNrNrNrNrNrNrNrNrNrNrNrNrGrUrUrUrUrArGrArGrCrUrArU*mG*mC*mU (SEQ ID NO: 2004), where N's are the residues of the indicated targeting domain. Shown is the percentage of each named cell population in edited and unedited cultures. Targeting domain of the edited cultures is as indicated.

Figure 27. % F cells in erythrocytes differentiated from populations of CD34+ cells edited with RNPs comprising dgRNAs targeting two sites within the HPFH region. "g2" is the positive control (targeting domain to a coding region of BCL11a gene); "cntrl" is negative control (introduction of Cas9 only).

Figure 28A. % Editing as determined by NGS in CD34+ HSPCs at day 2 following electroporation of RNP comprising the indicated dgRNA (unmod or modified as indicated). Controls include dgRNA comprising the targeting domain of CR00317 unmodified (CR00317-m), or electroporation in buffer only (No Cas9 or gRNA; "Mock").

Figure 28B. % Editing as determined by NGS in CD34+ HSPCs at day 2 following electroporation of RNP comprising the indicated dgRNA (unmod or modified as indicated). Controls include electroporation in buffer only (No Cas9 or gRNA; "Mock").

Figure 29. % Editing as determined by NGS in CD34+ HSPCs at day 2 following electroporation of RNP comprising the indicated sgRNA (unmod or modified as indicated. In each case the number corresponds to the CRxxxxxx identifier of the targeting domain, for example, Unmod sg312 refers to unmodified sgRNA comprising the targeting domain of CR00312). Controls include electroporation

of Cas9 protein only ("Cas9"), electroporation with buffer only ("mock"), or with no electroporation ("WT").

Figure 30A. Normalized % Erythrocytes (% F cells in "Mock" subtracted) that are HbF+ after electroporation of CD34+ HSPCs with RNP comprising the indicated dgRNA (unmod or modified as indicated) and then induced to differentiate by culture in erythroid differentiation medium. Controls include electroporation of buffer only ("mock").

Figure 30B. Normalized % Erythrocytes (% F cells in "Mock" subtracted) that are HbF+ after electroporation of CD34+ HSPCs with RNP comprising the indicated dgRNA (unmod or modified as indicated) and then in induced to differentiate by culture in erythroid differentiation medium. Controls include electroporation of buffer only ("mock").

Figure 31. Normalized % Erythrocytes (% F cells in "Mock" subtracted) that are HbF+ after electroporation of CD34+ HSPCs with RNP comprising the indicated sgRNA (unmod or modified as indicated. In each case the number corresponds to the CRxxxxxx identifier of the targeting domain, for example, Unmod sg312 refers to unmodified sgRNA comprising the targeting domain of CR00312) and then in induced to differentiate by culture in erythroid differentiation medium. Controls include electroporation of Cas9 protein and tracr only ("Cas9 + TracRNA only"), electroporation with buffer only ("Cells only + Pulse"), or with no electroporation ("Cells only no pulse").

Figure 32. Fold total cell expansion in culture at day 14 after erythroid differentiation after electroporation of RNP comprising the indicated sgRNA (in each case, the number corresponds to the CRxxxxxx identifier of the targeting domain, for example, Unmod sg312 refers to unmodified sgRNA comprising the targeting domain of CR00312) into CD34+ cells. Controls include electroporation of Cas9 protein and tracr only ("Cas9 + TracRNA only"), electroporation with buffer only ("Cells only + Pulse"), or with no electroporation ("Cells only no pulse").

Figure 33. Assessment of potential off-target sites cleaved by Cas9 directed by dgRNA molecules targeting the BCL11a enhancer region. Triangles represent the on-target site while open circles represent a potential off-target site for each guide RNA tested.

Figure 34. Editing efficiency at targeted B2M locus in CD34+ hematopoietic stem cells by different Cas9 variants, as evaluated by NGS and Flow cytometry. NLS = SV40 NLS; His6 or His8 refers to 6 or 8 histidine residues, respectively (SEQ ID NOS 2969 and 2670, respectively); TEV = tobacco etch virus cleavage site; Cas9 = wild type S. pyogenes Cas9 – mutations or variants are as indicated).

Figure 35. Data show fold increase in cell number after a total of 10 days of culturing in expansion medium (3 days of culturing prior to electroporation and 7 days of culturing following

electroporation). With all the guide RNAs tested, including both single and dual guide RNA formats, cell expansion ranged from 2-7 fold. CR00312 and CR001128, indicated by arrows, demonstrated a 3-6 fold increase after 10 days of cell expansion. Lables "Crxxxx" refer to dgRNA having the indicated targeting domain; "sgxxxx" refer to sgRNA having the targeting domain of the CRxxxxx identifier with the same number (e.g., sg312 has the targeting domain of CR00312); "Unmod" indicates no modification to theRNA(s); "O'MePS", when used in relation to a dgRNA refers to a crRNA which has three 3' and three 5' 2'-OMe modifications and phosphorothioate bonds, paired with an unmodified tracr; "O'MePS", when used in relation to a sgRNA refers to gRNA which has three 5'-terminal 2'-OMe modifications and phosphorothioate bonds, three 3'-terminal phosphorothioate bonds, and three 2'OMe modifications of the 4^{th}-to-last, 3^{rd}-to-last and 2^{nd}-to-last 3' nucelotides.

Figure 36. Gating strategy to distinguish different HSPC subpopulations.

Figure 37. Frequency of each hematopoietic subset after 48 hours ex vivo culture in the indicated medium (STF modified with IL6, Compound 4, or both IL6 and Compound 4), but before electroporation of a CRISPR system. STF = StemSpan SFEM.

Figure 38. Frequency of each hematopoietic subset 7 days after electroporation introducing a CRISPR system targeting the +58 enhancer of BCL11a, cultured in the indicated medium (STF modified with IL6, Compound 4, or both IL6 and Compound 4). STF = StemSpan SFEM.

Figure 39A. Cell viability upon gene editing using different RNP concentrations, with RNP containing dgRNAs targeting the +58 region.

Figure 39B. Cell viability upon gene editing using different RNP concentrations, with RNP containing sgRNAs targeting the +58 region.

Figure 40A. Gene editing efficiency measured by NGS upon gene editing using different RNP concentrations, with RNP containing dgRNAs targeting the +58 region.

Figure 40B Gene editing efficiency measured by NGS upon gene editing using different RNP concentrations, with RNP containing sgRNAs targeting the +58 region.

Figure 41A. Percentage of HbF induction measured by flow cytometry upon gene editing using different RNP concentrations, with RNP containing dgRNAs targeting the +58 region.

Figure 41B Percentage of HbF induction measured by flow cytometry upon gene editing using different RNP concentrations, with RNP containing sgRNAs targeting the +58 region.

Figure 42A. Gene editing efficiencies of RNPs with different Cas9 proteins. Gene editing was performed using different Cas9 variants (listed on the X-axis) coupled with either the unmodified

version of sgRNA CR00312 and sgRNA CR001128, or a modified version of sgRNA CR00312 and sgRNA CR001128. Edited cells were subjected to NGS to determine % edit (Y-axis).

Figure 42B. Induction of HbF+ cells upon gene editing using different Cas9 proteins. Gene editing was performed using different Cas9 variants (listed on the X-axis) coupled with either the unmodified version of sgRNA CR00312 and sgRNA CR001128, or a modified version of sgRNA CR00312 and sgRNA CR001128. Edited cells were differentiated into erythroid lineage and HbF production assessed by flow cytometry using an anti-HbF antibody conjugated with fluorophore.

Figure 43. % Editing as determined by NGS in CD34+ HSPCs by electroporation of RNP comprising the indicated dgRNA or sgRNA (unmod or modified as indicated) (labels refer to the gRNA sequences as indicated in Table 36). Editing was determined at either 2 days (black bars) or 6 days (gray bars) post-electroporation. Less than 1.5% editing was detected at each site after control electroporation of Cas9 protein and Tracr only ("none", data not shown). Mean + standard deviation of 2 electroporation replicates is shown.

Figure 44. Percent of viable cells that are CD71+ after electroporation into CD34+ HSPCs of RNP comprising the indicated dgRNA or sgRNA (unmod or modified as indicated) (labels refer to the gRNA sequences as indicated in Table 36) and culture in erythroid differentiation conditions for 7 days. After electroporation, cells were maintained by Protocol 1 (black bars) or Protocol 2 (gray bars), as described in Example 4.7. Controls include electroporation of Cas9 protein and Tracr only ("none"). Mean + standard deviation of 2 electroporation replicates is shown.

Figure 45. Percent of erythroid cells that are HbF+ after electroporation into CD34+ HSPCs of RNP comprising the indicated dgRNA or sgRNA (unmod or modified as indicated) (labels refer to the gRNA sequences as indicated in Table 36) and culture in erythroid differentiation conditions for 7 days. After electroporation, cells were maintained by Protocol 1 (black bars) or Protocol 2 (gray bars), as described in Example 4.7. Controls include electroporation of Cas9 protein and Tracr only ("none"). Mean + standard deviation of 2 electroporation replicates is shown.

Figure 46. Percent of cells that are HbF+ after electroporation into CD34+ HSPCs of RNP comprising the indicated dgRNA or sgRNA (unmod or modified as indicated) (labels refer to the gRNA sequences as indicated in Table 36) and cultured in erythroid differentiation conditions for 14 days. After electroporation, cells were maintained by Protocol 1 (black bars) or Protocol 2 (gray bars), as described in Example 4.7. Controls include electroporation of Cas9 protein and Tracr only ("none"). Mean + standard deviation of 2 electroporation replicates is shown.

Figure 47. Percent of cells that are HbF+ after electroporation into CD34+ HSPCs of RNP comprising the indicated dgRNA or sgRNA (unmod or modified as indicated) (labels refer to the gRNA

sequences as indicated in Table 36) and cultured in erythroid differentiation conditions for 21 days. After electroporation, cells were maintained by Protocol 1 (black bars) or Protocol 2 (gray bars), as described in Example 4.7. Controls include electroporation of Cas9 protein and Tracr only ("none"). Mean + standard deviation of 2 electroporation replicates is shown.

Figure 48. Fold total cell expansion in erythroid differentiation culture for 7 (black bars) or 21 days (black bars) after electroporation into CD34+ HSPCs of RNP comprising the indicated dgRNA or sgRNA (unmod or modified as indicated) (labels refer to the gRNA sequences as indicated in Table 36). After electroporation, cells were maintained by Protocol 2, as described in Example 4.7. Controls include electroporation of Cas9 protein and Tracr only ("none"). Mean + standard deviation of 2 electroporation replicates is shown.

Figure 49. Assessment of potential off-target sites cleaved by Cas9 directed by dgRNA molecules targeting an HPFH region. Triangles represent the on-target site while open circles represent a potential off-target site for each guide RNA tested.

DEFINITIONS

The terms "CRISPR system," "Cas system" or "CRISPR/Cas system" refer to a set of molecules comprising an RNA-guided nuclease or other effector molecule and a gRNA molecule that together are necessary and sufficient to direct and effect modification of nucleic acid at a target sequence by the RNA-guided nuclease or other effector molecule. In one embodiment, a CRISPR system comprises a gRNA and a Cas protein, e.g., a Cas9 protein. Such systems comprising a Cas9 or modified Cas9 molecule are referred to herein as "Cas9 systems" or "CRISPR/Cas9 systems." In one example, the gRNA molecule and Cas molecule may be complexed, to form a ribonuclear protein (RNP) complex.

The terms "guide RNA," "guide RNA molecule," "gRNA molecule" or "gRNA" are used interchangeably, and refer to a set of nucleic acid molecules that promote the specific directing of a RNA-guided nuclease or other effector molecule (typically in complex with the gRNA molecule) to a target sequence. In some embodiments, said directing is accomplished through hybridization of a portion of the gRNA to DNA (e.g., through the gRNA targeting domain), and by binding of a portion of the gRNA molecule to the RNA-guided nuclease or other effector molecule (e.g., through at least the gRNA tracr). In embodiments, a gRNA molecule consists of a single contiguous polynucleotide molecule, referred to herein as a "single guide RNA" or "sgRNA" and the like. In other embodiments, a gRNA molecule consists of a plurality, usually two, polynucleotide molecules, which are themselves capable of association, usually through hybridization, referred to herein as a "dual guide RNA" or "dgRNA," and the like. gRNA molecules are described in more detail below, but generally include a targeting domain and a tracr. In embodiments the targeting domain and tracr are

disposed on a single polynucleotide. In other embodiments, the targeting domain and tracr are disposed on separate polynucleotides.

The term "targeting domain" as the term is used in connection with a gRNA, is the portion of the gRNA molecule that recognizes, e.g., is complementary to, a target sequence, e.g., a target sequence within the nucleic acid of a cell, e.g., within a gene.

The term "crRNA" as the term is used in connection with a gRNA molecule, is a portion of the gRNA molecule that comprises a targeting domain and a region that interacts with a tracr to form a flagpole region.

The term "target sequence" refers to a sequence of nucleic acids complimentary, for example fully complementary, to a gRNA targeting domain. In embodiments, the target sequence is disposed on genomic DNA. In an embodiment the target sequence is adjacent to (either on the same strand or on the complementary strand of DNA) a protospacer adjacent motif (PAM) sequence recognized by a protein having nuclease or other effector activity, e.g., a PAM sequence recognized by Cas9. In embodiments, the target sequence is a target sequence within a gene or locus that affects expression of a globin gene, e.g., that affects expression of beta globin or fetal hemoglobin (HbF). In embodiments, the target sequence is a target sequence within the globin locus. In embodiments, the target sequence is a target sequence within the BCL11a gene. In embodiments, the target sequence is a target sequence within the BCL11a ehancer region. In embodiments, the target sequence is a target sequence within a HPFH region.

The term "flagpole" as used herein in connection with a gRNA molecule, refers to the portion of the gRNA where the crRNA and the tracr bind to, or hybridize to, one another.

The term "tracr" as used herein in connection with a gRNA molecule, refers to the portion of the gRNA that binds to a nuclease or other effector molecule. In embodiements, the tracr comprises nucleic acid sequence that binds specifically to Cas9. In embodiments, the tracr comprises nucleic acid sequence that forms part of the flagpole.

The terms "Cas9" or "Cas9 molecule" refer to an enzyme from bacterial Type II CRISPR/Cas system responsible for DNA cleavage. Cas9 also includes wild-type protein as well as functional and non-functinal mutants thereof. In embodiments, the Cas9 is a Cas9 of *S. pyogenes*.

The term "complementary" as used in connection with nucleic acid, refers to the pairing of bases, A with T or U, and G with C. The term complementary refers to nucleic acid molecules that are completely complementary, that is, form A to T or U pairs and G to C pairs across the entire reference sequence, as well as molecules that are at least 80%, 85%, 90%, 95%, 99% complementary.

"Template Nucleic Acid" as used in connection with homology-directed repair or homologous recombination, refers to nucleic acid to be inserted at the site of modification by the CRISPR system donor sequence for gene repair (insertion) at site of cutting.

An "indel," as the term is used herein, refers to a nucleic acid comprising one or more insertions of nucleotides, one or more deletions of nucleotides, or a combination of insertions and delections of nucleotides, relative to a reference nucleic acid, that results after being exposed to a composition comprising a gRNA molecule, for example a CRISPR system. Indels can be determined by sequencing nucleic acid after being exposed to a composition comprising a gRNA molecule, for example, by NGS. With respect to the site of an indel, an indel is said to be "at or near" a reference site (e.g., a site complementary to a targeting domain of a gRNA molecule) if it comprises at least one insertion or deletion within about 10, 9 , 8, 7, 6, 5, 4, 3, 2, or 1 nucleotide(s) of the reference site, or is overlapping with part or all of said refrence site (e.g., comprises at least one insertion or deletion overlapping with, or within 10, 9, 8, 7, 6, 5, 4, 3, 2, or 1 nucelotides of a site complementary to the targeting domain of a gRNA molecule, e.g., a gRNA molecule described herein).

An "indel pattern," as the term is used herein, refers to a set of indels that results after exposure to a composition comprising a gRNA molecule. In an embodiment, the indel pattern consists of the top three indels, by frequency of appearance. In an embodiment, the indel pattern consists of the top five indels, by frequency of appearance. In an embodiment, the indel pattern consists of the indels which are present at greater than about 5% frequency relative to all sequencing reads. In an embodiment, the indel pattern consists of the indels which are present at greater than about 10% frequency relative to to total number of indel sequencing reads (i.e., those reads that do not consist of the unmodified reference nucleic acid sequence). In an embodiment, the indel pattern includes of any 3 of the top five most frequently observed indels. The indel pattern may be determined, for example, by sequencing cells of a population of cells which were exposed to the gRNA molecule.

An "off-target indel," as the term I used herein, refers to an indel at or near a site other than the target sequence of the targeting domain of the gRNA molecule. Such sites may comprise, for example, 1, 2, 3, 4, 5 or more mismatch nucleotides relative to the sequence of the targeting domain of the gRNA. In exemplary embodiments, such sites are detected using targeted sequencing of in silico predicted off-target sites, or by an insertional method known in the art.

The term "a" and "an" refers to one or to more than one (i.e., to at least one) of the grammatical object of the article. By way of example, "an element" means one element or more than one element.

The term "about" when referring to a measurable value such as an amount, a temporal duration, and the like, is meant to encompass variations of ±20% or in some instances ±10%, or in some instances

±5%, or in some instances ±1%, or in some instances ±0.1% from the specified value, as such variations are appropriate to perform the disclosed methods.

The term "antigen" or "Ag" refers to a molecule that provokes an immune response. This immune response may involve either antibody production, or the activation of specific immunologically-competent cells, or both. The skilled artisan will understand that any macromolecule, including virtually all proteins or peptides, can serve as an antigen. Furthermore, antigens can be derived from recombinant or genomic DNA. A skilled artisan will understand that any DNA, which comprises a nucleotide sequences or a partial nucleotide sequence encoding a protein that elicits an immune response therefore encodes an "antigen" as that term is used herein. Furthermore, one skilled in the art will understand that an antigen need not be encoded solely by a full length nucleotide sequence of a gene. It is readily apparent that the present invention includes, but is not limited to, the use of partial nucleotide sequences of more than one gene and that these nucleotide sequences are arranged in various combinations to encode polypeptides that elicit the desired immune response. Moreover, a skilled artisan will understand that an antigen need not be encoded by a "gene" at all. It is readily apparent that an antigen can be synthesized or can be derived from a biological sample, or might be macromolecule besides a polypeptide. Such a biological sample can include, but is not limited to a tissue sample, a cell or a fluid with other biological components.

The term "autologous" refers to any material derived from the same individual into whom it is later to be re-introduced.

The term "allogeneic" refers to any material derived from a different animal of the same species as the individual to whom the material is introduced. Two or more individuals are said to be allogeneic to one another when the genes at one or more loci are not identical. In some aspects, allogeneic material from individuals of the same species may be sufficiently unlike genetically to interact antigenically

The term "xenogeneic" refers to a graft derived from an animal of a different species.

"Derived from" as that term is used herein, indicates a relationship between a first and a second molecule. It generally refers to structural similarity between the first molecule and a second molecule and does not connotate or include a process or source limitation on a first molecule that is derived from a second molecule.

The term "encoding" refers to the inherent property of specific sequences of nucleotides in a polynucleotide, such as a gene, a cDNA, or an mRNA, to serve as templates for synthesis of other polymers and macromolecules in biological processes having either a defined sequence of nucleotides (e.g., rRNA, tRNA and mRNA) or a defined sequence of amino acids and the biological properties resulting therefrom. Thus, a gene, cDNA, or RNA, encodes a protein if transcription and translation of

mRNA corresponding to that gene produces the protein in a cell or other biological system. Both the coding strand, the nucleotide sequence of which is identical to the mRNA sequence and is usually provided in sequence listings, and the non-coding strand, used as the template for transcription of a gene or cDNA, can be referred to as encoding the protein or other product of that gene or cDNA.

Unless otherwise specified, a "nucleotide sequence encoding an amino acid sequence" includes all nucleotide sequences that are degenerate versions of each other and that encode the same amino acid sequence. The phrase nucleotide sequence that encodes a protein or a RNA may also include introns to the extent that the nucleotide sequence encoding the protein may in some version contain an intron(s).

The term "effective amount" or "therapeutically effective amount" are used interchangeably herein, and refer to an amount of a compound, formulation, material, or composition, as described herein effective to achieve a particular biological result.

The term "endogenous" refers to any material from or produced inside an organism, cell, tissue or system.

The term "exogenous" refers to any material introduced from or produced outside an organism, cell, tissue or system.

The term "expression" refers to the transcription and/or translation of a particular nucleotide sequence driven by a promoter.

The term "transfer vector" refers to a composition of matter which comprises an isolated nucleic acid and which can be used to deliver the isolated nucleic acid to the interior of a cell. Numerous vectors are known in the art including, but not limited to, linear polynucleotides, polynucleotides associated with ionic or amphiphilic compounds, plasmids, and viruses. Thus, the term "transfer vector" includes an autonomously replicating plasmid or a virus. The term should also be construed to further include non-plasmid and non-viral compounds which facilitate transfer of nucleic acid into cells, such as, for example, a polylysine compound, liposome, and the like. Examples of viral transfer vectors include, but are not limited to, adenoviral vectors, adeno-associated virus vectors, retroviral vectors, lentiviral vectors, and the like.

The term "expression vector" refers to a vector comprising a recombinant polynucleotide comprising expression control sequences operatively linked to a nucleotide sequence to be expressed. An expression vector comprises sufficient cis-acting elements for expression; other elements for expression can be supplied by the host cell or in an in vitro expression system. Expression vectors include all those known in the art, including cosmids, plasmids (e.g., naked or contained in liposomes)

and viruses (e.g., lentiviruses, retroviruses, adenoviruses, and adeno-associated viruses) that incorporate the recombinant polynucleotide.

The term "homologous" or "identity" refers to the subunit sequence identity between two polymeric molecules, e.g., between two nucleic acid molecules, such as, two DNA molecules or two RNA molecules, or between two polypeptide molecules. When a subunit position in both of the two molecules is occupied by the same monomeric subunit; e.g., if a position in each of two DNA molecules is occupied by adenine, then they are homologous or identical at that position. The homology between two sequences is a direct function of the number of matching or homologous positions; e.g., if half (e.g., five positions in a polymer ten subunits in length) of the positions in two sequences are homologous, the two sequences are 50% homologous; if 90% of the positions (e.g., 9 of 10), are matched or homologous, the two sequences are 90% homologous.

The term "isolated" means altered or removed from the natural state. For example, a nucleic acid or a peptide naturally present in a living animal is not "isolated," but the same nucleic acid or peptide partially or completely separated from the coexisting materials of its natural state is "isolated." An isolated nucleic acid or protein can exist in substantially purified form, or can exist in a non-native environment such as, for example, a host cell.

The term "operably linked" or "transcriptional control" refers to functional linkage between a regulatory sequence and a heterologous nucleic acid sequence resulting in expression of the latter. For example, a first nucleic acid sequence is operably linked with a second nucleic acid sequence when the first nucleic acid sequence is placed in a functional relationship with the second nucleic acid sequence. For instance, a promoter is operably linked to a coding sequence if the promoter affects the transcription or expression of the coding sequence. Operably linked DNA sequences can be contiguous with each other and, e.g., where necessary to join two protein coding regions, are in the same reading frame.

The term "parenteral" administration of an immunogenic composition includes, e.g., subcutaneous (s.c.), intravenous (i.v.), intramuscular (i.m.), or intrasternal injection, intratumoral, or infusion techniques.

The term "nucleic acid" or "polynucleotide" refers to deoxyribonucleic acids (DNA) or ribonucleic acids (RNA) and polymers thereof in either single- or double-stranded form. Unless specifically limited, the term encompasses nucleic acids containing known analogues of natural nucleotides that have similar binding properties as the reference nucleic acid and are metabolized in a manner similar to naturally occurring nucleotides. Unless otherwise indicated, a particular nucleic acid sequence also implicitly encompasses conservatively modified variants thereof (e.g., degenerate codon substitutions), alleles, orthologs, SNPs, and complementary sequences as well as the sequence

explicitly indicated. Specifically, degenerate codon substitutions may be achieved by generating sequences in which the third position of one or more selected (or all) codons is substituted with mixed-base and/or deoxyinosine residues (Batzer et al., Nucleic Acid Res. 19:5081 (1991); Ohtsuka et al., J. Biol. Chem. 260:2605-2608 (1985); and Rossolini et al., Mol. Cell. Probes 8:91-98 (1994)).

The terms "peptide," "polypeptide," and "protein" are used interchangeably, and refer to a compound comprised of amino acid residues covalently linked by peptide bonds. A protein or peptide must contain at least two amino acids, and no limitation is placed on the maximum number of amino acids that can comprise a protein's or peptide's sequence. Polypeptides include any peptide or protein comprising two or more amino acids joined to each other by peptide bonds. As used herein, the term refers to both short chains, which also commonly are referred to in the art as peptides, oligopeptides and oligomers, for example, and to longer chains, which generally are referred to in the art as proteins, of which there are many types. "Polypeptides" include, for example, biologically active fragments, substantially homologous polypeptides, oligopeptides, homodimers, heterodimers, variants of polypeptides, modified polypeptides, derivatives, analogs, fusion proteins, among others. A polypeptide includes a natural peptide, a recombinant peptide, or a combination thereof.

The term "promoter" refers to a DNA sequence recognized by the synthetic machinery of the cell, or introduced synthetic machinery, required to initiate the specific transcription of a polynucleotide sequence.

The term "promoter/regulatory sequence" refers to a nucleic acid sequence which is required for expression of a gene product operably linked to the promoter/regulatory sequence. In some instances, this sequence may be the core promoter sequence and in other instances, this sequence may also include an enhancer sequence and other regulatory elements which are required for expression of the gene product. The promoter/regulatory sequence may, for example, be one which expresses the gene product in a tissue specific manner.

The term "constitutive" promoter refers to a nucleotide sequence which, when operably linked with a polynucleotide which encodes or specifies a gene product, causes the gene product to be produced in a cell under most or all physiological conditions of the cell.

The term "inducible" promoter refers to a nucleotide sequence which, when operably linked with a polynucleotide which encodes or specifies a gene product, causes the gene product to be produced in a cell substantially only when an inducer which corresponds to the promoter is present in the cell.

The term "tissue-specific" promoter refers to a nucleotide sequence which, when operably linked with a polynucleotide encodes or specified by a gene, causes the gene product to be produced in a cell substantially only if the cell is a cell of the tissue type corresponding to the promoter.

As used herein in connection with a messenger RNA (mRNA), a 5' cap (also termed an RNA cap, an RNA 7-methylguanosine cap or an RNA m7G cap) is a modified guanine nucleotide that has been added to the "front" or 5' end of a eukaryotic messenger RNA shortly after the start of transcription. The 5' cap consists of a terminal group which is linked to the first transcribed nucleotide. Its presence is critical for recognition by the ribosome and protection from RNases. Cap addition is coupled to transcription, and occurs co-transcriptionally, such that each influences the other. Shortly after the start of transcription, the 5' end of the mRNA being synthesized is bound by a cap-synthesizing complex associated with RNA polymerase. This enzymatic complex catalyzes the chemical reactions that are required for mRNA capping. Synthesis proceeds as a multi-step biochemical reaction. The capping moiety can be modified to modulate functionality of mRNA such as its stability or efficiency of translation.

As used herein, "in vitro transcribed RNA" refers to RNA, preferably mRNA, that has been synthesized in vitro. Generally, the in vitro transcribed RNA is generated from an in vitro transcription vector. The in vitro transcription vector comprises a template that is used to generate the in vitro transcribed RNA.

As used herein, a "poly(A)" is a series of adenosines attached by polyadenylation to the mRNA. In the preferred embodiment of a construct for transient expression, the polyA is between 50 and 5000 (SEQ ID NO: 6596), preferably greater than 64, more preferably greater than 100, most preferably greater than 300 or 400. poly(A) sequences can be modified chemically or enzymatically to modulate mRNA functionality such as localization, stability or efficiency of translation.

As used herein, "polyadenylation" refers to the covalent linkage of a polyadenylyl moiety, or its modified variant, to a messenger RNA molecule. In eukaryotic organisms, most messenger RNA (mRNA) molecules are polyadenylated at the 3' end. The 3' poly(A) tail is a long sequence of adenine nucleotides (often several hundred) added to the pre-mRNA through the action of an enzyme, polyadenylate polymerase. In higher eukaryotes, the poly(A) tail is added onto transcripts that contain a specific sequence, the polyadenylation signal. The poly(A) tail and the protein bound to it aid in protecting mRNA from degradation by exonucleases. Polyadenylation is also important for transcription termination, export of the mRNA from the nucleus, and translation. Polyadenylation occurs in the nucleus immediately after transcription of DNA into RNA, but additionally can also occur later in the cytoplasm. After transcription has been terminated, the mRNA chain is cleaved through the action of an endonuclease complex associated with RNA polymerase. The cleavage site is usually characterized by the presence of the base sequence AAUAAA near the cleavage site. After the mRNA has been cleaved, adenosine residues are added to the free 3' end at the cleavage site.

As used herein, "transient" refers to expression of a non-integrated transgene for a period of hours, days or weeks, wherein the period of time of expression is less than the period of time for expression of the gene if integrated into the genome or contained within a stable plasmid replicon in the host cell.

As used herein, the terms "treat", "treatment" and "treating" refer to the reduction or amelioration of the progression, severity and/or duration of a disorder, e.g., a hemoglobinopathy, or the amelioration of one or more symptoms (preferably, one or more discernible symptoms) of a disorder, e.g., a hemoglobinopathy, resulting from the administration of one or more therapies (e.g., one or more therapeutic agents such as a gRNA molecule, CRISPR system, or modified cell of the invention). In specific embodiments, the terms "treat", "treatment" and "treating" refer to the amelioration of at least one measurable physical parameter of a hemoglobinopathy disorder, not discernible by the patient. In other embodiments the terms "treat", "treatment" and "treating" refer to the inhibition of the progression of a disorder, either physically by, e.g., stabilization of a discernible symptom, physiologically by, e.g., stabilization of a physical parameter, or both. In other embodiments the terms "treat", "treatment" and "treating" refer to the reduction or stabilization of a symptom of a hemoglobinopathy, e.g., sickle cell disease or beta-thalassemia.

The term "signal transduction pathway" refers to the biochemical relationship between a variety of signal transduction molecules that play a role in the transmission of a signal from one portion of a cell to another portion of a cell. The phrase "cell surface receptor" includes molecules and complexes of molecules capable of receiving a signal and transmitting signal across the membrane of a cell.

The term "subject" is intended to include living organisms in which an immune response can be elicited (e.g., mammals, human).

The term, a "substantially purified" cell refers to a cell that is essentially free of other cell types. A substantially purified cell also refers to a cell which has been separated from other cell types with which it is normally associated in its naturally occurring state. In some instances, a population of substantially purified cells refers to a homogenous population of cells. In other instances, this term refers simply to cell that have been separated from the cells with which they are naturally associated in their natural state. In some aspects, the cells are cultured in vitro. In other aspects, the cells are not cultured in vitro.

The term "therapeutic" as used herein means a treatment. A therapeutic effect is obtained by reduction, suppression, remission, or eradication of a disease state.

The term "prophylaxis" as used herein means the prevention of or protective treatment for a disease or disease state.

The term "transfected" or "transformed" or "transduced" refers to a process by which exogenous nucleic acid and/or ptotein is transferred or introduced into the host cell. A "transfected" or "transformed" or "transduced" cell is one which has been transfected, transformed or transduced with exogenous nucleic acid and/or protein. The cell includes the primary subject cell and its progeny.

The term "specifically binds," refers to a molecule recognizing and binding with a binding partner (e.g., a protein or nucleic acid) present in a sample, but which molecule does not substantially recognize or bind other molecules in the sample.

The term "bioequivalent" refers to an amount of an agent other than the reference compound, required to produce an effect equivalent to the effect produced by the reference dose or reference amount of the reference compound.

"Refractory" as used herein refers to a disease, e.g., a hemoglobinopathy, that does not respond to a treatment. In embodiments, a refractory hemoglobinopathy can be resistant to a treatment before or at the beginning of the treatment. In other embodiments, the refractory hemoglobinopathy can become resistant during a treatment. A refractory hemoglobinopathy is also called a resistant hemoglobinopathy.

"Relapsed" as used herein refers to the return of a disease (e.g., hemoglobinopathy) or the signs and symptoms of a disease such as a hemoglobinopathy after a period of improvement, e.g., after prior treatment of a therapy, e.g., hemoglobinopathy therapy.

Ranges: throughout this disclosure, various aspects of the invention can be presented in a range format. It should be understood that the description in range format is merely for convenience and brevity and should not be construed as an inflexible limitation on the scope of the invention. Accordingly, the description of a range should be considered to have specifically disclosed all the possible subranges as well as individual numerical values within that range. For example, description of a range such as from 1 to 6 should be considered to have specifically disclosed subranges such as from 1 to 3, from 1 to 4, from 1 to 5, from 2 to 4, from 2 to 6, from 3 to 6 etc., as well as individual numbers within that range, for example, 1, 2, 2.7, 3, 4, 5, 5.3, and 6. As another example, a range such as 95-99% identity, includes something with 95%, 96%, 97%, 98% or 99% identity, and includes subranges such as 96-99%, 96-98%, 96-97%, 97-99%, 97-98% and 98-99% identity. This applies regardless of the breadth of the range.

The term "BCL11a" refers to B-cell lymphoma/leukemia 11A, a RNA polymerase II core promoter proximal region sequence-sepecific DNA binding protein, and the gene encoding said protein, together with all introns and exons. This gene encodes a C2H2 type zinc-finger protein. BCL11A has been found to play a role in the suppression of fetal hemoglobin production. BCL11a is also known

as B-Cell CLL/Lymphoma 11A (Zinc Finger Protein), CTIP1, EVI9, Ecotropic Viral Integration Site 9 Protein Homolog, COUP-TF-Interacting Protein 1, Zinc Finger Protein 856, KIAA1809, BCL-11A, ZNF856, EVI-9, and B-Cell CLL/Lymphoma 11A. The term encompasses all isoforms and splice variants of BLC11a. The human gene encoding BCL11a is mapped to chromosomal location 2p16.1 (by Ensembl). The human and murine amino acid and nucleic acid sequences can be found in a public database, such as GenBank, UniProt and Swiss-Prot., and the genomic sequence of human BCL11a can be found in GenBank at NC_000002.12. The BCL11a gene refers to this genomic location, including all introns and exons. There are multiple known isotypes of BCL11a.

The sequence of mRNA encoding isoform 1 of human BCL11a can be found at NM_022893.

The peptide sequence of isoform 1 of human BCL11a is:

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          10         20         30         40         50
MSRRKQGKPQ HLSKREFSPE PLEAILTDDE PDHGPLGAPE GDHDLLTCGQ
          60         70         80         90        100
CQMNFPLGDI LIFIEHKRKQ CNGSLCLEKA VDKPPSPSPI EMKKASNPVE
         110        120        130        140        150
VGIQVTPEDD DCLSTSSRGI CPKQEHIADK LLHWRGLSSP RSAHGALIPT
         160        170        180        190        200
PGMSAEYAPQ GICKDEPSSY TCTTCKQPFT SAWFLLQHAQ NTHGLRIYLE
         210        220        230        240        250
SEHGSPLTPR VGIPSGLGAE CPSQPPLHGI HIADNNPFNL LRIPGSVSRE
         260        270        280        290        300
ASGLAEGRFP PTPPLFSPPP RHHLDPHRIE RLGAEEMALA THHPSAFDRV
         310        320        330        340        350
LRLNPMAMEP PAMDFSRRLR ELAGNTSSPP LSPGRPSPMQ RLLQPFQPGS
         360        370        380        390        400
KPPFLATPPL PPLQSAPPPS QPPVKSKSCE FCGKTFKFQS NLVVHRRSHT
         410        420        430        440        450
GEKPYKCNLC DHACTQASKL KRHMKTHMHK SSPMTVKSDD GLSTASSPEP
         460        470        480        490        500
GTSDLVGSAS SALKSVVAKF KSENDPNLIP ENGDEEEEED DEEEEEEEEE
         510        520        530        540        550
EEEELTESER VDYGFGLSLE AARHHENSSR GAVVGVGDES RALPDVMQGM
         560        570        580        590        600
VLSSMQHFSE AFHQVLGEKH KRGHLAEAEG HRDTCDEDSV AGESDRIDDG
         610        620        630        640        650
TVNGRGCSPG ESASGGLSKK LLLGSPSSLS PFSKRIKLEK EFDLPPAAMP
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        660         670         680         690         700
NTENVYSQWL AGYAASRQLK DPFLSFGDSR QSPFASSSEH SSENGSLRFS
        710         720         730         740         750
TPPGELDGGI SGRSGTGSGG STPHISGPGP GRPSSKEGRR SDTCEYCGKV
        760         770         780         790         800
FKNCSNLTVH RRSHTGERPY KCELCNYACA QSSKLTRHMK THGQVGKDVY
        810         820         830
KCEICKMPFS VYSTLEKHMK KWHSDRVLNN DIKTE
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SEQ ID NO: 2005 (Identifier Q9H165-1; and NM_022893.3; and accession ADL14508.1).

The sequences of other BCL11a protein isoforms are provided at:

Isoform 2: Q9H165-2

Isoform 3: Q9H165-3

Isoform 4: Q9H165-4

Isoform 5: Q9H165-5

Isoform 6: Q9H165-6

As used herein, a human BCL11a protein also encompasses proteins that have over its full length at least about 70%, 71%, 72%, 73%, 74%, 75%, 76%, 77%, 78%, 79%, 80%, 81%, 82%, 83%, 84%, 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99% or 100% sequence identity with BCL11a isolorm 1-6, wherein such proteins still have at least one of the functions of BCL11a.

The term "globin locus" as used herein refers to the region of human chromosome 11 comprising genes for embryonic (ε), fetal (G(γ) and A(γ)), adult globin genes (γ and β), locus control regions and DNase I hypersensitivity sites.

The term "complementary" as used in connection with nucleic acid, refers to the pairing of bases, A with T or U, and G with C. The term complementary refers to nucleic acid molecules that are completely complementary, that is, form A to T or U pairs and G to C pairs across the entire reference sequence, as well as molecules that are at least 80%, 85%, 90%, 95%, 99% complementary.

The term "HPFH" refers to hereditary persistence of fetal hemoglobin, and is characterized in increased fetal hemoglobin in adult red blood cells. The term "HPFH region" refers to a genomic site which, when modified (e.g., mutated or deleted), causes increased HbF production in adult red blood cells, and includes HPFH sites identified in the literature (see e.g., the Online Mendelian Inheritance in Man: http://www.omim.org/entry/141749). In an exemplary embodiment, the HPFH region is a region within or encompassing the beta globin gene cluster on chromosome 11p15. In an exemplary

embodiment, the HPFH region is within or emcompasses at least part of the delta globin gene. In an exemplary embodiment, the HPFH region is a region of the promoter of HBG1. In an exemplary embodiment, the HPFH region is a region of the promoter of HBG1. In an exemplary embodiment, the HPFH region is a region described in Sankaran VG et al. NEJM (2011) 365:807-814. In an exemplary embodiment, the HPFH region is the French breakpoint deletional HPFH as described in Sankaran VG et al. NEJM (2011) 365:807-814. In an exemplary embodiment, the HPFH region is the Algerian HPFH as described in Sankaran VG et al. NEJM (2011) 365:807-814. In an exemplary embodiment, the HPFH region is the Sri Lankan HPFH as described in Sankaran VG et al. NEJM (2011) 365:807-814. In an exemplary embodiment, the HPFH region is the HPFH-3 as described in Sankaran VG et al. NEJM (2011) 365:807-814. In an exemplary embodiment, the HPFH region is the HPFH-2 as described in Sankaran VG et al. NEJM (2011) 365:807-814. In an embodiment, the HPFH-1 region is the HPFH-3 as described in Sankaran VG et al. NEJM (2011) 365:807-814. In an exemplary embodiment, the HPFH region is the Sri Lankan $(\delta\beta)^0$-thalassemia HPFH as described in Sankaran VG et al. NEJM (2011) 365:807-814. In an exemplary embodiment, the HPFH region is the Sicilian $(\delta\beta)^0$-thalassemia HPFH as described in Sankaran VG et al. NEJM (2011) 365:807-814. In an exemplary embodiment, the HPFH region is the Macedonian $(\delta\beta)^0$-thalassemia HPFH as described in Sankaran VG et al. NEJM (2011) 365:807-814. In an exemplary embodiment, the HPFH region is the Kurdish β^0-thalassemia HPFH as described in Sankaran VG et al. NEJM (2011) 365:807-814. In an exemplary embodiment, the HPFH region is the region located at Chr11:5213874-5214400 (hg18). In an exemplary embodiment, the HPFH region is the region located at Chr11:5215943-5215046 (hg18). In an exemplary embodiment, the HPFH region is the region located at Chr11:5234390-5238486 (hg38).

"BCL11a enhancer" as the term is used herein, refers to nucleic acid sequence which affects, e.g., enhances, expression or function of BCL11a. See e.g., Bauer et al., Science, vol. 342, 2013, pp. 253-257. The BCL11a enhancer may be, for example, operative only in certain cell types, for example, cells of the erythroid lineage. One example of a BCL11a enhancer is the nucleic acid sequence between exon 2 and exon 3 of the BCL11a gene gene (e.g., the nucleic acid at or corresponding to positions +55: Chr2:60497676- 60498941; +58: Chr2:60494251- 60495546; +62: Chr2:60490409-60491734 as recorded in hg38). In an embodiment, the BCL11a Enhancer is the +62 region of the nucleic acid sequence between exon 2 and exon 3 of the BCL11a gene. In an embodiment, the BCL11a Enhancer is the +58 region of the nucleic acid sequence between exon 2 and exon 3 of the BCL11a gene. In an embodiment, the BCL11a Enhancer is the +55 region of the nucleic acid sequence between exon 2 and exon 3 of the BCL11a gene.

The terms "hematopoietic stem and progenitor cell" or "HSPC" are used interchangeably, and refer to a population of cells comprising both hematopoietic stem cells ("HSCs") and hematopoietic progenitor cells ("HPCs"). Such cells are characterized, for example, as CD34+. In exemplary

embodiments, HSPCs are isolated from bone marrow. In other exemplary embodiments, HSPCs are isolated from peripheral blood. In other exemplary embodiments, HSPCs are isolated from umbilical cord blood.

"Stem cell expander" as used herein refers to a compound which causes cells, e.g., HSPCs, HSCs and/or HPCs to proliferate, e.g., increase in number, at a faster rate relative to the same cell types absent said agent. In one exemplary aspect, the stem cell expander is an inhibitor of the aryl hydrocarbon receptor pathway. Additional examples of stem cell expanders are provided below. In embodiments, the proliferation, e.g., increase in number, is accomplished *ex vivo*.

"Engraftment" or "engraft" refers to the incorporation of a cell or tissue, e.g., a population of HSPCs, into the body of a recipient, e.g., a mammal or human subject. In one example, engraftment includes the growth, expansion and/or differention of the engrafted cells in the recipient. In an example, engraftment of HSPCs includes the differentiation and growth of said HSPCs into erythroid cells within the body of the recipient.

The term "Hematopoietic progenitor cells" (HPCs) as used herein refers to primitive hematopoietic cells that have a limited capacity for self-renewal and the potential for multilineage differentiation (e.g., myeloid, lymphoid), mono-lineage differentiation (e.g., myeloid or lymphoid) or cell-type restricted differentiation (e.g., erythroid progenitor) depending on placement within the hematopoietic hierarchy (Doulatov et al., Cell Stem Cell 2012).

"Hematopoietic stem cells" (HSCs) as used herein refer to immature blood cells having the capacity to self-renew and to differentiate into more mature blood cells comprising granulocytes (e.g., promyelocytes, neutrophils, eosinophils, basophils), erythrocytes (e.g., reticulocytes, erythrocytes), thrombocytes (e.g., megakaryoblasts, platelet producing megakaryocytes, platelets), and monocytes (e.g., monocytes, macrophages). HSCs are interchangeably described as stem cells throughout the specification. It is known in the art that such cells may or may not include CD34+ cells. CD34+ cells are immature cells that express the CD34 cell surface marker. CD34+ cells are believed to include a subpopulation of cells with the stem cell properties defined above. It is well known in the art that HSCs are multipotent cells that can give rise to primitive progenitor cells (e.g., multipotent progenitor cells) and/or progenitor cells committed to specific hematopoietic lineages (e.g., lymphoid progenitor cells). The stem cells committed to specific hematopoietic lineages may be of T cell lineage, B cell lineage, dendritic cell lineage, Langerhans cell lineage and/or lymphoid tissue-specific macrophage cell lineage. In addition, HSCs also refer to long term HSC (LT-HSC) and short term HSC (ST-HSC). ST-HSCs are more active and more proliferative than LT-HSCs. However, LT-HSC have unlimited self renewal (i.e., they survive throughout adulthood), whereas ST-HSC have limited self renewal (i.e., they survive for only a limited period of time). Any of these HSCs can be used in any of the methods described herein. Optionally, ST-HSCs are useful because they are highly proliferative and

thus, quickly increase the number of HSCs and their progeny. Hematopoietic stem cells are optionally obtained from blood products. A blood product includes a product obtained from the body or an organ of the body containing cells of hematopoietic origin. Such sources include un-fractionated bone marrow, umbilical cord, peripheral blood (e.g., mobilized peripheral blood, e.g., moblized with a mobilization agent such as G-CSF or Plerixafor® (AMD3100)), liver, thymus, lymph and spleen. All of the aforementioned crude or un-fractionated blood products can be enriched for cells having hematopoietic stem cell characteristics in ways known to those of skill in the art. In an embodiment, HSCs are characterized as CD34+/CD38-/CD90+/CD45RA-. In embodiments, the HSC s are characterized as CD34+/CD90+/CD49f+ cells.

"Expansion" or "Expand" in the context of cells refers to an increase in the number of a characteristic cell type, or cell types, from an initial cell population of cells, which may or may not be identical. The initial cells used for expansion may not be the same as the cells generated from expansion.

"Cell population" refers to eukaryotic mammalian, preferably human, cells isolated from biological sources, for example, blood product or tissues and derived from more than one cell.

"Enriched" when used in the context of cell population refers to a cell population selected based on the presence of one or more markers, for example, CD34+.

The term "CD34+ cells" refers to cells that express at their surface CD34 marker. CD34+ cells can be detected and counted using for example flow cytometry and fluorescently labeled anti-CD34 antibodies.

"Enriched in CD34+ cells" means that a cell population has been selected based on the presence of CD34 marker. Accordingly, the percentage of CD34+ cells in the cell population after selection method is higher than the percentage of CD34+ cells in the initial cell population before selecting step based on CD34 markers. For example, CD34+ cells may represent at least 50%, 60%, 70%, 80% or at least 90% of the cells in a cell population enriched in CD34+ cells.

The terms "F cell" and "F-cell" refer to cells, ususally erythrocytes (e.g., red blood cells) which contain and/or produce (e.g., express) fetal hemoglobin. For example, an F-cell is a cell that contains or produces detectible levels of fetal hemoglobin. For example, an F-cell is a cell that contains or produces at least 5 picograms of fetal hemoglobin. In another example, an F-cell is a cell that contains or produces at least 6 picograms of fetal hemoglobin. In another example, an F-cell is a cell that contains or produces at least 7 picograms of fetal hemoglobin. In another example, an F-cell is a cell that contains or produces at least 8 picograms of fetal hemoglobin. In another example, an F-cell is a cell that contains or produces at least 9 picograms of fetal hemoglobin. In another example, an F-cell is a cell that contains or produces at least 10 picograms of fetal hemoglobin. Levels of fetal

hemoglobin may be measured using an assay described herein or by other method known in the art, for example, flow cytometry using an anti-fetal hemoglobin detection reagent, high performance liquid chromatography, mass spectrometry, or enzyme-linked immunoabsorbent assay.

Unless otherwise stated, all genome or chromosome coordinates are are according to hg38.

DETAILED DESCRIPTION

The gRNA molecules, compositions and methods described herein relate to genome editing in eukaryotic cells using the CRISPR/Cas9 system. In particular, the gRNA molecules, compositions and methods described herein relate to regulation of globin levels and are useful, for example, in regulating expression and production of globin genes and protein. The gRNA molecules, compositions and methods can be useful in the treatment of hemoglobinopathies.

I . gRNA Molecules

A gRNA molecule may have a number of domains, as described more fully below, however, a gRNA molecule typically comprises at least a crRNA domain (comprising a targeting domain) and a tracr. The gRNA molecules of the invention, used as a component of a CRISPR system, are useful for modifying (e.g., modifying the sequence) DNA at or near a target site. Such modifications include deletions and or insertions that result in, for example, reduced or eliminated expression of a functional product of the gene comprising the target site. These uses, and additional uses, are described more fully below.

In an embodiment, a unimolecular, or sgRNA comprises, preferably from 5' to 3' : a crRNA (which contains a targeting domain complementary to a target sequence and a region that forms part of a flagpole (i.e., a crRNA flagpole region)); a loop; and a tracr (which contains a domain complementary to the crRNA flagpole region, and a domain which additionally binds a nuclease or other effector molecule, e.g., a Cas molecule, e.g., aCas9 molecule), and may take the following format (from 5’ to 3’):

[targeting domain] – [crRNA flagpole region] – [optional first flagpole extension] – [loop] – [optional first tracr extension] – [tracr flagpole region] – [tracr nuclease binding domain].

In embodiments, the tracr nuclease binding domain binds to a Cas protein, e.g., a Cas9 protein.

In an embodiment, a bimolecular, or dgRNA comprises two polynucleotides; the first, preferably from 5' to 3': a crRNA (which contains a targeting domain complementary to a target sequence and a region that forms part of a flagpole; and the second, preferrably from 5’ to 3’: a tracr (which contains a domain complementary to the crRNA flagpole region, and a domain which additionally binds a nuclease or other effector molecule, e.g., a Cas molecule, e.g., Cas9 molecule), and may take the following format (from 5’ to 3’):

Polynucleotide 1 (crRNA): [targeting domain] – [crRNA flagpole region] – [optional first flagpole extension] – [optional second flagpole extension]

Polynucleotide 2 (tracr): [optional first tracr extension] – [tracr flagpole region] - [tracr nuclease binding domain]

In embodiments, the tracr nuclease binding domain binds to a Cas protein, e.g., a Cas9 protein.

In some aspects, the targeting domain comprises or consists of a targeting domain sequence described herein, e.g., a targeting domain described in Table 1, 2, 3, 4, 5, or 6, or a targeting domain comprising or consisting of 17, 18, 19, 20, 21, 22, 23, 24, or 25 (preferably 20) consecutive nucleotides of a targeting domain sequence described in Table 1, 2, 3, 4, 5, or 6.

In some aspects, the flagpole, e.g., the crRNA flagpole region, comprises, from 5' to 3': GUUUUAGAGCUA (SEQ ID NO: 6584).

In some aspects, the flagpole, e.g., the crRNA flagpole region, comprises, from 5' to 3': GUUUAAGAGCUA (SEQ ID NO: 6585).

In some aspects the loop comprises, from 5' to 3': GAAA (SEQ ID NO: 6588).

In some aspects the tracr comprises, from 5' to 3': UAGCAAGUUAAAAUAAGGCUAGUCCGUUAUCAACUUGAAAAAGUGGCACCGAGUCGG UGC (SEQ ID NO: 6589) and is preferably used in a gRNA molecule comprising SEQ ID NO 6584.

In some aspects the tracr comprises, from 5' to 3': UAGCAAGUUUAAAUAAGGCUAGUCCGUUAUCAACUUGAAAAAGUGGCACCGAGUCGG UGC (SEQ ID NO: 6590) and is preferably used in a gRNA molecule comprising SEQ ID NO 6585.

In some aspects, the gRNA may also comprise, at the 3' end, additional U nucleic acids. For example the gRNA may comprise an additional 1, 2, 3, 4, 5, 6, 7, 8, 9, or 10 U nucleic acids at the 3' end (SEQ ID NO: 2006). In an embodiment, the gRNA comprises an additional 4 U nucleic acids at the 3' end. In the case of dgRNA, one or more of the polynucleotides of the dgRNA (e.g., the polynucleotide comprising the targeting domain and the polynucleotide comprising the tracr) may comprise, at the 3' end, additional U nucleic acids. For example, the case of dgRNA, one or more of the polynucleotides of the dgRNA (e.g., the polynucleotide comprising the targeting domain and the polynucleotide comprising the tracr) may comprise an additional 1, 2, 3, 4, 5, 6, 7, 8, 9, or 10 U nucleic acids at the 3' end (SEQ ID NO: 2006). In an embodiment, in the case of dgRNA, one or more of the polynucleotides of the dgRNA (e.g., the polynucleotide comprising the targeting domain and the polynucleotide comprising the tracr) comprises an additional 4 U nucleic acids at the 3' end. In an embodiment of a dgRNA, only the polynucleotide comprising the tracr comprises the additional U nucleic acid(s), e.g., 4 U nucleic acids. In an emebodiment of a dgRNA, only the polynucleotide

comprising the targeting domain comprises the additional U nucleic acid(s). In an embodiment of a dgRNA, both the polynucleotide comprising the targeting domain and the polynucleotide comprising the tracr comprise the additional U nucleic acids, e.g., 4 U nucleic acids.

In some aspects, the gRNA may also comprise, at the 3' end, additional A nucleic acids. For example the gRNA may comprise an additional 1, 2, 3, 4, 5, 6, 7, 8, 9, or 10 A nucleic acids at the 3' end (SEQ ID NO: 2007). In an embodiment, the gRNA comprises an additional 4 A nucleic acids at the 3' end. In the case of dgRNA, one or more of the polynucleotides of the dgRNA (e.g., the polynucleotide comprising the targeting domain and the polynucleotide comprising the tracr) may comprise, at the 3' end, additional A nucleic acids. For example, the case of dgRNA, one or more of the polynucleotides of the dgRNA (e.g., the polynucleotide comprising the targeting domain and the polynucleotide comprising the tracr) may comprise an additional 1, 2, 3, 4, 5, 6, 7, 8, 9, or 10 A nucleic acids at the 3' end (SEQ ID NO: 2007). In an embodiment, in the case of dgRNA, one or more of the polynucleotides of the dgRNA (e.g., the polynucleotide comprising the targeting domain and the polynucleotide comprising the tracr) comprises an additional 4 A nucleic acids at the 3' end. In an embodiment of a dgRNA, only the polynucleotide comprising the tracr comprises the additional A nucleic acid(s), e.g., 4 A nucleic acids. In an emebodiment of a dgRNA, only the polynucleotide comprising the targeting domain comprises the additional A nucleic acid(s). In an embodiment of a dgRNA, both the polynucleotide comprising the targeting domain and the polynucleotide comprising the tracr comprise the additional U nucleic acids, e.g., 4 A nucleic acids.

In embodiments, one or more of the polynucleotides of the gRNA molecule may comprise a cap at the 5' end.

In an embodiment, a unimolecular, or sgRNA comprises, preferably from 5' to 3': a crRNA (which contains a targeting domain complementary to a target sequence; a crRNA flagpole region; first flagpole extension; a loop; a first tracr extension (which contains a domain complementary to at least a portion of the first flagpole extension); and a tracr (which contains a domain complementary to the crRNA flagpole region, and a domain which additionally binds a Cas9 molecule). In some aspects, the targeting domain comprises a targeting domain sequence described herein, e.g., a targeting domain described in Table 1, 2, 3, 4, 5, or 6, or a targeting domain comprising or consisting of 17, 18, 19, 20, 21, 22, 23, 24, or 25 (preferably 20) consecutive nucleotides of a targeting domain sequence described in Table 1, 2, 3, 4, 5, or 6, for example the 3' 17, 18, 19, 20, 21, 22, 23, 24 or 25 (preferably 20) consecutive nucleotides of a targeting domain sequence described in Table 1, 2, 3, 4, 5, or 6.

In aspects comprising a first flagpole extension and/or a first tracr extension, the flagpole, loop and tracr sequences may be as described above. In general any first flagpole extension and first tracr extension may be employed, provided that they are complementary. In embodiments, the first

flagpole extension and first tracr extension consist of 3, 4, 5, 6, 7, 8, 9, 10 or more complementary nucleotides.

In some aspects, the first flagpole extension comprises, from 5' to 3': UGCUG (SEQ ID NO: 6586). In some aspects, the first flagpole extension consists of SEQ ID NO: 6586.

In some aspects, the first tracr extension comprises, from 5' to 3': CAGCA (SEQ ID NO: 6591). In some aspects, the first tracr extension consists of SEQ ID NO: 6591.

In an embodiment, a dgRNA comprises two nucleic acid molecules. In some aspects, the dgRNA comprises a first nucleic acid which contains, preferably from 5' to 3' : a targeting domain complementary to a target sequence; a crRNA flagpole region; optionally a first flagpole extension; and, optionally, a second flagpole extension; and a second nucleic acid (which may be referred to herein as a tracr), and comprises at least a domain which binds a Cas molecule, e.g., a Cas9 molecule) comprising preferably from 5' to 3': optionally a first tracr extension; and a tracr (which contains a domain complementary to the crRNA flagpole region, and a domain which additionally binds a Cas, e.g., Cas9, molecule). The second nucleic acid may additionally comprise, at the 3' end (e.g., 3' to the tracr) additional U nucleic acids. For example the tracr may comprise an additional 1, 2, 3, 4, 5, 6, 7, 8, 9, or 10 U nucleic acids at the 3' end (SEQ ID NO: 2006) (e.g., 3' to the tracr). The second nucleic acid may additionally or alternately comprise, at the 3' end (e.g., 3' to the tracr) additional A nucleic acids. For example the tracr may comprise an additional 1, 2, 3, 4, 5, 6, 7, 8, 9, or 10 A nucleic acids at the 3' end (SEQ ID NO: 2007) (e.g., 3' to the tracr). In some aspects, the targeting domain comprises a targeting domain sequence described herein, e.g., a targeting domain described in Table 1, 2, 3, 4, 5, or 6, or a targeting domain comprising or consisting of 17, 18, 19, 20, 21, 22, 23, 24, or 25 (preferably 20) consecutive nucleotides of a targeting domain sequence described in Table 1, 2, 3, 4, 5, or 6.

In aspects involving a dgRNA, the crRNA flagpole region, optional first flagpole extension, optional first tracr extension and tracr sequences may be as described above.

In some aspects, the optional second flagpole extension comprises, from 5' to 3': UUUUG (SEQ ID NO: 6587).

In embodiments, the 3' 1, 2, 3, 4, or 5 nucleotides, the 5' 1, 2, 3, 4, or 5 nucleotides, or both the 3' and 5' 1, 2, 3, 4, or 5 nucleotides of the gRNA molecule (and in the case of a dgRNA molecule, the polynucleotide comprising the targeting domain and/or the polynucleotide comprising the tracr) are modified nucleic acids, as described more fully in section XIII, below.

The domains are discussed briefly below:

1) The Targeting Domain:

Guidance on the selection of targeting domains can be found, e.g., in Fu Y el al. NAT BIOTECHNOL 2014 (doi: 10.1038/nbt.2808) and Sternberg SH el al. NATURE 2014 (doi: 10.1038/naturel3011).

The targeting domain comprises a nucleotide sequence that is complementary, e.g., at least 80, 85, 90, 95, or 99% complementary, e.g., fully complementary, to the target sequence on the target nucleic acid. The targeting domain is part of an RNA molecule and will therefore comprise the base uracil (U), while any DNA encoding the gRNA molecule will comprise the base thymine (T). While not wishing to be bound by theory, it is believed that the complementarity of the targeting domain with the target sequence contributes to specificity of the interaction of the gRNA molecule/Cas9 molecule complex with a target nucleic acid. It is understood that in a targeting domain and target sequence pair, the uracil bases in the targeting domain will pair with the adenine bases in the target sequence.

In an embodiment, the targeting domain is 5 to 50, e.g., 10 to 40, e.g., 10 to 30, e.g., 15 to 30, e.g., 15 to 25 nucleotides in length. In an embodiment, the targeting domain is 15, 16, 17, 18, 19, 20, 21, 22, 23, 24 or 25 nucleotides in length. In an embodiment, the targeting domain is 16 nucleotides in length. In an embodiment, the targeting domain is 17 nucleotides in length. In an embodiment, the targeting domain is 18 nucleotides in length. In an embodiment, the targeting domain is 19 nucleotides in length. In an embodiment, the targeting domain is 20 nucleotides in length. In an embodiment, the targeting domain is 21 nucleotides in length. In an embodiment, the targeting domain is 22 nucleotides in length. In an embodiment, the targeting domain is 23 nucleotides in length. In an embodiment, the targeting domain is 24 nucleotides in length. In an embodiment, the targeting domain is 25 nucleotides in length. In embodiments, the aforementioned 16, 17, 18, 19, 20, 21, 22, 23, 24, or 25 nucleotides comprise the 5'- 16, 17, 18, 19, 20, 21, 22, 23, 24, or 25 nucleotides from a targeting domain described in Table 1, 2, 3, 4, 5, or 6. In embodiments, the aforementioned 16, 17, 18, 19, 20, 21, 22, 23, 24, or 25 nucleotides comprise the 3'- 16, 17, 18, 19, 20, 21, 22, 23, 24, or 25 nucleotides from a targeting domain described in Table 1, 2, 3, 4, 5, or 6.

Without being bound by theory, it is believed that the 8, 9, 10, 11 or 12 nucleic acids of the targeting domain disposed at the 3' end of the targeting domain is important for targeting the target sequence, and may thus be referred to as the "core" region of the targeting domain. In an embodiment, the core domain is fully complementary with the target sequence.

The strand of the target nucleic acid with which the targeting domain is complementary is referred to herein as the target sequence. In some aspects, the target sequence is disposed on a chromosome, e.g., is a target within a gene. In some aspects the target sequence is disposed within an exon of a gene. In some aspects the target sequence is disposed within an intron of a gene. In some aspects, the target sequence comprises, or is proximal (e.g., within 10, 20, 30, 40, 50, 100, 200, 300, 400, 500, or 1000 nucleic acids) to a binding site of a regulatory element, e.g., a promoter or transcription factor binding

site, of a gene of interest. Some or all of the nucleotides of the domain can have a modification, e.g., modification found in Section XIII herein.

2) crRNA Flagpole Region:

The flagpole contains portions from both the crRNA and the tracr. The crRNA flagpole region is complementary with a portion of the tracr, and in an embodiment, has sufficient complementarity to a portion of the tracr to form a duplexed region under at least some physiological conditions, for example, normal physiological conditions. In an embodiment, the crRNA flagpole region is 5 to 30 nucleotides in length. In an embodiment, the crRNA flagpole region is 5 to 25 nucleotides in length. The crRNA flagpole region can share homology with, or be derived from, a naturally occurring portion of the repeat sequence from a bacterial CRISPR array. In an embodiment, it has at least 50% homology with a crRNA flagpole region disclosed herein, e.g., an S. pyogenes, or S. thermophilus, crRNA flagpole region.

In an embodiment, the flagpole, e.g., the crRNA flagpole region, comprises SEQ ID NO: 6584. In an embodiment, the flagpole, e.g., the crRNA flagpole region, comprises sequence having at least 50%, 60%, 70%, 80%, 85%, 90%, 95% or 99% homology with SEQ ID NO: 6584. In an embodiment, the flagpole, e.g., the crRNA flagpole region, comprises at least 5, 6, 7, 8, 9, 10, or 11 nucleotides of SEQ ID NO: 6584. In an embodiment, the flagpole, e.g., the crRNA flagpole region, comprises SEQ ID NO: 6585. In an embodiment, the flagpole comprises sequence having at least 50%, 60%, 70%, 80%, 85%, 90%, 95% or 99% homology with SEQ ID NO: 6585. In an embodiment, the flagpole, e.g., the crRNA flagpole region, comprises at least 5, 6, 7, 8, 9, 10, or 11 nucleotides of SEQ ID NO: 6585.

Some or all of the nucleotides of the domain can have a modification, e.g., modification described in Section XIII herein.

3) First Flagpole Extension

When a tracr comprising a first tracr extension is used, the crRNA may comprise a first flagpole extension. In general any first flagpole extension and first tracr extension may be employed, provided that they are complementary. In embodiments, the first flagpole extension and first tracr extension consist of 3, 4, 5, 6, 7, 8, 9, 10 or more complementary nucleotides.

The first flagpole extension may comprise nucleotides that are complementary, e.g., 80%, 85%, 90%, 95% or 99%, e.g., fully complementary, with nucleotides of the first tracr extension. In some aspects, the first flagpole extension nucleotides that hybridize with complementary nucleotides of the first tracr extension are contiguous. In some aspects, the first flagpole extension nucleotides that hybridize with complementary nucleotides of the first tracr extension are discontinuous, e.g., comprises two or more regions of hybridization separated by nucleotides that do not base pair with nucleotides of the first tracr extension. In some aspects, the first flagpole extension comprises at least 2, 3, 4, 5, 6, 7, 8,

9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20 or more nucleotides. In some aspects, the first flagpole extension comprises, from 5' to 3': UGCUG (SEQ ID NO: 6586). In some aspects, the first flagpole extension consists of SEQ ID NO: 6586. In some aspects the first flagpole extension comprises nucleic acid that is at least 80%, 85%, 90%, 95% or 99% homology to SEQ ID NO: 6586.

Some or all of the nucleotides of the first tracr extension can have a modification, e.g., modification found in Section XIII herein.

3) The Loop

A loop serves to link the crRNA flagpole region (or optionally the first flagpole extension, when present) with the tracr (or optionally the first tracr extension, when present) of a sgRNA. The loop can link the crRNA flagpole region and tracr covalently or non-covalently. In an embodiment, the linkage is covalent. In an embodiment, the loop covalently couples the crRNA flagpole region and tracr. In an embodiment, the loop covalently couples the first flagpole extension and the first tracr extension. In an embodiment, the loop is, or comprises, a covalent bond interposed between the crRNA flagpole region and the domain of the tracr which hybridizes to the crRNA flagpole region. Typically, the loop comprises one or more, e.g., 2, 3, 4, 5, 6, 7, 8, 9, or 10 nucleotides.

In dgRNA molecules the two molecules can be associated by virtue of the hybridization between at least a portion of the crRNA (e.g., the crRNA flagpole region) and at least a portion of the tracr (e.g., the domain of the tracr which is complementary to the crRNA flagpole region).

A wide variety of loops are suitable for use in sgRNAs. Loops can consist of a covalent bond, or be as short as one or a few nucleotides, e.g., 1 , 2, 3, 4, or 5 nucleotides in length. In an embodiment, a loop is 2, 3, 4, 5, 6, 7, 8, 9, 10, 15, 20, or 25 or more nucleotides in length. In an embodiment, a loop is 2 to 50, 2 to 40, 2 to 30, 2 to 20, 2 to 10, or 2 to 5 nucleotides in length. In an embodiment, a loop shares homology with, or is derived from, a naturally occurring sequence. In an embodiment, the loop has at least 50% homology with a loop disclosed herein. In an embodiment, the loop comprises SEQ ID NO: 6588.

Some or all of the nucleotides of the domain can have a modification, e.g., modification described in Section XIII herein.

4) The Second Flagpole Extension

In an embodiment, a dgRNA can comprise additional sequence, 3' to the crRNA flagpole region or, when present, the first flagpole extension, referred to herein as the second flagpole extension. In an embodiment, the second flagpole extension is, 2-10, 2-9, 2-8, 2-7, 2-6, 2-5, or 2-4 nucleotides in length. In an embodiment, the second flagpole extension is 2, 3, 4, 5, 6, 7, 8, 9, or 10 or more nucleotides in length. In an embodiment, the second flagpole extension comprises SEQ ID NO: 6587.

5) The Tracr:

The tracr is the nucleic acid sequence required for nuclease, e.g., Cas9, binding. Without being bound by theory, it is believed that each Cas9 species is associated with a particular tracr sequence. Tracr sequences are utilized in both sgRNA and in dgRNA systems. In an embodiment, the tracr comprises sequence from, or derived from, an *S. pyogenes* tracr. In some aspects, the tracr has a portion that hybridizes to the flagpole portion of the crRNA, e.g., has sufficient complementarity to the crRNA flagpole region to form a duplexed region under at least some physiological conditions (sometimes referred to herein as the tracr flagpole region or a tracr domain complementary to the crRNA flagpole region). In embodiments, the domain of the tracr that hybridizes with the crRNA flagpole region comprises at least 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, or 20 nucleotides that hybridize with complementary nucleotides of the crRNA flagpole region. In some aspects, the tracr nucleotides that hybridize with complementary nucleotides of the crRNA flagpole region are contiguous. In some aspects, the tracr nucleotides that hybridize with complementary nucleotides of the crRNA flagpole region are discontinuous, e.g., comprises two or more regions of hybridization separated by nucleotides that do not base pair with nucleotides of the crRNA flagpole region. In some aspects, the portion of the tracr that hybridizes to the crRNA flagpole region comprises, from 5' to 3': UAGCAAGUUAAAA (SEQ ID NO: 6597). In some aspects, the portion of the tracr that hybridizes to the crRNA flagpole regioncomprises, from 5' to 3': UAGCAAGUUUAAA (SEQ ID NO: 6598). In embodiments, the sequence that hybridizes with the crRNA flagpole region is disposed on the tracr 5'- to the sequence of the tracr that additionally binds a nuclease, e.g., a Cas molecule, e.g., a Cas9 molecule.

The tracr further comprises a domain that additionally binds to a nuclease, e.g., a Cas molecule, e.g., a Cas9 molecule. Without being bound by theory, it is believed that Cas9 from different species bind to different tracr sequences. In some aspects, the tracr comprises sequence that binds to a *S. pyogenes* Cas9 molecule. In some aspects, the tracr comprises sequence that binds to a Cas9 molecule disclosed herein. In some aspects, the domain that additionally binds a Cas9 molecule comprises, from 5' to 3': UAAGGCUAGUCCGUUAUCAACUUGAAAAAGUGGCACCGAGUCGGUGC (SEQ ID NO: 6599). In some aspects the domain that additionally binds a Cas9 molecule comprises, from 5' to 3':
UAAGGCUAGUCCGUUAUCAACUUGAAAAAGUGGCACCGAGUCGGUGCUUUU (SEQ ID NO: 6600).

In some embodiments, the tracr comprises SEQ ID NO: 6589. In some embodiments, the tracr comprises SEQ ID NO: 6590.

Some or all of the nucleotides of the tracr can have a modification, e.g., modification found in Section XIII herein. In embodiments, the gRNA (e.g., the sgRNA or the tracr and/or crRNA of a dgRNA),

e.g., any of the gRNA or gRNA components described above, comprises an inverted abasic residue at the 5' end, the 3' end or both the 5' and 3' end of the gRNA. In embodiments, the gRNA (e.g., the sgRNA or the tracr and/or crRNA of a dgRNA), e.g., any of the gRNA or gRNA components described above, comprises one or more phosphorothioate bonds between residues at the 5' end of the polynucleotide, for example, a phosphrothioate bond between the first two 5' residues, between each of the first three 5' residues, between each of the first four 5' residues, or between each of the first five 5' residues. In embodiments, the gRNA or gRNA component may alternatviely or additionally comprise one or more phosphorothioate bonds between residues at the 3' end of the polynucleotide, for example, a phosphrothioate bond between the first two 3' residues, between each of the first three 3' residues, between each of the first four 3' residues, or between each of the first five 3' residues. In an embodiment, the gRNA (e.g., the sgRNA or the tracr and/or crRNA of a dgRNA), e.g., any of the gRNA or gRNA components described above, comprises a phosphorothioate bond between each of the first four 5' residues (e.g., comprises, e.g., consists of, three phosphorothioate bonds at the 5' end(s)), and a phosphorothioate bond between each of the first four 3' residues (e.g., comprises, e.g., consists of, three phosphorothioate bonds at the 3' end(s)). In an embodiment, any of the phosphorothioate modificaitons described above are combined with an inverted abasic residue at the 5' end, the 3' end, or both the 5' and 3' ends of the polynucleotide. In such embodiments, the inverted abasic nucleotide may be linked to the 5' and/or 3' nucelotide by a phosphate bond or a phosphorothioate bond. In embodiments, the gRNA (e.g., the sgRNA or the tracr and/or crRNA of a dgRNA), e.g., any of the gRNA or gRNA components described above, comprises one or more nucleotides that include a 2' O-methyl modification. In embodiments, each of the first 1, 2, 3, or more of the 5' residues comprise a 2' O-methyl modification. In embodiments, each of the first 1, 2, 3, or more of the 3' residues comprise a 2' O-methyl modification. In embodiments, the 4th-to-terminal, 3rd-to-terminal, and 2nd-to-terminal 3' residues comprise a 2' O-methyl modification. In embodiments, each of the first 1, 2, 3 or more of the 5' residues comprise a 2' O-methyl modification, and each of the first 1, 2, 3 or more of the 3' residues comprise a 2' O-methyl modification. In an embodiment, each of the first 3 of the 5' residues comprise a 2' O-methyl modification, and each of the first 3 of the 3' residues comprise a 2' O-methyl modification. In embodiments, each of the first 3 of the 5' residues comprise a 2' O-methyl modification, and the 4th-to-terminal, 3rd-to-terminal, and 2nd-to-terminal 3' residues comprise a 2' O-methyl modification. In embodiments, any of the 2' O-methyl modfications, e.g., as described above, may be combined with one or more phosphorothioate modifications, e.g., as described above, and/or one or more inverted abasic modifications, e.g., as described above. In an embodiment, the gRNA (e.g., the sgRNA or the tracr and/or crRNA of a dgRNA), e.g., any of the gRNA or gRNA components described above, comprises, e.g., consists of, a phosphorothioate bond between each of the first four 5' residues (e.g., comprises, e.g., consists of three phosphorothioate bonds at the 5' end of the polynucleotide(s)), a phosphorothioate bond between each of the first four 3' residues (e.g., comprises, e.g., consists of three phosphorothioate

bonds at the 5' end of the polynucleotide(s)), a 2' O-methyl modification at each of the first three 5' residues, and a 2' O-methyl modification at each of the first three 3' residues. In an embodiment, the gRNA (e.g., the sgRNA or the tracr and/or crRNA of a dgRNA), e.g., any of the gRNA or gRNA components described above, comprises, e.g., consists of, a phosphorothioate bond between each of the first four 5' residues (e.g., comprises, e.g., consists of three phosphorothioate bonds at the 5' end of the polynucleotide(s)), a phosphorothioate bond between each of the first four 3' residues (e.g., comprises, e.g., consists of three phosphorothioate bonds at the 5' end of the polynucleotide(s)), a 2' O-methyl modification at each of the first three 5' residues, and a 2' O-methyl modification at each of the 4^{th}-to-terminal, 3^{rd}-to-terminal, and 2^{nd}-to-terminal 3' residues.

In an embodiment, the gRNA (e.g., the sgRNA or the tracr and/or crRNA of a dgRNA), e.g., any of the gRNA or gRNA components described above, comprises, e.g., consists of, a phosphorothioate bond between each of the first four 5' residues (e.g., comprises, e.g., consists of three phosphorothioate bonds at the 5' end of the polynucleotide(s)), a phosphorothioate bond between each of the first four 3' residues (e.g., comprises, e.g., consists of three phosphorothioate bonds at the 5' end of the polynucleotide(s)), a 2' O-methyl modification at each of the first three 5' residues, a 2' O-methyl modification at each of the first three 3' residues, and an additional inverted abasic residue at each of the 5' and 3' ends.

In an embodiment, the gRNA (e.g., the sgRNA or the tracr and/or crRNA of a dgRNA), e.g., any of the gRNA or gRNA components described above, comprises, e.g., consists of, a phosphorothioate bond between each of the first four 5' residues (e.g., comprises, e.g., consists of three phosphorothioate bonds at the 5' end of the polynucleotide(s)), a phosphorothioate bond between each of the first four 3' residues (e.g., comprises, e.g., consists of three phosphorothioate bonds at the 5' end of the polynucleotide(s)), a 2' O-methyl modification at each of the first three 5' residues, and a 2' O-methyl modification at each of the 4^{th}-to-terminal, 3^{rd}-to-terminal, and 2^{nd}-to-terminal 3' residues, and an additional inverted abasic residue at each of the 5' and 3' ends.

In an embodiment, the gRNA is a dgRNA and comprises, e.g., consists of:

crRNA:

mN*mN*mN*NNNNNNNNNNNNNNNNNNGUUUUAGAGCUAU*mG*mC*mU (SEQ ID NO: 2008), where m indicates a base with 2'O-Methyl modification, * indicates a phosphorothioate bond, and N's indicate the residues of the targeting domain, e.g., as described herein, (optionally with an inverted abasic residue at the 5' and/or 3' terminus); and

tracr:

AACAGCAUAGCAAGUUAAAAUAAGGCUAGUCCGUUAUCAACUUGAAAAAGUGGCACC GAGUCGGUGCUUUUUUU (SEQ ID NO: 6660) (optionally with an inverted abasic residue at the 5' and/or 3' terminus).

In an embodiment, the gRNA is a dgRNA and comprises, e.g., consists of:

crRNA:

mN*mN*mN*NNNNNNNNNNNNNNNNNGUUUUAGAGCUAU*mG*mC*mU (SEQ ID NO: 2009), where m indicates a base with 2'O-Methyl modification, * indicates a phosphorothioate bond, and N's indicate the residues of the targeting domain, e.g., as described herein, (optionally with an inverted abasic residue at the 5' and/or 3' terminus); and

tracr:

mA*mA*mC*AGCAUAGCAAGUUAAAAUAAGGCUAGUCCGUUAUCAACUUGAAAAAGUG GCACCGAGUCGGUGCUUUU*mU*mU*mU (SEQ ID NO: 346), where m indicates a base with 2'O-Methyl modification, * indicates a phosphorothioate bond, and N's indicate the residues of the targeting domain, e.g., as described herein, (optionally with an inverted abasic residue at the 5' and/or 3' terminus).

In an embodiment, the gRNA is a dgRNA and comprises, e.g., consists of:

crRNA:

mN*mN*mN*NNNNNNNNNNNNNNNNNGUUUUAGAGCUAUGCUGUU*mU*mU*mG (SEQ ID NO: 2010), where m indicates a base with 2'O-Methyl modification, * indicates a phosphorothioate bond, and N's indicate the residues of the targeting domain, e.g., as described herein, (optionally with an inverted abasic residue at the 5' and/or 3' terminus); and

tracr:

AACAGCAUAGCAAGUUAAAAUAAGGCUAGUCCGUUAUCAACUUGAAAAAGUGGCACC GAGUCGGUGCUUUUUUU (SEQ ID NO: 6660) (optionally with an inverted abasic residue at the 5' and/or 3' terminus).

In an embodiment, the gRNA is a dgRNA and comprises, e.g., consists of:

crRNA:

mN*mN*mN*NNNNNNNNNNNNNNNNNGUUUUAGAGCUAUGCUGUU*mU*mU*mG (SEQ ID NO: 2011), where m indicates a base with 2'O-Methyl modification, * indicates a phosphorothioate bond, and N's indicate the residues of the targeting domain, e.g., as described herein, (optionally with an inverted abasic residue at the 5' and/or 3' terminus); and

tracr:

mA*mA*mC*AGCAUAGCAAGUUAAAAUAAGGCUAGUCCGUUAUCAACUUGAAAAAGUG GCACCGAGUCGGUGCUUUU*mU*mU*mU (SEQ ID NO: 346), where m indicates a base with 2'O-Methyl modification, and * indicates a phosphorothioate bond (optionally with an inverted abasic residue at the 5' and/or 3' terminus).

In an embodiment, the gRNA is a dgRNA and comprises, e.g., consists of:

crRNA:

NNNNNNNNNNNNNNNNNNNNGUUUUAGAGCUAUGCUGUUUUG (SEQ ID NO: 2012), where N's indicate the residues of the targeting domain, e.g., as described herein, (optionally with an inverted abasic residue at the 5' and/or 3' terminus); and

tracr:

mA*mA*mC*AGCAUAGCAAGUUAAAAUAAGGCUAGUCCGUUAUCAACUUGAAAAAGUG GCACCGAGUCGGUGCUUUU*mU*mU*mU (SEQ ID NO: 346), where m indicates a base with 2'O-Methyl modification, and * indicates a phosphorothioate bond (optionally with an inverted abasic residue at the 5' and/or 3' terminus).

In an embodiment, the gRNA is a sgRNA and comprises, e.g., consists of:

NNNNNNNNNNNNNNNNNNNNGUUUUAGAGCUAGAAAUAGCAAGUUAAAAUAAGGCUA GUCCGUUAUCAACUUGAAAAAGUGGCACCGAGUCGGUGCUUUU (SEQ ID NO: 2013), where m indicates a base with 2'O-Methyl modification, * indicates a phosphorothioate bond, and N's indicate the residues of the targeting domain, e.g., as described herein, (optionally with an inverted abasic residue at the 5' and/or 3' terminus).

In an embodiment, the gRNA is a sgRNA and comprises, e.g., consists of:

mN*mN*mN*NNNNNNNNNNNNNNNNNGUUUUAGAGCUAGAAAUAGCAAGUUAAAAUA AGGCUAGUCCGUUAUCAACUUGAAAAAGUGGCACCGAGUCGGUGCU*mU*mU*mU (SEQ ID NO: 2014), where m indicates a base with 2'O-Methyl modification, * indicates a phosphorothioate bond, and N's indicate the residues of the targeting domain, e.g., as described herein, (optionally with an inverted abasic residue at the 5' and/or 3' terminus).

In an embodiment, the gRNA is a sgRNA and comprises, e.g., consists of:

mN*mN*mN*NNNNNNNNNNNNNNNNNGUUUUAGAGCUAGAAAUAGCAAGUUAAAAUA AGGCUAGUCCGUUAUCAACUUGAAAAAGUGGCACCGAGUCGGUGCmU*mU*mU*U (SEQ ID NO: 2015), where m indicates a base with 2'O-Methyl modification, * indicates a

phosphorothioate bond, and N's indicate the residues of the targeting domain, e.g., as described herein, (optionally with an inverted abasic residue at the 5' and/or 3' terminus).

6) First Tracr Extension

Where the gRNA comprises a first flagpole extension, the tracr may comprise a first tracr extension. The first tracr extension may comprise nucleotides that are complementary, e.g., 80%, 85%, 90%, 95% or 99%, e.g., fully complementary, with nucleotides of the first flagpole extension. In some aspects, the first tracr extension nucleotides that hybridize with complementary nucleotides of the first flagpole extension are contiguous. In some aspects, the first tracr extension nucleotides that hybridize with complementary nucleotides of the first flagpole extension are discontinuous, e.g., comprises two or more regions of hybridization separated by nucleotides that do not base pair with nucleotides of the first flagpole extension. In some aspects, the first tracr extension comprises at least 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20 or more nucleotides. In some aspects, the first tracr extension comprises SEQ ID NO: 6591. In some aspects the first tracr extension comprises nucleic acid that is at least 80%, 85%, 90%, 95% or 99% homology to SEQ ID NO: 6591.

Some or all of the nucleotides of the first tracr extension can have a modification, e.g., modification found in Section XIII herein.

In some embodiments, the sgRNA may comprise, from 5' to 3', disposed 3' to the targeting domain:

a)
GUUUUAGAGCUAGAAAUAGCAAGUUAAAAUAAGGCUAGUCCGUUAUCAACUUGAAAA AGUGGCACCGAGUCGGUGC (SEQ ID NO: 6601);

b)

GUUUAAGAGCUAGAAAUAGCAAGUUUAAAUAAGGCUAGUCCGUUAUCAACUUGAAAA AGUGGCACCGAGUCGGUGC (SEQ ID NO: 6602);

c)

GUUUUAGAGCUAUGCUGGAAACAGCAUAGCAAGUUAAAAUAAGGCUAGUCCGUUAUC AACUUGAAAAAGUGGCACCGAGUCGGUGC (SEQ ID NO: 6603);

d)

GUUUAAGAGCUAUGCUGGAAACAGCAUAGCAAGUUUAAAUAAGGCUAGUCCGUUAUC AACUUGAAAAAGUGGCACCGAGUCGGUGC (SEQ ID NO: 6604);

e) any of a) to d), above, further comprising, at the 3' end, at least 1, 2, 3, 4, 5, 6 or 7 uracil (U) nucleotides, e.g., 1, 2, 3, 4, 5, 6, or 7 uracil (U) nucleotides;

f) any of a) to d), above, further comprising, at the 3' end, at least 1, 2, 3, 4, 5, 6 or 7 adenine (A) nucleotides, e.g., 1, 2, 3, 4, 5, 6, or 7 adenine (A) nucleotides; or

g) any of a) to f), above, further comprising, at the 5' end (e.g., at the 5' terminus, e.g., 5' to the targeting domain), at least 1, 2, 3, 4, 5, 6 or 7 adenine (A) nucleotides, e.g., 1, 2, 3, 4, 5, 6, or 7 adenine (A) nucleotides. In embodiments, any of a) to g) above is disposed directly 3' to the targeting domain.

In an embodiment, a sgRNA of the invention comprises, e.g., consists of, from 5' to 3': [targeting domain]-GUUUUAGAGCUAGAAAUAGCAAGUUAAAAUAAGGCUAGUCCGUUAUCAACUUGAAAAAGUGGCACCGAGUCGGUGCUUUU (SEQ ID NO: 7811).

In an embodiment, a sgRNA of the invention comprises, e.g., consists of, from 5' to 3': [targeting domain]-GUUUAAGAGCUAUGCUGGAAACAGCAUAGCAAGUUUAAAUAAGGCUAGUCCGUUAUCAACUUGAAAAAGUGGCACCGAGUCGGUGCUUUU (SEQ ID NO: 7807).

In some embodiments, the dgRNA may comprise:

A crRNA comprising, from 5' to 3', preferrably disposed directly 3' to the targeting domain:

a) GUUUUAGAGCUA (SEQ ID NO: 6584);

b) GUUUAAGAGCUA (SEQ ID NO: 6585);

c) GUUUUAGAGCUAUGCUG (SEQ ID NO: 6605);

d) GUUUAAGAGCUAUGCUG (SEQ ID NO: 6606);

e) GUUUUAGAGCUAUGCUGUUUUG (SEQ ID NO: 6607);

f) GUUUAAGAGCUAUGCUGUUUUG (SEQ ID NO: 6608); or

g) GUUUUAGAGCUAUGCU (SEQ ID NO: 7806):

and a tracr comprising, from 5' to 3':

a) UAGCAAGUUAAAAUAAGGCUAGUCCGUUAUCAACUUGAAAAAGUGGCACCGAGUCGGUGC (SEQ ID NO: 6589);

b) UAGCAAGUUUAAAUAAGGCUAGUCCGUUAUCAACUUGAAAAAGUGGCACCGAGUCGGUGC (SEQ ID NO: 6590);

c)
CAGCAUAGCAAGUUAAAAUAAGGCUAGUCCGUUAUCAACUUGAAAAAGUGGCACCGA
GUCGGUGC (SEQ ID NO: 6609);

d)
CAGCAUAGCAAGUUUAAAUAAGGCUAGUCCGUUAUCAACUUGAAAAAGUGGCACCGA
GUCGGUGC (SEQ ID NO: 6610);

e)
AACAGCAUAGCAAGUUAAAAUAAGGCUAGUCCGUUAUCAACUUGAAAAAGUGGCACC
GAGUCGGUGCUUUUUUU (SEQ ID NO: 6660);

f)
AACAGCAUAGCAAGUUUAAAUAAGGCUAGUCCGUUAUCAACUUGAAAAAGUGGCACC
GAGUCGGUGCUUUUUUU (SEQ ID NO: 6661);

g)
AACAGCAUAGCAAGUUAAAAUAAGGCUAGUCCGUUAUCAACUUGAAAAAGUGGCACC
GAGUCGGUGC (SEQ ID NO: 7812)

h)
GUUUAAGAGCUAUGCUGGAAACAGCAUAGCAAGUUUAAAUAAGGCUAGUCCGUUAUC
AACUUGAAAAAGUGGCACCGAGUCGGUGCUUUU (SEQ ID NO: 7807);

i)
AGCAUAGCAAGUUAAAAUAAGGCUAGUCCGUUAUCAACUUGAAAAAGUGGCACCGAG
UCGGUGCUUU (SEQ ID NO: 7808);

j)
GUUGGAACCAUUCAAAACAGCAUAGCAAGUUAAAAUAAGGCUAGUCCGUUAUCAACU
UGAAAAAGUGGCACCGAGUCGGUGCUUU (SEQ ID NO: 7809);

k) any of a) to j), above, further comprising, at the 3' end, at least 1, 2, 3, 4, 5, 6 or 7 uracil (U) nucleotides, e.g., 1, 2, 3, 4, 5, 6, or 7 uracil (U) nucleotides;

l) any of a) to j), above, further comprising, at the 3' end, at least 1, 2, 3, 4, 5, 6 or 7 adenine (A) nucleotides, e.g., 1, 2, 3, 4, 5, 6, or 7 adenine (A) nucleotides; or

m) any of a) to l), above, further comprising, at the 5' end (e.g., at the 5' terminus), at least 1, 2, 3, 4, 5, 6 or 7 adenine (A) nucleotides, e.g., 1, 2, 3, 4, 5, 6, or 7 adenine (A) nucleotides.

In an embodiment, the sequence of k), above comprises the 3' sequence UUUUUU, e.g., if a U6 promoter is used for transcription. In an embodiment, the sequence of k), above, comprises the 3'

sequence UUUU, e.g., if an HI promoter is used for transcription. In an embodiment, sequence of k), above, comprises variable numbers of 3' U's depending, e.g., on the termination signal of the pol-III promoter used. In an embodiment, the sequence of k), above, comprises variable 3' sequence derived from the DNA template if a T7 promoter is used. In an embodiment, the sequence of k), above, comprises variable 3' sequence derived from the DNA template, e.g., if in vitro transcription is used to generate the RNA molecule. In an embodiment, the sequence of k), above, comprises variable 3' sequence derived from the DNA template, e.g, if a pol-II promoter is used to drive transcription.

In an embodiment, the crRNA comprises, e.g., consists of, a targeting domain and, disposed 3' to the targeting domain (e.g., disposed directly 3' to the targeting domain), a sequence comprising, e.g., consisting of, SEQ ID NO: 6607, and the tracr comprises, e.g., consists of AACAGCAUAGCAAGUUAAAAUAAGGCUAGUCCGUUAUCAACUUGAAAAAGUGGCACC GAGUCGGUGCUUUUUUU (SEQ ID NO: 6660).

In an embodiment, the crRNA comprises, e.g., consists of, a targeting domain and, disposed 3' to the targeting domain (e.g., disposed directly 3' to the targeting domain), a sequence comprising, e.g., consisting of, SEQ ID NO: 6608, and the tracr comprises, e.g., consists of, AACAGCAUAGCAAGUUUAAAUAAGGCUAGUCCGUUAUCAACUUGAAAAAGUGGCACC GAGUCGGUGCUUUUUUU (SEQ ID NO: 6661).

In an embodiment, the crRNA comprises, e.g., consists of, a targeting domain and, disposed 3' to the targeting domain (e.g., disposed directly 3' to the targeting domain), a sequence comprising, e.g., consisting of, GUUUUAGAGCUAUGCU (SEQ ID NO: 7806), and the tracr comprises, e.g., consists of, GUUUAAGAGCUAUGCUGGAAACAGCAUAGCAAGUUUAAAUAAGGCUAGUCCGUUAUC AACUUGAAAAAGUGGCACCGAGUCGGUGCUUUU (SEQ ID NO: 7807).

In an embodiment, the crRNA comprises, e.g., consists of, a targeting domain and, disposed 3' to the targeting domain (e.g., disposed directly 3' to the targeting domain), a sequence comprising, e.g., consisting of, GUUUUAGAGCUAUGCU (SEQ ID NO: 7806), and the tracr comprises, e.g., consists of, AGCAUAGCAAGUUAAAAUAAGGCUAGUCCGUUAUCAACUUGAAAAAGUGGCACCGAG UCGGUGCUUU (SEQ ID NO: 7808).

In an embodiment, the crRNA comprises, e.g., consists of, a targeting domain and, disposed 3' to the targeting domain (e.g., disposed directly 3' to the targeting domain), a sequence comprising, e.g., consisting of, GUUUUAGAGCUAUGCUGUUUUG (SEQ ID NO: 6607), and the tracr comprises, e.g., consists of, GUUGGAACCAUUCAAAACAGCAUAGCAAGUUAAAAUAAGGCUAGUCCGUUAUCAACU UGAAAAAGUGGCACCGAGUCGGUGCUUU (SEQ ID NO: 7809).

II. Targeting Domains Useful for Altering Expression of Globin Genes

Provided in the tables below are targeting domains for gRNA molecules for use in the various aspect of the present invention, for example, in altering expression of globin genes, for example, a fetal hemoglobin gene or a hemoglobin beta gene.

Table 1: gRNA targeting domains directed to BLC11a exon regions

Id.	Target	Target Region	Strand	Targeting Site (hg38)	gRNA Targeting Domain	SEQ ID NO:
53335_5_1	BCL11a	Exon 5	+	chr2:60451170-60451195	CAGUCAUUAUUUAUUAUGAAUAAGC	400
53335_5_2	BCL11a	Exon 5	+	chr2:60451196-60451221	GGAAAUAAUUCACAUGCCAAUUAUU	401
53335_5_3	BCL11a	Exon 5	+	chr2:60451217-60451242	UAUUUGGCUAUCUUUUCACUAAGCU	402
53335_5_4	BCL11a	Exon 5	+	chr2:60451233-60451258	CACUAAGCUAGGUAAUCUAGCCAGA	403
53335_5_5	BCL11a	Exon 5	+	chr2:60451236-60451261	UAAGCUAGGUAAUCUAGCCAGAAGG	404
53335_5_6	BCL11a	Exon 5	+	chr2:60451241-60451266	UAGGUAAUCUAGCCAGAAGGUGGAU	405
53335_5_7	BCL11a	Exon 5	+	chr2:60451245-60451270	UAAUCUAGCCAGAAGGUGGAUAGGU	406
53335_5_8	BCL11a	Exon 5	+	chr2:60451261-60451286	UGGAUAGGUAGGAUUUUCCCCACUU	407
53335_5_9	BCL11a	Exon 5	+	chr2:60451268-60451293	GUAGGAUUUUCCCCACUUAGGUUCA	408
53335_5_10	BCL11a	Exon 5	+	chr2:60451295-60451320	GCCUGUAUGUGAAUCUACAGCACAC	409
53335_5_11	BCL11a	Exon 5	+	chr2:60451359-60451384	UGCUAUGUUGUUUCUAAUUCUCUUC	410
53335_5_12	BCL11a	Exon 5	+	chr2:60451414-60451439	UGAGAAAAGUUCUGUGCAAAUUAAC	411
53335_5_13	BCL11a	Exon 5	+	chr2:60451415-60451440	GAGAAAAGUUCUGUGCAAAUUAACU	412
53335_5_14	BCL11	Exon 5	+	chr2:60451462-	CCUGUUUGUAGAUGUAACU	413

	a			60451487	UAUUUG	
53335_5_15	BCL11a	Exon 5	+	chr2:60451477-60451502	AACUUAUUUGUGGCACUAAUUUCUA	414
53335_5_16	BCL11a	Exon 5	+	chr2:60451625-60451650	GUCUGCAUUAAGAUAUAUUUCCUGA	415
53335_5_17	BCL11a	Exon 5	+	chr2:60451630-60451655	CAUUAAGAUAUAUUUCCUGAAGGUU	416
53335_5_18	BCL11a	Exon 5	+	chr2:60451631-60451656	AUUAAGAUAUAUUUCCUGAAGGUUU	417
53335_5_19	BCL11a	Exon 5	+	chr2:60451687-60451712	ACUACUGACAUUUAUCACCUUCUUU	418
53335_5_20	BCL11a	Exon 5	+	chr2:60451754-60451779	UUAAAAGACAAAUUCAAAUCCUGCA	419
53335_5_21	BCL11a	Exon 5	+	chr2:60451786-60451811	CACCAAAAGCAUAUAUUUGAAAAAC	420
53335_5_22	BCL11a	Exon 5	+	chr2:60451792-60451817	AAGCAUAUAUUUGAAAAACAGGAUU	421
53335_5_23	BCL11a	Exon 5	+	chr2:60451819-60451844	GCGUGCCAUAUUAUGCAUUAUUUAA	422
53335_5_24	BCL11a	Exon 5	+	chr2:60451847-60451872	UAUGCAAAUUAUAAGUCAGACAGUU	423
53335_5_25	BCL11a	Exon 5	+	chr2:60451971-60451996	UUGAAAAUUUAUGCCAUCUGAUAAG	424
53335_5_26	BCL11a	Exon 5	+	chr2:60452037-60452062	AAAUCUGUUCCUCCUACCCACCCGA	425
53335_5_27	BCL11a	Exon 5	+	chr2:60452038-60452063	AAUCUGUUCCUCCUACCCACCCGAU	426
53335_5_28	BCL11a	Exon 5	+	chr2:60452048-60452073	UCCUACCCACCCGAUGGGUGUCUGU	427
53335_5_29	BCL11a	Exon 5	+	chr2:60452055-60452080	CACCCGAUGGGUGUCUGUAGGAAAC	428
53335_5_30	BCL11a	Exon 5	+	chr2:60452203-60452228	AGACAACAUAGAAUGUAUAGAAACA	429
53335_5_31	BCL11a	Exon 5	+	chr2:60452204-60452229	GACAACAUAGAAUGUAUAGAAACAA	430
53335_5_32	BCL11	Exon 5	+	chr2:60452205-	ACAACAUAGAAUGUAUAGA	431

	a			60452230	AACAAG	
53335_5_33	BCL11a	Exon 5	+	chr2:60452209-60452234	CAUAGAAUGUAUAGAAACAAGGGGU	432
53335_5_34	BCL11a	Exon 5	+	chr2:60452210-60452235	AUAGAAUGUAUAGAAACAAGGGGUU	433
53335_5_35	BCL11a	Exon 5	+	chr2:60452211-60452236	UAGAAUGUAUAGAAACAAGGGGUUG	434
53335_5_36	BCL11a	Exon 5	+	chr2:60452237-60452262	GGACUCAUGCGCAUUUCCACAAUAC	435
53335_5_37	BCL11a	Exon 5	+	chr2:60452245-60452270	GCGCAUUUCCACAAUACAGGUAAUU	436
53335_5_38	BCL11a	Exon 5	+	chr2:60452249-60452274	AUUUCCACAAUACAGGUAAUUAGGU	437
53335_5_39	BCL11a	Exon 5	+	chr2:60452253-60452278	CCACAAUACAGGUAAUUAGGUUGGC	438
53335_5_40	BCL11a	Exon 5	+	chr2:60452263-60452288	GGUAAUUAGGUUGGCUGGUUUCAGA	439
53335_5_41	BCL11a	Exon 5	+	chr2:60452264-60452289	GUAAUUAGGUUGGCUGGUUUCAGAA	440
53335_5_42	BCL11a	Exon 5	+	chr2:60452269-60452294	UAGGUUGGCUGGUUUCAGAAGGGCC	441
53335_5_43	BCL11a	Exon 5	+	chr2:60452270-60452295	AGGUUGGCUGGUUUCAGAAGGGCCA	442
53335_5_44	BCL11a	Exon 5	+	chr2:60452291-60452316	GCCAGGGCAUCACUCAUGACAGCGA	443
53335_5_45	BCL11a	Exon 5	+	chr2:60452298-60452323	CAUCACUCAUGACAGCGAUGGUCCA	444
53335_5_46	BCL11a	Exon 5	+	chr2:60452299-60452324	AUCACUCAUGACAGCGAUGGUCCAC	445
53335_5_47	BCL11a	Exon 5	+	chr2:60452311-60452336	AGCGAUGGUCCACGGGCCCUCUCUA	446
53335_5_48	BCL11a	Exon 5	+	chr2:60452312-60452337	GCGAUGGUCCACGGGCCCUCUCUAU	447
53335_5_49	BCL11a	Exon 5	+	chr2:60452335-60452360	AUGGGACUGAUUCACUGUUCCAAUG	448
53335_5_50	BCL11	Exon 5	+	chr2:60452336-	UGGGACUGAUUCACUGUUC	449

	a			60452361	CAAUGU	
53335_5_51	BCL11a	Exon 5	+	chr2:60452383-60452408	UUUUUAUUAAAAAAUAUAAAUAAAA	450
53335_5_52	BCL11a	Exon 5	+	chr2:60452392-60452417	AAAAAUAUAAAUAAAAUGGCGCUGC	451
53335_5_53	BCL11a	Exon 5	+	chr2:60452398-60452423	AUAAAUAAAAUGGCGCUGCAGGCCU	452
53335_5_54	BCL11a	Exon 5	+	chr2:60452402-60452427	AUAAAAUGGCGCUGCAGGCCUAGGC	453
53335_5_55	BCL11a	Exon 5	+	chr2:60452406-60452431	AAUGGCGCUGCAGGCCUAGGCUGGA	454
53335_5_56	BCL11a	Exon 5	+	chr2:60452416-60452441	CAGGCCUAGGCUGGAAGGACUCUGC	455
53335_5_57	BCL11a	Exon 5	+	chr2:60452436-60452461	UCUGCAGGACUCUGUCUUCGCACAA	456
53335_5_58	BCL11a	Exon 5	+	chr2:60452444-60452469	ACUCUGUCUUCGCACAACGGCUUCU	457
53335_5_59	BCL11a	Exon 5	+	chr2:60452447-60452472	CUGUCUUCGCACAACGGCUUCUUGG	458
53335_5_60	BCL11a	Exon 5	+	chr2:60452478-60452503	CUGUCAGAAAACAUCACAAACUAGC	459
53335_5_61	BCL11a	Exon 5	+	chr2:60452505-60452530	GAUGACAGACCACGCUGACGUCGAC	460
53335_5_62	BCL11a	Exon 5	+	chr2:60452506-60452531	AUGACAGACCACGCUGACGUCGACU	461
53335_5_63	BCL11a	Exon 5	+	chr2:60452509-60452534	ACAGACCACGCUGACGUCGACUGGG	462
53335_5_64	BCL11a	Exon 5	+	chr2:60452531-60452556	GGGCGGCACGCGUCCACCCCACCCC	463
53335_5_65	BCL11a	Exon 5	+	chr2:60452532-60452557	GGCGGCACGCGUCCACCCCACCCCU	464
53335_5_66	BCL11a	Exon 5	+	chr2:60452533-60452558	GCGGCACGCGUCCACCCCACCCCUG	465
53335_5_67	BCL11a	Exon 5	+	chr2:60452534-60452559	CGGCACGCGUCCACCCCACCCCUGG	466
53335_5_68	BCL11	Exon 5	+	chr2:60452559-	GGGCUUCAAAUUUUCUCAG	467

	a			60452584	AACUUA	
53335_5_69	BCL11a	Exon 5	+	chr2:60452560-60452585	GGCUUCAAAUUUUCUCAGAACUUAA	468
53335_5_70	BCL11a	Exon 5	+	chr2:60452607-60452632	AAACUGCCACACAUCUUGAGCUCUC	469
53335_5_71	BCL11a	Exon 5	+	chr2:60452608-60452633	AACUGCCACACAUCUUGAGCUCUCU	470
53335_5_72	BCL11a	Exon 5	+	chr2:60452623-60452648	UGAGCUCUCUGGGUACUACGCCGAA	471
53335_5_73	BCL11a	Exon 5	+	chr2:60452624-60452649	GAGCUCUCUGGGUACUACGCCGAAU	472
53335_5_74	BCL11a	Exon 5	+	chr2:60452625-60452650	AGCUCUCUGGGUACUACGCCGAAUG	473
53335_5_75	BCL11a	Exon 5	+	chr2:60452626-60452651	GCUCUCUGGGUACUACGCCGAAUGG	474
53335_5_76	BCL11a	Exon 5	+	chr2:60452649-60452674	GGGGGUGUGUGAAGAACCUAGAAAG	475
53335_5_77	BCL11a	Exon 5	+	chr2:60452653-60452678	GUGUGUGAAGAACCUAGAAAGAGGU	476
53335_5_78	BCL11a	Exon 5	+	chr2:60452662-60452687	GAACCUAGAAAGAGGUUGGAGACAG	477
53335_5_79	BCL11a	Exon 5	-	chr2:60451215-60451240	CUUAGUGAAAAGAUAGCCAAAUAAU	478
53335_5_80	BCL11a	Exon 5	-	chr2:60451256-60451281	GGGAAAAUCCUACCUAUCCACCUUC	479
53335_5_81	BCL11a	Exon 5	-	chr2:60451281-60451306	CACAUACAGGCCGUGAACCUAAGUG	480
53335_5_82	BCL11a	Exon 5	-	chr2:60451282-60451307	UCACAUACAGGCCGUGAACCUAAGU	481
53335_5_83	BCL11a	Exon 5	-	chr2:60451283-60451308	UUCACAUACAGGCCGUGAACCUAAG	482
53335_5_84	BCL11a	Exon 5	-	chr2:60451299-60451324	ACCUGUGUGCUGUAGAUUCACAUAC	483
53335_5_85	BCL11a	Exon 5	-	chr2:60451350-60451375	UAGAAACAACAUAGCAAAUUAAAAU	484
53335_5_86	BCL11	Exon 5	-	chr2:60451394-	UCUCAGUUUGGUAUUUUUU	485

	a			60451419	ACUGCU	
53335_5_87	BCL11a	Exon 5	-	chr2:60451411-60451436	AAUUUGCACAGAACUUUUCUCAGUU	486
53335_5_88	BCL11a	Exon 5	-	chr2:60451446-60451471	ACAAACAGGUGGUAAAAAUUCUUUC	487
53335_5_89	BCL11a	Exon 5	-	chr2:60451462-60451487	CAAAUAAGUUACAUCUACAAACAGG	488
53335_5_90	BCL11a	Exon 5	-	chr2:60451465-60451490	CCACAAAUAAGUUACAUCUACAAAC	489
53335_5_91	BCL11a	Exon 5	-	chr2:60451552-60451577	GAUUUUAGAGGGGGGAAAUUAUAGG	490
53335_5_92	BCL11a	Exon 5	-	chr2:60451555-60451580	GCAGAUUUUAGAGGGGGGAAAUUAU	491
53335_5_93	BCL11a	Exon 5	-	chr2:60451565-60451590	GAAAUUUGGGGCAGAUUUUAGAGGG	492
53335_5_94	BCL11a	Exon 5	-	chr2:60451566-60451591	GGAAAUUUGGGGCAGAUUUUAGAGG	493
53335_5_95	BCL11a	Exon 5	-	chr2:60451567-60451592	AGGAAAUUUGGGGCAGAUUUUAGAG	494
53335_5_96	BCL11a	Exon 5	-	chr2:60451568-60451593	CAGGAAAUUUGGGGCAGAUUUUAGA	495
53335_5_97	BCL11a	Exon 5	-	chr2:60451569-60451594	UCAGGAAAUUUGGGGCAGAUUUUAG	496
53335_5_98	BCL11a	Exon 5	-	chr2:60451582-60451607	UUUAGUACUUACAUCAGGAAAUUUG	497
53335_5_99	BCL11a	Exon 5	-	chr2:60451583-60451608	CUUUAGUACUUACAUCAGGAAAUUU	498
53335_5_100	BCL11a	Exon 5	-	chr2:60451584-60451609	UCUUUAGUACUUACAUCAGGAAAUU	499
53335_5_101	BCL11a	Exon 5	-	chr2:60451592-60451617	AUAAAACUUCUUUAGUACUUACAUC	500
53335_5_102	BCL11a	Exon 5	-	chr2:60451648-60451673	UCUAAUUUUAGGUUCCCAAACCUUC	501
53335_5_103	BCL11a	Exon 5	-	chr2:60451664-60451689	GUUUCUUAUUAAAUAUUCUAAUUUU	502
53335_5_10	BCL11	Exon 5	-	chr2:60451707-	CUGGGCGAGCGGUAAAUCC	503

4	a			60451732	UAAAGA	
53335_5_105	BCL11a	Exon 5	-	chr2:60451723-60451748	UUAGGAAAGAACAUCACUGGGCGAG	504
53335_5_106	BCL11a	Exon 5	-	chr2:60451730-60451755	AUUUAGCUUAGGAAAGAACAUCACU	505
53335_5_107	BCL11a	Exon 5	-	chr2:60451731-60451756	AAUUUAGCUUAGGAAAGAACAUCAC	506
53335_5_108	BCL11a	Exon 5	-	chr2:60451746-60451771	UUGAAUUUGUCUUUUAAUUUAGCUU	507
53335_5_109	BCL11a	Exon 5	-	chr2:60451776-60451801	UAUAUGCUUUUGGUGGCUACCAUGC	508
53335_5_110	BCL11a	Exon 5	-	chr2:60451788-60451813	CUGUUUUUCAAAUAUAUGCUUUUGG	509
53335_5_111	BCL11a	Exon 5	-	chr2:60451791-60451816	AUCCUGUUUUUCAAAUAUAUGCUUU	510
53335_5_112	BCL11a	Exon 5	-	chr2:60451827-60451852	GCAUACCAUUAAAUAAUGCAUAAUA	511
53335_5_113	BCL11a	Exon 5	-	chr2:60451882-60451907	AUUGCUGUUUAUUAAUGCUGAAGUG	512
53335_5_114	BCL11a	Exon 5	-	chr2:60451949-60451974	CAAGGAGAAUCAAAAUGCAAAACUU	513
53335_5_115	BCL11a	Exon 5	-	chr2:60451950-60451975	UCAAGGAGAAUCAAAAUGCAAAACU	514
53335_5_116	BCL11a	Exon 5	-	chr2:60451972-60451997	GCUUAUCAGAUGGCAUAAAUUUUCA	515
53335_5_117	BCL11a	Exon 5	-	chr2:60451987-60452012	GGGAACUAGGUUACCGCUUAUCAGA	516
53335_5_118	BCL11a	Exon 5	-	chr2:60452005-60452030	GGGCAGGAGAUGUAGGAGGGGAACU	517
53335_5_119	BCL11a	Exon 5	-	chr2:60452012-60452037	GAGAAAUGGGCAGGAGAUGUAGGAG	518
53335_5_120	BCL11a	Exon 5	-	chr2:60452013-60452038	UGAGAAAUGGGCAGGAGAUGUAGGA	519
53335_5_121	BCL11a	Exon 5	-	chr2:60452014-60452039	UUGAGAAAUGGGCAGGAGAUGUAGG	520
53335_5_12	BCL11	Exon 5	-	chr2:60452017-	GAUUUGAGAAAUGGGCAGG	521

2	a			60452042	AGAUGU	
53335_5_123	BCL11a	Exon 5	-	chr2:60452026-60452051	GGAGGAACAGAUUUGAGAAAUGGGC	522
53335_5_124	BCL11a	Exon 5	-	chr2:60452030-60452055	GGUAGGAGGAACAGAUUUGAGAAAU	523
53335_5_125	BCL11a	Exon 5	-	chr2:60452031-60452056	GGGUAGGAGGAACAGAUUUGAGAAA	524
53335_5_126	BCL11a	Exon 5	-	chr2:60452049-60452074	UACAGACACCCAUCGGGUGGGUAGG	525
53335_5_127	BCL11a	Exon 5	-	chr2:60452052-60452077	UCCUACAGACACCCAUCGGGUGGGU	526
53335_5_128	BCL11a	Exon 5	-	chr2:60452056-60452081	UGUUUCCUACAGACACCCAUCGGGU	527
53335_5_129	BCL11a	Exon 5	-	chr2:60452057-60452082	CUGUUUCCUACAGACACCCAUCGGG	528
53335_5_130	BCL11a	Exon 5	-	chr2:60452060-60452085	UACCUGUUUCCUACAGACACCCAUC	529
53335_5_131	BCL11a	Exon 5	-	chr2:60452061-60452086	GUACCUGUUUCCUACAGACACCCAU	530
53335_5_132	BCL11a	Exon 5	-	chr2:60452111-60452136	AAUUUUUAAUGCUUAUAAGACAAUG	531
53335_5_133	BCL11a	Exon 5	-	chr2:60452155-60452180	ACACAAUAAAUGUUGGAGCUUUAGG	532
53335_5_134	BCL11a	Exon 5	-	chr2:60452158-60452183	UUGACACAAUAAAUGUUGGAGCUUU	533
53335_5_135	BCL11a	Exon 5	-	chr2:60452167-60452192	UGCUUAACAUUGACACAAUAAAUGU	534
53335_5_136	BCL11a	Exon 5	-	chr2:60452256-60452281	CCAGCCAACCUAAUUACCUGUAUUG	535
53335_5_137	BCL11a	Exon 5	-	chr2:60452295-60452320	ACCAUCGCUGUCAUGAGUGAUGCCC	536
53335_5_138	BCL11a	Exon 5	-	chr2:60452323-60452348	GAAUCAGUCCCAUAGAGAGGGCCCG	537
53335_5_139	BCL11a	Exon 5	-	chr2:60452330-60452355	GAACAGUGAAUCAGUCCCAUAGAGA	538
53335_5_14	BCL11	Exon 5	-	chr2:60452331-	GGAACAGUGAAUCAGUCCC	539

0	a			60452356	AUAGAG	
53335_5_141	BCL11a	Exon 5	-	chr2:60452357-60452382	UAAAAACAAAAAAACAGACCCACAU	540
53335_5_142	BCL11a	Exon 5	-	chr2:60452423-60452448	GAGUCCUGCAGAGUCCUUCCAGCCU	541
53335_5_143	BCL11a	Exon 5	-	chr2:60452517-60452542	GCGUGCCGCCCAGUCGACGUCAGCG	542
53335_5_144	BCL11a	Exon 5	-	chr2:60452547-60452572	AAAUUUGAAGCCCCCAGGGGUGGGG	543
53335_5_145	BCL11a	Exon 5	-	chr2:60452550-60452575	AGAAAAUUUGAAGCCCCCAGGGGUG	544
53335_5_146	BCL11a	Exon 5	-	chr2:60452551-60452576	GAGAAAAUUUGAAGCCCCCAGGGGU	545
53335_5_147	BCL11a	Exon 5	-	chr2:60452552-60452577	UGAGAAAAUUUGAAGCCCCCAGGGG	546
53335_5_148	BCL11a	Exon 5	-	chr2:60452555-60452580	UUCUGAGAAAAUUUGAAGCCCCCAG	547
53335_5_149	BCL11a	Exon 5	-	chr2:60452556-60452581	GUUCUGAGAAAAUUUGAAGCCCCCA	548
53335_5_150	BCL11a	Exon 5	-	chr2:60452557-60452582	AGUUCUGAGAAAAUUUGAAGCCCCC	549
53335_5_151	BCL11a	Exon 5	-	chr2:60452602-60452627	CUCAAGAUGUGUGGCAGUUUUCGGA	550
53335_5_152	BCL11a	Exon 5	-	chr2:60452606-60452631	AGAGCUCAAGAUGUGUGGCAGUUUU	551
53335_5_153	BCL11a	Exon 5	-	chr2:60452616-60452641	UAGUACCCAGAGAGCUCAAGAUGUG	552
53335_5_154	BCL11a	Exon 5	-	chr2:60452646-60452671	UCUAGGUUCUUCACACACCCCCAUU	553
53335_4_1	BCL11a	Exon 4	+	chr2:60457199-60457224	UUAAUUUUUUUUAUUUUUUCAAUAA	554
53335_4_2	BCL11a	Exon 4	+	chr2:60457200-60457225	UAAUUUUUUUUAUUUUUUCAAUAAA	555
53335_4_3	BCL11a	Exon 4	+	chr2:60457209-60457234	UUAUUUUUUCAAUAAAGGGACAAAA	556
53335_4_4	BCL11	Exon 4	+	chr2:60457210-	UAUUUUUUCAAUAAAGGGA	557

	a			60457235	CAAAAU	
53335_4_5	BCL11a	Exon 4	+	chr2:60457222-60457247	AAAGGGACAAAAUGGGUGUAUGAAC	558
53335_4_6	BCL11a	Exon 4	+	chr2:60457259-60457284	ACAACUGCCAAAAAAACACAGACAG	559
53335_4_7	BCL11a	Exon 4	+	chr2:60457312-60457337	CCAGAAACAAAUACAAUAAAAAGCC	560
53335_4_8	BCL11a	Exon 4	+	chr2:60457328-60457353	UAAAAAGCCAGGUUGUAAUGACCUU	561
53335_4_9	BCL11a	Exon 4	+	chr2:60457401-60457426	CAAAUUAAGUGCCUCUGUUUUGAAC	562
53335_4_10	BCL11a	Exon 4	+	chr2:60457402-60457427	AAAUUAAGUGCCUCUGUUUUGAACA	563
53335_4_11	BCL11a	Exon 4	+	chr2:60457480-60457505	AGUUACGACAAACAGCUUUCAUUAC	564
53335_4_12	BCL11a	Exon 4	+	chr2:60457491-60457516	ACAGCUUUCAUUACAGGAAUAGAAA	565
53335_4_13	BCL11a	Exon 4	+	chr2:60457545-60457570	AUUUACAAAAAAGUAUUGACUAAAG	566
53335_4_14	BCL11a	Exon 4	+	chr2:60457546-60457571	UUUACAAAAAAGUAUUGACUAAAGC	567
53335_4_15	BCL11a	Exon 4	+	chr2:60457616-60457641	UAAAUAUAAAGCACCAUUUAGUUUU	568
53335_4_16	BCL11a	Exon 4	+	chr2:60457642-60457667	GGCAAUGAAAAAAACUGCAAAACAU	569
53335_4_17	BCL11a	Exon 4	+	chr2:60457695-60457720	UCUUUCUUUCUUUUACUGCAUAUGA	570
53335_4_18	BCL11a	Exon 4	+	chr2:60457706-60457731	UUUACUGCAUAUGAAGGUAAGAUGC	571
53335_4_19	BCL11a	Exon 4	+	chr2:60457714-60457739	AUAUGAAGGUAAGAUGCUGGAAUGU	572
53335_4_20	BCL11a	Exon 4	+	chr2:60457715-60457740	UAUGAAGGUAAGAUGCUGGAAUGUA	573
53335_4_21	BCL11a	Exon 4	+	chr2:60457725-60457750	AGAUGCUGGAAUGUAGGGUGAUAGA	574
53335_4_22	BCL11	Exon 4	+	chr2:60457730-	CUGGAAUGUAGGGUGAUAG	575

	a			60457755	AAGGAA	
53335_4_23	BCL11a	Exon 4	+	chr2:60457731-60457756	UGGAAUGUAGGGUGAUAGAAGGAAA	576
53335_4_24	BCL11a	Exon 4	+	chr2:60457792-60457817	UUAGCUUGCAGUACUGCAUACAGUA	577
53335_4_25	BCL11a	Exon 4	+	chr2:60457799-60457824	GCAGUACUGCAUACAGUAUGGCAGC	578
53335_4_26	BCL11a	Exon 4	+	chr2:60457806-60457831	UGCAUACAGUAUGGCAGCAGGAAAA	579
53335_4_27	BCL11a	Exon 4	+	chr2:60457817-60457842	UGGCAGCAGGAAAAAGGAACAAAAA	580
53335_4_28	BCL11a	Exon 4	+	chr2:60457863-60457888	ACAGCCAUCCAUGUGACAUUCUAGC	581
53335_4_29	BCL11a	Exon 4	+	chr2:60457887-60457912	CAGGCUCCCCCAAACCGCCAUUAUA	582
53335_4_30	BCL11a	Exon 4	+	chr2:60457996-60458021	CCUGCCAAAUUAAAAAAAUAUACUG	583
53335_4_31	BCL11a	Exon 4	+	chr2:60458031-60458056	UCUUUUUUUUUUCCACUACCAAAAA	584
53335_4_32	BCL11a	Exon 4	+	chr2:60458178-60458203	AAAGACCAUAAAUGUAUUUUAGCAU	585
53335_4_33	BCL11a	Exon 4	+	chr2:60458274-60458299	UUUUUUUUUUUUACAACCUGAAGAG	586
53335_4_34	BCL11a	Exon 4	+	chr2:60458287-60458312	CAACCUGAAGAGCGGUGUGUAUCCA	587
53335_4_35	BCL11a	Exon 4	+	chr2:60458317-60458342	UAGAAUUUCCACUACCAUUUUUAAA	588
53335_4_36	BCL11a	Exon 4	+	chr2:60458350-60458375	AAGUCUUGUAACACCACCAAGACAA	589
53335_4_37	BCL11a	Exon 4	+	chr2:60458564-60458589	UAAGUAAGCUCAAUAGUCAAGUAAA	590
53335_4_38	BCL11a	Exon 4	+	chr2:60458568-60458593	UAAGCUCAAUAGUCAAGUAAAUGGC	591
53335_4_39	BCL11a	Exon 4	+	chr2:60458677-60458702	UUCCCUUAAGUAUAGACCUGUAAAC	592
53335_4_40	BCL11	Exon 4	+	chr2:60458678-	UCCCUUAAGUAUAGACCUG	593

	a			60458703	UAAACU	
53335_4_41	BCL11a	Exon 4	+	chr2:60458717-60458742	GUGCACUUAAUUGUCCUAUCUGAGC	594
53335_4_42	BCL11a	Exon 4	+	chr2:60458775-60458800	AUUAGAGAAAAGAUACAGAUAUCAC	595
53335_4_43	BCL11a	Exon 4	+	chr2:60458806-60458831	AGUCAAGUGCUAUUUGAACACCAAC	596
53335_4_44	BCL11a	Exon 4	+	chr2:60458807-60458832	GUCAAGUGCUAUUUGAACACCAACU	597
53335_4_45	BCL11a	Exon 4	+	chr2:60458808-60458833	UCAAGUGCUAUUUGAACACCAACUG	598
53335_4_46	BCL11a	Exon 4	+	chr2:60458904-60458929	GUUAACACAAAUAGCACACAGUGUA	599
53335_4_47	BCL11a	Exon 4	+	chr2:60458930-60458955	GGAAAAGAAAUGAAGUACAACUUUU	600
53335_4_48	BCL11a	Exon 4	+	chr2:60458931-60458956	GAAAAGAAAUGAAGUACAACUUUUA	601
53335_4_49	BCL11a	Exon 4	+	chr2:60459074-60459099	CUUAUAUACCUGUUCUAGUUUUAAA	602
53335_4_50	BCL11a	Exon 4	+	chr2:60459165-60459190	UAUUGUCAGCCUCUUCCUUUCAAUA	603
53335_4_51	BCL11a	Exon 4	+	chr2:60459174-60459199	CCUCUUCCUUUCAAUAUGGUAUACA	604
53335_4_52	BCL11a	Exon 4	+	chr2:60459223-60459248	UGUCCACUUGACAACCAAGUAGAUC	605
53335_4_53	BCL11a	Exon 4	+	chr2:60459238-60459263	CAAGUAGAUCUGGAUCUAUUUCUUU	606
53335_4_54	BCL11a	Exon 4	+	chr2:60459322-60459347	UUACUAGUGUAUUUAAUUGCGUUCC	607
53335_4_55	BCL11a	Exon 4	+	chr2:60459323-60459348	UACUAGUGUAUUUAAUUGCGUUCCA	608
53335_4_56	BCL11a	Exon 4	+	chr2:60459378-60459403	UCAUUGUUUAAAAAAAAUAAAACUU	609
53335_4_57	BCL11a	Exon 4	+	chr2:60459379-60459404	CAUUGUUUAAAAAAAAUAAAACUUU	610
53335_4_58	BCL11	Exon 4	+	chr2:60459413-	AGCCCAUUUCUUUUAAGCU	611

	a			60459438	CUCACC	
53335_4_59	BCL11a	Exon 4	+	chr2:60459435-60459460	ACCAGGAGCAAAGUAGCUUUUAUAC	612
53335_4_60	BCL11a	Exon 4	+	chr2:60459470-60459495	AGUUUUGUUUAUAAAAUUAAACUAA	613
53335_4_61	BCL11a	Exon 4	+	chr2:60459490-60459515	ACUAAAGGAAAAAUGAUGAUUAACU	614
53335_4_62	BCL11a	Exon 4	+	chr2:60459499-60459524	AAAAUGAUGAUUAACUAGGACAUAA	615
53335_4_63	BCL11a	Exon 4	+	chr2:60459500-60459525	AAAUGAUGAUUAACUAGGACAUAAU	616
53335_4_64	BCL11a	Exon 4	+	chr2:60459513-60459538	CUAGGACAUAAUGGGUCAUCUUUUU	617
53335_4_65	BCL11a	Exon 4	+	chr2:60459564-60459589	AUAUAGAAUUAUAUGCUAGUUCCUA	618
53335_4_66	BCL11a	Exon 4	+	chr2:60459632-60459657	UAACAAGUAGAAAGAACCAUCGAUG	619
53335_4_67	BCL11a	Exon 4	+	chr2:60459649-60459674	CAUCGAUGUGGUUUUAAUAGAUCCA	620
53335_4_68	BCL11a	Exon 4	+	chr2:60459718-60459743	GUUUUUCUGUUAAUUUGUCAAUUCA	621
53335_4_69	BCL11a	Exon 4	+	chr2:60459818-60459843	UCAGUGCUAUCUAUUCUGUCUAUAG	622
53335_4_70	BCL11a	Exon 4	+	chr2:60459819-60459844	CAGUGCUAUCUAUUCUGUCUAUAGA	623
53335_4_71	BCL11a	Exon 4	+	chr2:60459900-60459925	UAUGUAUUACAGAAUGUAUGCAGCA	624
53335_4_72	BCL11a	Exon 4	+	chr2:60459937-60459962	CUCUCUCUCUCUUUUUCUCUCAGAA	625
53335_4_73	BCL11a	Exon 4	+	chr2:60459943-60459968	CUCUCUUUUUCUCUCAGAACGGAAC	626
53335_4_74	BCL11a	Exon 4	+	chr2:60459977-60460002	CAACAUGUUUGCUCAGCAACGAAUU	627
53335_4_75	BCL11a	Exon 4	+	chr2:60459978-60460003	AACAUGUUUGCUCAGCAACGAAUUA	628
53335_4_76	BCL11	Exon 4	+	chr2:60460068-	ACAUGUAAAUUAUUGCACA	629

	a			60460093	AGAGAA	
53335_4_77	BCL11a	Exon 4	+	chr2:60460126-60460151	GCCCCAUACAGAUCAUGCAUUCAAA	630
53335_4_78	BCL11a	Exon 4	+	chr2:60460140-60460165	AUGCAUUCAAACGGUGAGAACAUAA	631
53335_4_79	BCL11a	Exon 4	+	chr2:60460193-60460218	AAAGAAAAAGAAAAAGAAAAAAAC	632
53335_4_80	BCL11a	Exon 4	+	chr2:60460201-60460226	AGAAAAAGAAAAAAAACAGGUGUGC	633
53335_4_81	BCL11a	Exon 4	+	chr2:60460269-60460294	UGUUUGUUUGUUUGUUUAAAUCACA	634
53335_4_82	BCL11a	Exon 4	+	chr2:60460270-60460295	GUUUGUUUGUUUGUUUAAAUCACAU	635
53335_4_83	BCL11a	Exon 4	+	chr2:60460291-60460316	ACAUGGGACUAGAAAAAAAUCCUAC	636
53335_4_84	BCL11a	Exon 4	+	chr2:60460292-60460317	CAUGGGACUAGAAAAAAAUCCUACA	637
53335_4_85	BCL11a	Exon 4	+	chr2:60460297-60460322	GACUAGAAAAAAAUCCUACAGGGAG	638
53335_4_86	BCL11a	Exon 4	+	chr2:60460298-60460323	ACUAGAAAAAAAUCCUACAGGGAGU	639
53335_4_87	BCL11a	Exon 4	+	chr2:60460299-60460324	CUAGAAAAAAAUCCUACAGGGAGUG	640
53335_4_88	BCL11a	Exon 4	+	chr2:60460303-60460328	AAAAAAAUCCUACAGGGAGUGGGGC	641
53335_4_89	BCL11a	Exon 4	+	chr2:60460306-60460331	AAAAUCCUACAGGGAGUGGGGCUGG	642
53335_4_90	BCL11a	Exon 4	+	chr2:60460307-60460332	AAAUCCUACAGGGAGUGGGGCUGGA	643
53335_4_91	BCL11a	Exon 4	+	chr2:60460313-60460338	UACAGGGAGUGGGGCUGGAGGGCGA	644
53335_4_92	BCL11a	Exon 4	+	chr2:60460314-60460339	ACAGGGAGUGGGGCUGGAGGGCGAU	645
53335_4_93	BCL11a	Exon 4	+	chr2:60460315-60460340	CAGGGAGUGGGGCUGGAGGGCGAUG	646
53335_4_94	BCL11	Exon 4	+	chr2:60460319-	GAGUGGGGCUGGAGGGCGA	647

	a			60460344	UGGGGA	
53335_4_95	BCL11a	Exon 4	+	chr2:60460320-60460345	AGUGGGGCUGGAGGGCGAUGGGGAA	648
53335_4_96	BCL11a	Exon 4	+	chr2:60460321-60460346	GUGGGGCUGGAGGGCGAUGGGGAAG	649
53335_4_97	BCL11a	Exon 4	+	chr2:60460326-60460351	GCUGGAGGGCGAUGGGGAAGGGGAG	650
53335_4_98	BCL11a	Exon 4	+	chr2:60460335-60460360	CGAUGGGGAAGGGGAGUGGUGAAAA	651
53335_4_99	BCL11a	Exon 4	+	chr2:60460336-60460361	GAUGGGGAAGGGGAGUGGUGAAAAA	652
53335_4_100	BCL11a	Exon 4	+	chr2:60460337-60460362	AUGGGGAAGGGGAGUGGUGAAAAAG	653
53335_4_101	BCL11a	Exon 4	+	chr2:60460338-60460363	UGGGGAAGGGGAGUGGUGAAAAAGG	654
53335_4_102	BCL11a	Exon 4	+	chr2:60460345-60460370	GGGGAGUGGUGAAAAAGGGGUGUC	655
53335_4_103	BCL11a	Exon 4	+	chr2:60460348-60460373	GAGUGGUGAAAAAGGGGGUGUCAGG	656
53335_4_104	BCL11a	Exon 4	+	chr2:60460349-60460374	AGUGGUGAAAAAGGGGGUGUCAGGU	657
53335_4_105	BCL11a	Exon 4	+	chr2:60460356-60460381	AAAAAGGGGGUGUCAGGUGGGAGUG	658
53335_4_106	BCL11a	Exon 4	+	chr2:60460357-60460382	AAAAGGGGGUGUCAGGUGGGAGUGA	659
53335_4_107	BCL11a	Exon 4	+	chr2:60460360-60460385	AGGGGGUGUCAGGUGGGAGUGAGGG	660
53335_4_108	BCL11a	Exon 4	+	chr2:60460361-60460386	GGGGGUGUCAGGUGGGAGUGAGGGA	661
53335_4_109	BCL11a	Exon 4	+	chr2:60460362-60460387	GGGGUGUCAGGUGGGAGUGAGGGAG	662
53335_4_110	BCL11a	Exon 4	+	chr2:60460442-60460467	GUGCCAUUUUUUCAUGUGUUUCUCC	663
53335_4_111	BCL11a	Exon 4	+	chr2:60460443-60460468	UGCCAUUUUUUCAUGUGUUUCUCCA	664
53335_4_11	BCL11	Exon 4	+	chr2:60460462-	UCUCCAGGGUACUGUACAC	665

2	a			60460487	GCUAAA	
53335_4_113	BCL11a	Exon 4	+	chr2:60460505-60460530	ACAUUUGUAAACGUCCUUCCCCACC	666
53335_4_114	BCL11a	Exon 4	+	chr2:60460527-60460552	ACCUGGCCAUGCGUUUUCAUGUGCC	667
53335_4_115	BCL11a	Exon 4	+	chr2:60460544-60460569	CAUGUGCCUGGUGAGCUUGCUACUC	668
53335_4_116	BCL11a	Exon 4	+	chr2:60460545-60460570	AUGUGCCUGGUGAGCUUGCUACUCU	669
53335_4_117	BCL11a	Exon 4	+	chr2:60460551-60460576	CUGGUGAGCUUGCUACUCUGGGCAC	670
53335_4_118	BCL11a	Exon 4	+	chr2:60460579-60460604	CAUAGUUGCACAGCUCGCAUUUAUA	671
53335_4_119	BCL11a	Exon 4	+	chr2:60460595-60460620	GCAUUUAUAAGGCCUUUCGCCCGUG	672
53335_4_120	BCL11a	Exon 4	+	chr2:60460607-60460632	CCUUUCGCCCGUGUGGCUUCUCCUG	673
53335_4_121	BCL11a	Exon 4	+	chr2:60460686-60460711	UCGCUGCGUCUGCCCUCUUUUUGAGC	674
53335_4_122	BCL11a	Exon 4	+	chr2:60460687-60460712	CGCUGCGUCUGCCCUCUUUUGAGCU	675
53335_4_123	BCL11a	Exon 4	+	chr2:60460696-60460721	UGCCCUCUUUUGAGCUGGGCCUGCC	676
53335_4_124	BCL11a	Exon 4	+	chr2:60460697-60460722	GCCCUCUUUUGAGCUGGGCCUGCCC	677
53335_4_125	BCL11a	Exon 4	+	chr2:60460702-60460727	CUUUUGAGCUGGGCCUGCCCGGGCC	678
53335_4_126	BCL11a	Exon 4	+	chr2:60460715-60460740	CCUGCCCGGGCCCGGACCACUAAUA	679
53335_4_127	BCL11a	Exon 4	+	chr2:60460716-60460741	CUGCCCGGGCCCGGACCACUAAUAU	680
53335_4_128	BCL11a	Exon 4	+	chr2:60460717-60460742	UGCCCGGGCCCGGACCACUAAUAUG	681
53335_4_129	BCL11a	Exon 4	+	chr2:60460776-60460801	CCCGAGAUCCCUCCGUCCAGCUCCC	682
53335_4_13	BCL11	Exon 4	+	chr2:60460777-	CCGAGAUCCCUCCGUCCAG	683

0	a			60460802	CUCCCC	
53335_4_131	BCL11a	Exon 4	+	chr2:60460780-60460805	AGAUCCCUCCGUCCAGCUCCCCGGG	684
53335_4_132	BCL11a	Exon 4	+	chr2:60460785-60460810	CCUCCGUCCAGCUCCCCGGGCGGUG	685
53335_4_133	BCL11a	Exon 4	+	chr2:60460812-60460837	GAGAAGCGCAAACUCCCGUUCUCCG	686
53335_4_134	BCL11a	Exon 4	+	chr2:60460827-60460852	CCGUUCUCCGAGGAGUGCUCCGACG	687
53335_4_135	BCL11a	Exon 4	+	chr2:60460830-60460855	UUCUCCGAGGAGUGCUCCGACGAGG	688
53335_4_136	BCL11a	Exon 4	+	chr2:60460837-60460862	AGGAGUGCUCCGACGAGGAGGCAAA	689
53335_4_137	BCL11a	Exon 4	+	chr2:60460848-60460873	GACGAGGAGGCAAAAGGCGAUUGUC	690
53335_4_138	BCL11a	Exon 4	+	chr2:60460865-60460890	CGAUUGUCUGGAGUCUCCGAAGCUA	691
53335_4_139	BCL11a	Exon 4	+	chr2:60460869-60460894	UGUCUGGAGUCUCCGAAGCUAAGGA	692
53335_4_140	BCL11a	Exon 4	+	chr2:60460870-60460895	GUCUGGAGUCUCCGAAGCUAAGGAA	693
53335_4_141	BCL11a	Exon 4	+	chr2:60460887-60460912	CUAAGGAAGGGAUCUUUGAGCUGCC	694
53335_4_142	BCL11a	Exon 4	+	chr2:60460890-60460915	AGGAAGGGAUCUUUGAGCUGCCUGG	695
53335_4_143	BCL11a	Exon 4	+	chr2:60460902-60460927	UUGAGCUGCCUGGAGGCCGCGUAGC	696
53335_4_144	BCL11a	Exon 4	+	chr2:60460935-60460960	CACUGCGAGUACACGUUCUCCGUGU	697
53335_4_145	BCL11a	Exon 4	+	chr2:60460936-60460961	ACUGCGAGUACACGUUCUCCGUGUU	698
53335_4_146	BCL11a	Exon 4	+	chr2:60460944-60460969	UACACGUUCUCCGUGUUGGGCAUCG	699
53335_4_147	BCL11a	Exon 4	+	chr2:60460948-60460973	CGUUCUCCGUGUUGGGCAUCGCGGC	700
53335_4_14	BCL11	Exon 4	+	chr2:60460949-	GUUCUCCGUGUUGGGCAUC	701

8	a			60460974	GCGGCC	
53335_4_149	BCL11a	Exon 4	+	chr2:60460950-60460975	UUCUCCGUGUUGGGCAUCGCGGCCG	702
53335_4_150	BCL11a	Exon 4	+	chr2:60460951-60460976	UCUCCGUGUUGGGCAUCGCGGCCGG	703
53335_4_151	BCL11a	Exon 4	+	chr2:60460955-60460980	CGUGUUGGGCAUCGCGGCCGGGGGC	704
53335_4_152	BCL11a	Exon 4	+	chr2:60460992-60461017	UUCUCGAGCUUGAUGCGCUUAGAGA	705
53335_4_153	BCL11a	Exon 4	+	chr2:60460993-60461018	UCUCGAGCUUGAUGCGCUUAGAGAA	706
53335_4_154	BCL11a	Exon 4	+	chr2:60460994-60461019	CUCGAGCUUGAUGCGCUUAGAGAAG	707
53335_4_155	BCL11a	Exon 4	+	chr2:60461007-60461032	CGCUUAGAGAAGGGGCUCAGCGAGC	708
53335_4_156	BCL11a	Exon 4	+	chr2:60461008-60461033	GCUUAGAGAAGGGGCUCAGCGAGCU	709
53335_4_157	BCL11a	Exon 4	+	chr2:60461009-60461034	CUUAGAGAAGGGGCUCAGCGAGCUG	710
53335_4_158	BCL11a	Exon 4	+	chr2:60461031-60461056	CUGGGGCUGCCCAGCAGCAGCUUUU	711
53335_4_159	BCL11a	Exon 4	+	chr2:60461036-60461061	GCUGCCCAGCAGCAGCUUUUUGGAC	712
53335_4_160	BCL11a	Exon 4	+	chr2:60461046-60461071	AGCAGCUUUUUGGACAGGCCCCCCG	713
53335_4_161	BCL11a	Exon 4	+	chr2:60461059-60461084	ACAGGCCCCCCGAGGCCGACUCGCC	714
53335_4_162	BCL11a	Exon 4	+	chr2:60461060-60461085	CAGGCCCCCCGAGGCCGACUCGCCC	715
53335_4_163	BCL11a	Exon 4	+	chr2:60461061-60461086	AGGCCCCCCGAGGCCGACUCGCCCG	716
53335_4_164	BCL11a	Exon 4	+	chr2:60461072-60461097	GGCCGACUCGCCCGGGGAGCAGCCG	717
53335_4_165	BCL11a	Exon 4	+	chr2:60461099-60461124	GCCAUUAACAGUGCCAUCGUCUAUG	718
53335_4_16	BCL11	Exon 4	+	chr2:60461112-	CCAUCGUCUAUGCGGUCCG	719

6	a			60461137	ACUCGC	
53335_4_167	BCL11a	Exon 4	+	chr2:60461144-60461169	CGAGUCUUCGUCGCAAGUGUCCCUG	720
53335_4_168	BCL11a	Exon 4	+	chr2:60461151-60461176	UCGUCGCAAGUGUCCCUGUGGCCCU	721
53335_4_169	BCL11a	Exon 4	+	chr2:60461157-60461182	CAAGUGUCCCUGUGGCCCUCGGCCU	722
53335_4_170	BCL11a	Exon 4	+	chr2:60461162-60461187	GUCCCUGUGGCCCUCGGCCUCGGCC	723
53335_4_171	BCL11a	Exon 4	+	chr2:60461165-60461190	CCUGUGGCCCUCGGCCUCGGCCAGG	724
53335_4_172	BCL11a	Exon 4	+	chr2:60461189-60461214	GUGGCCGCGCUUAUGCUUCUCGCCC	725
53335_4_173	BCL11a	Exon 4	+	chr2:60461195-60461220	GCGCUUAUGCUUCUCGCCCAGGACC	726
53335_4_174	BCL11a	Exon 4	+	chr2:60461198-60461223	CUUAUGCUUCUCGCCCAGGACCUGG	727
53335_4_175	BCL11a	Exon 4	+	chr2:60461202-60461227	UGCUUCUCGCCCAGGACCUGGUGGA	728
53335_4_176	BCL11a	Exon 4	+	chr2:60461223-60461248	UGGAAGGCCUCGCUGAAGUGCUGCA	729
53335_4_177	BCL11a	Exon 4	+	chr2:60461253-60461278	CUGAGCACCAUGCCCUGCAUGACGU	730
53335_4_178	BCL11a	Exon 4	+	chr2:60461254-60461279	UGAGCACCAUGCCCUGCAUGACGUC	731
53335_4_179	BCL11a	Exon 4	+	chr2:60461258-60461283	CACCAUGCCCUGCAUGACGUCGGGC	732
53335_4_180	BCL11a	Exon 4	+	chr2:60461259-60461284	ACCAUGCCCUGCAUGACGUCGGGCA	733
53335_4_181	BCL11a	Exon 4	+	chr2:60461264-60461289	GCCCUGCAUGACGUCGGGCAGGGCG	734
53335_4_182	BCL11a	Exon 4	+	chr2:60461312-60461337	GACCGCGCCCCGCGAGCUGUUCUCG	735
53335_4_183	BCL11a	Exon 4	+	chr2:60461315-60461340	CGCGCCCCGCGAGCUGUUCUCGUGG	736
53335_4_18	BCL11	Exon 4	+	chr2:60461330-	GUUCUCGUGGUGGCGCGCC	737

4	a			60461355	GCCUCC	
53335_4_185	BCL11a	Exon 4	+	chr2:60461446-60461471	CCUCUUCCUCCUCGUCCCCG UUCUC	738
53335_4_186	BCL11a	Exon 4	+	chr2:60461447-60461472	CUCUUCCUCCUCGUCCCCG UUCUCC	739
53335_4_187	BCL11a	Exon 4	+	chr2:60461453-60461478	CUCCUCGUCCCCGUUCUCC GGGAUC	740
53335_4_188	BCL11a	Exon 4	+	chr2:60461457-60461482	UCGUCCCCGUUCUCCGGGA UCAGGU	741
53335_4_189	BCL11a	Exon 4	+	chr2:60461458-60461483	CGUCCCCGUUCUCCGGGAU CAGGUU	742
53335_4_190	BCL11a	Exon 4	+	chr2:60461459-60461484	GUCCCCGUUCUCCGGGAUC AGGUUG	743
53335_4_191	BCL11a	Exon 4	+	chr2:60461481-60461506	UUGGGGUCGUUCUCGCUCU UGAACU	744
53335_4_192	BCL11a	Exon 4	+	chr2:60461490-60461515	UUCUCGCUCUUGAACUUGG CCACCA	745
53335_4_193	BCL11a	Exon 4	+	chr2:60461508-60461533	GCCACCACGGACUUGAGCG CGCUGC	746
53335_4_194	BCL11a	Exon 4	+	chr2:60461529-60461554	CUGCUGGCGCUGCCCACCA AGUCGC	747
53335_4_195	BCL11a	Exon 4	+	chr2:60461535-60461560	GCGCUGCCCACCAAGUCGC UGGUGC	748
53335_4_196	BCL11a	Exon 4	+	chr2:60461536-60461561	CGCUGCCCACCAAGUCGCU GGUGCC	749
53335_4_197	BCL11a	Exon 4	+	chr2:60461542-60461567	CCACCAAGUCGCUGGUGCC GGGUUC	750
53335_4_198	BCL11a	Exon 4	+	chr2:60461543-60461568	CACCAAGUCGCUGGUGCCG GGUUCC	751
53335_4_199	BCL11a	Exon 4	+	chr2:60461544-60461569	ACCAAGUCGCUGGUGCCGG GUUCCG	752
53335_4_200	BCL11a	Exon 4	+	chr2:60461550-60461575	UCGCUGGUGCCGGGUUCCG GGGAGC	753
53335_4_201	BCL11a	Exon 4	+	chr2:60461553-60461578	CUGGUGCCGGGUUCCGGGG AGCUGG	754
53335_4_20	BCL11	Exon 4	+	chr2:60461556-	GUGCCGGGUUCCGGGGAGC	755

2	a			60461581	UGGCGG	
53335_4_203	BCL11a	Exon 4	+	chr2:60461571-60461596	GAGCUGGCGGUGGAGAGACCGUCGU	756
53335_4_204	BCL11a	Exon 4	+	chr2:60461586-60461611	AGACCGUCGUCGGACUUGACCGUCA	757
53335_4_205	BCL11a	Exon 4	+	chr2:60461587-60461612	GACCGUCGUCGGACUUGACCGUCAU	758
53335_4_206	BCL11a	Exon 4	+	chr2:60461588-60461613	ACCGUCGUCGGACUUGACCGUCAUG	759
53335_4_207	BCL11a	Exon 4	+	chr2:60461589-60461614	CCGUCGUCGGACUUGACCGUCAUGG	760
53335_4_208	BCL11a	Exon 4	+	chr2:60461618-60461643	CGAUUUGUGCAUGUGCGUCUUCAUG	761
53335_4_209	BCL11a	Exon 4	+	chr2:60461634-60461659	GUCUUCAUGUGGCGCUUCAGCUUGC	762
53335_4_210	BCL11a	Exon 4	+	chr2:60461639-60461664	CAUGUGGCGCUUCAGCUUGCUGGCC	763
53335_4_211	BCL11a	Exon 4	+	chr2:60461640-60461665	AUGUGGCGCUUCAGCUUGCUGGCCU	764
53335_4_212	BCL11a	Exon 4	+	chr2:60461651-60461676	CAGCUUGCUGGCCUGGGUGCACGCG	765
53335_4_213	BCL11a	Exon 4	+	chr2:60461660-60461685	GGCCUGGGUGCACGCGUGGUCGCAC	766
53335_4_214	BCL11a	Exon 4	+	chr2:60461673-60461698	GCGUGGUCGCACAGGUUGCACUUGU	767
53335_4_215	BCL11a	Exon 4	+	chr2:60461674-60461699	CGUGGUCGCACAGGUUGCACUUGUA	768
53335_4_216	BCL11a	Exon 4	+	chr2:60461690-60461715	GCACUUGUAGGGCUUCUCGCCCGUG	769
53335_4_217	BCL11a	Exon 4	+	chr2:60461699-60461724	GGGCUUCUCGCCCGUGUGGCUGCGC	770
53335_4_218	BCL11a	Exon 4	+	chr2:60461711-60461736	CGUGUGGCUGCGCCGGUGCACCACC	771
53335_4_219	BCL11a	Exon 4	+	chr2:60461757-60461782	GUCUUGCCGCAGAACUCGCAUGACU	772
53335_4_22	BCL11	Exon 4	+	chr2:60461767-	AGAACUCGCAUGACUUGGA	773

0	a			60461792	CUUGAC	
53335_4_221	BCL11a	Exon 4	+	chr2:60461768-60461793	GAACUCGCAUGACUUGGACUUGACC	774
53335_4_222	BCL11a	Exon 4	+	chr2:60461769-60461794	AACUCGCAUGACUUGGACUUGACCG	775
53335_4_223	BCL11a	Exon 4	+	chr2:60461770-60461795	ACUCGCAUGACUUGGACUUGACCGG	776
53335_4_224	BCL11a	Exon 4	+	chr2:60461774-60461799	GCAUGACUUGGACUUGACCGGGGGC	777
53335_4_225	BCL11a	Exon 4	+	chr2:60461775-60461800	CAUGACUUGGACUUGACCGGGGCU	778
53335_4_226	BCL11a	Exon 4	+	chr2:60461778-60461803	GACUUGGACUUGACCGGGGGCUGGG	779
53335_4_227	BCL11a	Exon 4	+	chr2:60461779-60461804	ACUUGGACUUGACCGGGGGCUGGGA	780
53335_4_228	BCL11a	Exon 4	+	chr2:60461782-60461807	UGGACUUGACCGGGGGCUGGGAGGG	781
53335_4_229	BCL11a	Exon 4	+	chr2:60461785-60461810	ACUUGACCGGGGGCUGGGAGGGAGG	782
53335_4_230	BCL11a	Exon 4	+	chr2:60461786-60461811	CUUGACCGGGGGCUGGGAGGGAGGA	783
53335_4_231	BCL11a	Exon 4	+	chr2:60461787-60461812	UUGACCGGGGGCUGGGAGGGAGGAG	784
53335_4_232	BCL11a	Exon 4	+	chr2:60461790-60461815	ACCGGGGGCUGGGAGGGAGGAGGGG	785
53335_4_233	BCL11a	Exon 4	+	chr2:60461800-60461825	GGGAGGGAGGAGGGGCGGAUUGCAG	786
53335_4_234	BCL11a	Exon 4	+	chr2:60461803-60461828	AGGGAGGAGGGGCGGAUUGCAGAGG	787
53335_4_235	BCL11a	Exon 4	+	chr2:60461804-60461829	GGGAGGAGGGGCGGAUUGCAGAGGA	788
53335_4_236	BCL11a	Exon 4	+	chr2:60461807-60461832	AGGAGGGGCGGAUUGCAGAGGAGGG	789
53335_4_237	BCL11a	Exon 4	+	chr2:60461808-60461833	GGAGGGGCGGAUUGCAGAGGAGGGA	790
53335_4_23	BCL11	Exon 4	+	chr2:60461809-	GAGGGGCGGAUUGCAGAGG	791

8	a			60461834	AGGGAG	
53335_4_239	BCL11a	Exon 4	+	chr2:60461810-60461835	AGGGGCGGAUUGCAGAGGAGGGAGG	792
53335_4_240	BCL11a	Exon 4	+	chr2:60461811-60461836	GGGGCGGAUUGCAGAGGAGGGAGGG	793
53335_4_241	BCL11a	Exon 4	+	chr2:60461812-60461837	GGGCGGAUUGCAGAGGAGGGAGGGG	794
53335_4_242	BCL11a	Exon 4	+	chr2:60461822-60461847	CAGAGGAGGGAGGGGGGGCGUCGCC	795
53335_4_243	BCL11a	Exon 4	+	chr2:60461826-60461851	GGAGGGAGGGGGGGCGUCGCCAGGA	796
53335_4_244	BCL11a	Exon 4	+	chr2:60461827-60461852	GAGGGAGGGGGGGCGUCGCCAGGAA	797
53335_4_245	BCL11a	Exon 4	+	chr2:60461830-60461855	GGAGGGGGGGCGUCGCCAGGAAGGG	798
53335_4_246	BCL11a	Exon 4	+	chr2:60461842-60461867	UCGCCAGGAAGGGCGGCUUGCUACC	799
53335_4_247	BCL11a	Exon 4	+	chr2:60461846-60461871	CAGGAAGGGCGGCUUGCUACCUGGC	800
53335_4_248	BCL11a	Exon 4	+	chr2:60461851-60461876	AGGGCGGCUUGCUACCUGGCUGGAA	801
53335_4_249	BCL11a	Exon 4	+	chr2:60461872-60461897	GGAAUGGUUGCAGUAACCUUUGCAU	802
53335_4_250	BCL11a	Exon 4	+	chr2:60461873-60461898	GAAUGGUUGCAGUAACCUUUGCAUA	803
53335_4_251	BCL11a	Exon 4	+	chr2:60461877-60461902	GGUUGCAGUAACCUUUGCAUAGGGC	804
53335_4_252	BCL11a	Exon 4	+	chr2:60461878-60461903	GUUGCAGUAACCUUUGCAUAGGGCU	805
53335_4_253	BCL11a	Exon 4	+	chr2:60461882-60461907	CAGUAACCUUUGCAUAGGGCUGGGC	806
53335_4_254	BCL11a	Exon 4	+	chr2:60461887-60461912	ACCUUUGCAUAGGGCUGGGCCGGCC	807
53335_4_255	BCL11a	Exon 4	+	chr2:60461888-60461913	CCUUUGCAUAGGGCUGGGCCGGCCU	808
53335_4_25	BCL11	Exon 4	+	chr2:60461889-	CUUUGCAUAGGGCUGGGCC	809

6	a			60461914	GGCCUG	
53335_4_257	BCL11a	Exon 4	+	chr2:60461896-60461921	UAGGGCUGGGCCGGCCUGGGGACAG	810
53335_4_258	BCL11a	Exon 4	+	chr2:60461899-60461924	GGCUGGGCCGGCCUGGGGACAGCGG	811
53335_4_259	BCL11a	Exon 4	+	chr2:60461900-60461925	GCUGGGCCGGCCUGGGGACAGCGGU	812
53335_4_260	BCL11a	Exon 4	+	chr2:60461949-60461974	UCUCUAAGUCUCCUAGAGAAAUCCA	813
53335_4_261	BCL11a	Exon 4	+	chr2:60461952-60461977	CUAAGUCUCCUAGAGAAAUCCAUGG	814
53335_4_262	BCL11a	Exon 4	+	chr2:60461953-60461978	UAAGUCUCCUAGAGAAAUCCAUGGC	815
53335_4_263	BCL11a	Exon 4	+	chr2:60461956-60461981	GUCUCCUAGAGAAAUCCAUGGCGGG	816
53335_4_264	BCL11a	Exon 4	+	chr2:60461971-60461996	CCAUGGCGGGAGGCUCCAUAGCCAU	817
53335_4_265	BCL11a	Exon 4	+	chr2:60461997-60462022	GGAUUCAACCGCAGCACCCUGUCAA	818
53335_4_266	BCL11a	Exon 4	+	chr2:60462004-60462029	ACCGCAGCACCCUGUCAAAGGCACU	819
53335_4_267	BCL11a	Exon 4	+	chr2:60462005-60462030	CCGCAGCACCCUGUCAAAGGCACUC	820
53335_4_268	BCL11a	Exon 4	+	chr2:60462011-60462036	CACCCUGUCAAAGGCACUCGGGUGA	821
53335_4_269	BCL11a	Exon 4	+	chr2:60462012-60462037	ACCCUGUCAAAGGCACUCGGGUGAU	822
53335_4_270	BCL11a	Exon 4	+	chr2:60462015-60462040	CUGUCAAAGGCACUCGGGUGAUGGG	823
53335_4_271	BCL11a	Exon 4	+	chr2:60462020-60462045	AAAGGCACUCGGGUGAUGGGUGGCC	824
53335_4_272	BCL11a	Exon 4	+	chr2:60462021-60462046	AAGGCACUCGGGUGAUGGGUGGCCA	825
53335_4_273	BCL11a	Exon 4	+	chr2:60462041-60462066	GGCCAGGGCCAUCUCUUCCGCCCCC	826
53335_4_27	BCL11	Exon 4	+	chr2:60462053-	CUCUUCCGCCCCCAGGCGC	827

4	a			60462078	UCUAUG	
53335_4_275	BCL11a	Exon 4	+	chr2:60462056-60462081	UUCCGCCCCCAGGCGCUCUAUGCGG	828
53335_4_276	BCL11a	Exon 4	+	chr2:60462057-60462082	UCCGCCCCCAGGCGCUCUAUGCGGU	829
53335_4_277	BCL11a	Exon 4	+	chr2:60462058-60462083	CCGCCCCCAGGCGCUCUAUGCGGUG	830
53335_4_278	BCL11a	Exon 4	+	chr2:60462059-60462084	CGCCCCCAGGCGCUCUAUGCGGUGG	831
53335_4_279	BCL11a	Exon 4	+	chr2:60462076-60462101	UGCGGUGGGGGUCCAAGUGAUGUCU	832
53335_4_280	BCL11a	Exon 4	+	chr2:60462079-60462104	GGUGGGGGUCCAAGUGAUGUCUCGG	833
53335_4_281	BCL11a	Exon 4	+	chr2:60462082-60462107	GGGGGUCCAAGUGAUGUCUCGGUGG	834
53335_4_282	BCL11a	Exon 4	+	chr2:60462092-60462117	GUGAUGUCUCGGUGGUGGACUAAAC	835
53335_4_283	BCL11a	Exon 4	+	chr2:60462093-60462118	UGAUGUCUCGGUGGUGGACUAAACA	836
53335_4_284	BCL11a	Exon 4	+	chr2:60462094-60462119	GAUGUCUCGGUGGUGGACUAAACAG	837
53335_4_285	BCL11a	Exon 4	+	chr2:60462095-60462120	AUGUCUCGGUGGUGGACUAAACAGG	838
53335_4_286	BCL11a	Exon 4	+	chr2:60462096-60462121	UGUCUCGGUGGUGGACUAAACAGGG	839
53335_4_287	BCL11a	Exon 4	+	chr2:60462097-60462122	GUCUCGGUGGUGGACUAAACAGGGG	840
53335_4_288	BCL11a	Exon 4	+	chr2:60462102-60462127	GGUGGUGGACUAAACAGGGGGGGAG	841
53335_4_289	BCL11a	Exon 4	+	chr2:60462103-60462128	GUGGUGGACUAAACAGGGGGGGAGU	842
53335_4_290	BCL11a	Exon 4	+	chr2:60462106-60462131	GUGGACUAAACAGGGGGGGAGUGGG	843
53335_4_291	BCL11a	Exon 4	+	chr2:60462125-60462150	AGUGGGUGGAAAGCGCCCUUCUGCC	844
53335_4_29	BCL11	Exon 4	+	chr2:60462129-	GGUGGAAAGCGCCCUUCUG	845

2	a			60462154	CCAGGC	
53335_4_293	BCL11a	Exon 4	+	chr2:60462154-60462179	CGGAAGCCUCUCUCGAUACUGAUCC	846
53335_4_294	BCL11a	Exon 4	+	chr2:60462167-60462192	CGAUACUGAUCCUGGUAUUCUUAGC	847
53335_4_295	BCL11a	Exon 4	+	chr2:60462174-60462199	GAUCCUGGUAUUCUUAGCAGGUUAA	848
53335_4_296	BCL11a	Exon 4	+	chr2:60462175-60462200	AUCCUGGUAUUCUUAGCAGGUUAAA	849
53335_4_297	BCL11a	Exon 4	+	chr2:60462176-60462201	UCCUGGUAUUCUUAGCAGGUUAAAG	850
53335_4_298	BCL11a	Exon 4	+	chr2:60462203-60462228	GUUAUUGUCUGCAAUAUGAAUCCCA	851
53335_4_299	BCL11a	Exon 4	+	chr2:60462208-60462233	UGUCUGCAAUAUGAAUCCCAUGGAG	852
53335_4_300	BCL11a	Exon 4	+	chr2:60462211-60462236	CUGCAAUAUGAAUCCCAUGGAGAGG	853
53335_4_301	BCL11a	Exon 4	+	chr2:60462215-60462240	AAUAUGAAUCCCAUGGAGAGGUGGC	854
53335_4_302	BCL11a	Exon 4	+	chr2:60462216-60462241	AUAUGAAUCCCAUGGAGAGGUGGCU	855
53335_4_303	BCL11a	Exon 4	+	chr2:60462220-60462245	GAAUCCCAUGGAGAGGUGGCUGGGA	856
53335_4_304	BCL11a	Exon 4	+	chr2:60462244-60462269	AAGGACAUUCUGCACCUAGUCCUGA	857
53335_4_305	BCL11a	Exon 4	+	chr2:60462245-60462270	AGGACAUUCUGCACCUAGUCCUGAA	858
53335_4_306	BCL11a	Exon 4	+	chr2:60462259-60462284	CUAGUCCUGAAGGGAUACCAACCCG	859
53335_4_307	BCL11a	Exon 4	+	chr2:60462260-60462285	UAGUCCUGAAGGGAUACCAACCCGC	860
53335_4_308	BCL11a	Exon 4	+	chr2:60462261-60462286	AGUCCUGAAGGGAUACCAACCCGCG	861
53335_4_309	BCL11a	Exon 4	+	chr2:60462266-60462291	UGAAGGGAUACCAACCCGCGGGGUC	862
53335_4_31	BCL11	Exon 4	+	chr2:60462267-	GAAGGGAUACCAACCCGCG	863

0	a			60462292	GGGUCA	
53335_4_311	BCL11a	Exon 4	+	chr2:60462268-60462293	AAGGGAUACCAACCCGCGGGGUCAG	864
53335_4_312	BCL11a	Exon 4	+	chr2:60462345-60462370	GCGUGUUGCAAGAGAAACCAUGCAC	865
53335_4_313	BCL11a	Exon 4	+	chr2:60462352-60462377	GCAAGAGAAACCAUGCACUGGUGAA	866
53335_4_314	BCL11a	Exon 4	+	chr2:60462384-60462409	UUGCAAGUUGUACAUGUGUAGCUGC	867
53335_4_315	BCL11a	Exon 4	+	chr2:60462385-60462410	UGCAAGUUGUACAUGUGUAGCUGCU	868
53335_4_316	BCL11a	Exon 4	-	chr2:60457269-60457294	GGAAAAACCACUGUCUGUGUUUUUU	869
53335_4_317	BCL11a	Exon 4	-	chr2:60457295-60457320	GUUUCUGGUCUUUGUUAAGUUCUAU	870
53335_4_318	BCL11a	Exon 4	-	chr2:60457315-60457340	CCUGGCUUUUUAUUGUAUUUGUUUC	871
53335_4_319	BCL11a	Exon 4	-	chr2:60457338-60457363	AAGAUGACCAAAGGUCAUUACAACC	872
53335_4_320	BCL11a	Exon 4	-	chr2:60457352-60457377	AAAAAAAAAAAUAAAAGAUGACCAA	873
53335_4_321	BCL11a	Exon 4	-	chr2:60457415-60457440	UGCUUAUGUGCCCUGUUCAAAACAG	874
53335_4_322	BCL11a	Exon 4	-	chr2:60457459-60457484	AACUUGAAAUUUUAUCUUUUACUAU	875
53335_4_323	BCL11a	Exon 4	-	chr2:60457460-60457485	UAACUUGAAAUUUUAUCUUUUACUA	876
53335_4_324	BCL11a	Exon 4	-	chr2:60457522-60457547	AUGGCAAUGCAGAAUAUUUUGUUAU	877
53335_4_325	BCL11a	Exon 4	-	chr2:60457546-60457571	GCUUUAGUCAAUACUUUUUUGUAAA	878
53335_4_326	BCL11a	Exon 4	-	chr2:60457613-60457638	ACUAAAUGGUGCUUUAUAUUUAGAU	879
53335_4_327	BCL11a	Exon 4	-	chr2:60457632-60457657	GUUUUUUUCAUUGCCAAAAACUAAA	880
53335_4_32	BCL11	Exon 4	-	chr2:60457786-	AUGCAGUACUGCAAGCUAA	881

8	a			60457811	UAACGU	
53335_4_329	BCL11a	Exon 4	-	chr2:60457858-60457883	AAUGUCACAUGGAUGGCUGUCAUAG	882
53335_4_330	BCL11a	Exon 4	-	chr2:60457859-60457884	GAAUGUCACAUGGAUGGCUGUCAUA	883
53335_4_331	BCL11a	Exon 4	-	chr2:60457860-60457885	AGAAUGUCACAUGGAUGGCUGUCAU	884
53335_4_332	BCL11a	Exon 4	-	chr2:60457870-60457895	GGAGCCUGCUAGAAUGUCACAUGGA	885
53335_4_333	BCL11a	Exon 4	-	chr2:60457874-60457899	UGGGGGAGCCUGCUAGAAUGUCACA	886
53335_4_334	BCL11a	Exon 4	-	chr2:60457896-60457921	GAGAAGCCAUAUAAUGGCGGUUUGG	887
53335_4_335	BCL11a	Exon 4	-	chr2:60457897-60457922	UGAGAAGCCAUAUAAUGGCGGUUUG	888
53335_4_336	BCL11a	Exon 4	-	chr2:60457898-60457923	AUGAGAAGCCAUAUAAUGGCGGUUU	889
53335_4_337	BCL11a	Exon 4	-	chr2:60457899-60457924	GAUGAGAAGCCAUAUAAUGGCGGUU	890
53335_4_338	BCL11a	Exon 4	-	chr2:60457904-60457929	UUACAGAUGAGAAGCCAUAUAAUGG	891
53335_4_339	BCL11a	Exon 4	-	chr2:60457907-60457932	ACAUUACAGAUGAGAAGCCAUAUAA	892
53335_4_340	BCL11a	Exon 4	-	chr2:60457999-60458024	CCACAGUAUAUUUUUUUAAUUUGGC	893
53335_4_341	BCL11a	Exon 4	-	chr2:60458003-60458028	GCUGCCACAGUAUAUUUUUUUAAUU	894
53335_4_342	BCL11a	Exon 4	-	chr2:60458030-60458055	UUUUGGUAGUGGAAAAAAAAAAGAC	895
53335_4_343	BCL11a	Exon 4	-	chr2:60458046-60458071	GGUAUCAAUGUACCUUUUUUGGUAG	896
53335_4_344	BCL11a	Exon 4	-	chr2:60458052-60458077	UUAAAAGGUAUCAAUGUACCUUUUU	897
53335_4_345	BCL11a	Exon 4	-	chr2:60458072-60458097	UUUAACUGUUGCUUGUUCUCUUAAA	898
53335_4_34	BCL11	Exon 4	-	chr2:60458130-	UUGAAUUAAAUGUUCAUCU	899

6	a			60458155	AGUGUU	
53335_4_347	BCL11a	Exon 4	-	chr2:60458161-60458186	UGGUCUUUUUUCUGUAUUUCUAGAA	900
53335_4_348	BCL11a	Exon 4	-	chr2:60458186-60458211	UGAUUCCUAUGCUAAAAUACAUUUA	901
53335_4_349	BCL11a	Exon 4	-	chr2:60458231-60458256	UUAAGAUUAUAUAGUACUUAAAUAU	902
53335_4_350	BCL11a	Exon 4	-	chr2:60458260-60458285	AAAAAAAAAAACAUACAUUGGGGAA	903
53335_4_351	BCL11a	Exon 4	-	chr2:60458265-60458290	UUGUAAAAAAAAAAAAACAUACAUUG	904
53335_4_352	BCL11a	Exon 4	-	chr2:60458266-60458291	GUUGUAAAAAAAAAAAAACAUACAUU	905
53335_4_353	BCL11a	Exon 4	-	chr2:60458267-60458292	GGUUGUAAAAAAAAAAAAACAUACAU	906
53335_4_354	BCL11a	Exon 4	-	chr2:60458293-60458318	AUGCCUUGGAUACACACCGCUCUUC	907
53335_4_355	BCL11a	Exon 4	-	chr2:60458312-60458337	AAAUGGUAGUGGAAAUUCUAUGCCU	908
53335_4_356	BCL11a	Exon 4	-	chr2:60458328-60458353	CUUGUUAUCCAUUUAAAAAUGGUAG	909
53335_4_357	BCL11a	Exon 4	-	chr2:60458334-60458359	ACAAGACUUGUUAUCCAUUUAAAAA	910
53335_4_358	BCL11a	Exon 4	-	chr2:60458366-60458391	GCAUUUUAGGGUUCCAUUGUCUUGG	911
53335_4_359	BCL11a	Exon 4	-	chr2:60458369-60458394	ACUGCAUUUUAGGGUUCCAUUGUCU	912
53335_4_360	BCL11a	Exon 4	-	chr2:60458383-60458408	AUGUUUAGGGGGGAACUGCAUUUUA	913
53335_4_361	BCL11a	Exon 4	-	chr2:60458384-60458409	UAUGUUUAGGGGGGAACUGCAUUUU	914
53335_4_362	BCL11a	Exon 4	-	chr2:60458398-60458423	AAAAAACACUUCAUUAUGUUUAGGG	915
53335_4_363	BCL11a	Exon 4	-	chr2:60458399-60458424	UAAAAAACACUUCAUUAUGUUUAGG	916
53335_4_36	BCL11	Exon 4	-	chr2:60458400-	UUAAAAAACACUUCAUUAU	917

4	a			60458425	GUUUAG	
53335_4_365	BCL11a	Exon 4	-	chr2:60458401-60458426	UUUAAAAAACACUUCAUUAUGUUUA	918
53335_4_366	BCL11a	Exon 4	-	chr2:60458402-60458427	UUUUAAAAAACACUUCAUUAUGUUU	919
53335_4_367	BCL11a	Exon 4	-	chr2:60458478-60458503	UGAUUGCUUUCGCUUCUACAGUGCA	920
53335_4_368	BCL11a	Exon 4	-	chr2:60458535-60458560	GACGCAACAUUGCAAGCGCUGUGAA	921
53335_4_369	BCL11a	Exon 4	-	chr2:60458562-60458587	UACUUGACUAUUGAGCUUACUUACU	922
53335_4_370	BCL11a	Exon 4	-	chr2:60458634-60458659	AAAAAAAUUGAACACAAUCUCAUUG	923
53335_4_371	BCL11a	Exon 4	-	chr2:60458682-60458707	UCCCAGUUUACAGGUCUAUACUUAA	924
53335_4_372	BCL11a	Exon 4	-	chr2:60458683-60458708	UUCCCAGUUUACAGGUCUAUACUUA	925
53335_4_373	BCL11a	Exon 4	-	chr2:60458696-60458721	GCACUGUACAAUUUUCCCAGUUUAC	926
53335_4_374	BCL11a	Exon 4	-	chr2:60458734-60458759	GAGUAUAAAAUAAACCUGCUCAGAU	927
53335_4_375	BCL11a	Exon 4	-	chr2:60458764-60458789	AUCUUUUCUCUAAUCAGAGAUACAG	928
53335_4_376	BCL11a	Exon 4	-	chr2:60458829-60458854	AAUAAAAGCUAGCAUCUGCCCCAGU	929
53335_4_377	BCL11a	Exon 4	-	chr2:60458897-60458922	UGUGCUAUUUGUGUUAACAUGGAAG	930
53335_4_378	BCL11a	Exon 4	-	chr2:60458903-60458928	ACACUGUGUGCUAUUUGUGUUAACA	931
53335_4_379	BCL11a	Exon 4	-	chr2:60459085-60459110	ACUAUUUGCCAUUUAAAACUAGAAC	932
53335_4_380	BCL11a	Exon 4	-	chr2:60459114-60459139	AAUAAUAUGAUUUAUUAGCACAACG	933
53335_4_381	BCL11a	Exon 4	-	chr2:60459152-60459177	AGGCUGACAAUAAGGUUUGACAGAG	934
53335_4_38	BCL11	Exon 4	-	chr2:60459153-	GAGGCUGACAAUAAGGUUU	935

2	a			60459178	GACAGA	
53335_4_383	BCL11a	Exon 4	-	chr2:60459154-60459179	AGAGGCUGACAAUAAGGUUUGACAG	936
53335_4_384	BCL11a	Exon 4	-	chr2:60459165-60459190	UAUUGAAAGGAAGAGGCUGACAAUA	937
53335_4_385	BCL11a	Exon 4	-	chr2:60459177-60459202	CCUUGUAUACCAUAUUGAAAGGAAG	938
53335_4_386	BCL11a	Exon 4	-	chr2:60459183-60459208	UUAAGACCUUGUAUACCAUAUUGAA	939
53335_4_387	BCL11a	Exon 4	-	chr2:60459229-60459254	GAUCCAGAUCUACUUGGUUGUCAAG	940
53335_4_388	BCL11a	Exon 4	-	chr2:60459240-60459265	CAAAAGAAAUAGAUCCAGAUCUACU	941
53335_4_389	BCL11a	Exon 4	-	chr2:60459271-60459296	UUUAAUAAUGUCUUUUUAAAAAUAC	942
53335_4_390	BCL11a	Exon 4	-	chr2:60459323-60459348	UGGAACGCAAUUAAAUACACUAGUA	943
53335_4_391	BCL11a	Exon 4	-	chr2:60459348-60459373	UUGAAUGUGUAAUGUGCAAAAGCCC	944
53335_4_392	BCL11a	Exon 4	-	chr2:60459418-60459443	CUCCUGGUGAGAGCUUAAAAGAAAU	945
53335_4_393	BCL11a	Exon 4	-	chr2:60459419-60459444	GCUCCUGGUGAGAGCUUAAAAGAAA	946
53335_4_394	BCL11a	Exon 4	-	chr2:60459439-60459464	ACCAGUAUAAAAGCUACUUUGCUCC	947
53335_4_395	BCL11a	Exon 4	-	chr2:60459547-60459572	UUCUAUAUUGUAUUUCUCACAACAA	948
53335_4_396	BCL11a	Exon 4	-	chr2:60459588-60459613	AGCAUUGGGUGAGGUAAUAAACCUU	949
53335_4_397	BCL11a	Exon 4	-	chr2:60459602-60459627	UUGUAGCUUAAUUCAGCAUUGGGUG	950
53335_4_398	BCL11a	Exon 4	-	chr2:60459607-60459632	UAAACUUGUAGCUUAAUUCAGCAUU	951
53335_4_399	BCL11a	Exon 4	-	chr2:60459608-60459633	AUAAACUUGUAGCUUAAUUCAGCAU	952
53335_4_40	BCL11	Exon 4	-	chr2:60459651-	CUUGGAUCUAUUAAAACCA	953

0	a			60459676	CAUCGA	
53335_4_401	BCL11a	Exon 4	-	chr2:60459674-60459699	AUUUGGUUUUAAAAUAUGAGUGCCU	954
53335_4_402	BCL11a	Exon 4	-	chr2:60459696-60459721	AACAGAACAAGUUUAUUCUAUCAUU	955
53335_4_403	BCL11a	Exon 4	-	chr2:60459749-60459774	UGUAUCAAUUGGAAAGGAAGAAAAA	956
53335_4_404	BCL11a	Exon 4	-	chr2:60459760-60459785	AAAGGGUUAAAUGUAUCAAUUGGAA	957
53335_4_405	BCL11a	Exon 4	-	chr2:60459765-60459790	UCUCUAAAGGGUUAAAUGUAUCAAU	958
53335_4_406	BCL11a	Exon 4	-	chr2:60459782-60459807	UAUGAGCUAAAUGUCUGUCUCUAAA	959
53335_4_407	BCL11a	Exon 4	-	chr2:60459783-60459808	CUAUGAGCUAAAUGUCUGUCUCUAA	960
53335_4_408	BCL11a	Exon 4	-	chr2:60459855-60459880	UAACGUGAGGAGGAAAAACAGUCUU	961
53335_4_409	BCL11a	Exon 4	-	chr2:60459870-60459895	UACAGUUUUAUUUUAUAACGUGAGG	962
53335_4_410	BCL11a	Exon 4	-	chr2:60459873-60459898	AUGUACAGUUUUAUUUUAUAACGUG	963
53335_4_411	BCL11a	Exon 4	-	chr2:60460023-60460048	CUUAGACAGCAUGUAUGGUAUGUUA	964
53335_4_412	BCL11a	Exon 4	-	chr2:60460033-60460058	UUUUUUUAAACUUAGACAGCAUGUA	965
53335_4_413	BCL11a	Exon 4	-	chr2:60460130-60460155	ACCGUUUGAAUGCAUGAUCUGUAUG	966
53335_4_414	BCL11a	Exon 4	-	chr2:60460131-60460156	CACCGUUUGAAUGCAUGAUCUGUAU	967
53335_4_415	BCL11a	Exon 4	-	chr2:60460132-60460157	UCACCGUUUGAAUGCAUGAUCUGUA	968
53335_4_416	BCL11a	Exon 4	-	chr2:60460314-60460339	AUCGCCCUCCAGCCCCACUCCCUGU	969
53335_4_417	BCL11a	Exon 4	-	chr2:60460403-60460428	GAAUAAUGAUAUAAAAACUGAAUAG	970
53335_4_41	BCL11	Exon 4	-	chr2:60460448-	UACCCUGGAGAAACACAUG	971

8	a			60460473	AAAAAA	
53335_4_419	BCL11a	Exon 4	-	chr2:60460468-60460493	AUGCCUUUUAGCGUGUACAGUACCC	972
53335_4_420	BCL11a	Exon 4	-	chr2:60460522-60460547	AUGAAAACGCAUGGCCAGGUGGGGA	973
53335_4_421	BCL11a	Exon 4	-	chr2:60460526-60460551	GCACAUGAAAACGCAUGGCCAGGUG	974
53335_4_422	BCL11a	Exon 4	-	chr2:60460527-60460552	GGCACAUGAAAACGCAUGGCCAGGU	975
53335_4_423	BCL11a	Exon 4	-	chr2:60460528-60460553	AGGCACAUGAAAACGCAUGGCCAGG	976
53335_4_424	BCL11a	Exon 4	-	chr2:60460531-60460556	ACCAGGCACAUGAAAACGCAUGGCC	977
53335_4_425	BCL11a	Exon 4	-	chr2:60460536-60460561	AGCUCACCAGGCACAUGAAAACGCA	978
53335_4_426	BCL11a	Exon 4	-	chr2:60460553-60460578	CUGUGCCCAGAGUAGCAAGCUCACC	979
53335_4_427	BCL11a	Exon 4	-	chr2:60460610-60460635	CCACAGGAGAAGCCACACGGGCGAA	980
53335_4_428	BCL11a	Exon 4	-	chr2:60460617-60460642	UCACUGUCCACAGGAGAAGCCACAC	981
53335_4_429	BCL11a	Exon 4	-	chr2:60460618-60460643	CUCACUGUCCACAGGAGAAGCCACA	982
53335_4_430	BCL11a	Exon 4	-	chr2:60460631-60460656	GAACUGUAGCAAUCUCACUGUCCAC	983
53335_4_431	BCL11a	Exon 4	-	chr2:60460670-60460695	ACGCAGCGACACUUGUGAGUACUGU	984
53335_4_432	BCL11a	Exon 4	-	chr2:60460671-60460696	GACGCAGCGACACUUGUGAGUACUG	985
53335_4_433	BCL11a	Exon 4	-	chr2:60460701-60460726	GCCCGGGCAGGCCCAGCUCAAAAGA	986
53335_4_434	BCL11a	Exon 4	-	chr2:60460702-60460727	GGCCCGGGCAGGCCCAGCUCAAAAG	987
53335_4_435	BCL11a	Exon 4	-	chr2:60460718-60460743	CCAUAUUAGUGGUCCGGGCCCGGGC	988
53335_4_43	BCL11	Exon 4	-	chr2:60460722-	CGCCCCAUAUUAGUGGUCC	989

6	a			60460747	GGGCCC	
53335_4_437	BCL11a	Exon 4	-	chr2:60460723-60460748	ACGCCCCAUAUUAGUGGUCCGGGCC	990
53335_4_438	BCL11a	Exon 4	-	chr2:60460728-60460753	GGAGCACGCCCCAUAUUAGUGGUCC	991
53335_4_439	BCL11a	Exon 4	-	chr2:60460729-60460754	GGGAGCACGCCCCAUAUUAGUGGUC	992
53335_4_440	BCL11a	Exon 4	-	chr2:60460734-60460759	GUGGAGGGAGCACGCCCCAUAUUAG	993
53335_4_441	BCL11a	Exon 4	-	chr2:60460754-60460779	GGGGCGCAGCGGCACGGGAAGUGGA	994
53335_4_442	BCL11a	Exon 4	-	chr2:60460755-60460780	CGGGGCGCAGCGGCACGGGAAGUGG	995
53335_4_443	BCL11a	Exon 4	-	chr2:60460758-60460783	UCUCGGGGCGCAGCGGCACGGGAAG	996
53335_4_444	BCL11a	Exon 4	-	chr2:60460764-60460789	GAGGGAUCUCGGGGCGCAGCGGCAC	997
53335_4_445	BCL11a	Exon 4	-	chr2:60460765-60460790	GGAGGGAUCUCGGGGCGCAGCGGCA	998
53335_4_446	BCL11a	Exon 4	-	chr2:60460770-60460795	UGGACGGAGGGAUCUCGGGGCGCAG	999
53335_4_447	BCL11a	Exon 4	-	chr2:60460778-60460803	CGGGGAGCUGGACGGAGGGAUCUCG	1000
53335_4_448	BCL11a	Exon 4	-	chr2:60460779-60460804	CCGGGGAGCUGGACGGAGGGAUCUC	1001
53335_4_449	BCL11a	Exon 4	-	chr2:60460780-60460805	CCCGGGGAGCUGGACGGAGGGAUCU	1002
53335_4_450	BCL11a	Exon 4	-	chr2:60460787-60460812	CACACCGCCCGGGGAGCUGGACGGA	1003
53335_4_451	BCL11a	Exon 4	-	chr2:60460788-60460813	CCACACCGCCCGGGGAGCUGGACGG	1004
53335_4_452	BCL11a	Exon 4	-	chr2:60460791-60460816	UCUCCACACCGCCCGGGGAGCUGGA	1005
53335_4_453	BCL11a	Exon 4	-	chr2:60460795-60460820	CGCUUCUCCACACCGCCCGGGGAGC	1006
53335_4_45	BCL11	Exon 4	-	chr2:60460801-	AGUUUGCGCUUCUCCACAC	1007

4	a			60460826	CGCCCG	
53335_4_455	BCL11a	Exon 4	-	chr2:60460802-60460827	GAGUUUGCGCUUCUCCACACCGCCC	1008
53335_4_456	BCL11a	Exon 4	-	chr2:60460803-60460828	GGAGUUUGCGCUUCUCCACACCGCC	1009
53335_4_457	BCL11a	Exon 4	-	chr2:60460829-60460854	CUCGUCGGAGCACUCCUCGGAGAAC	1010
53335_4_458	BCL11a	Exon 4	-	chr2:60460830-60460855	CCUCGUCGGAGCACUCCUCGGAGAA	1011
53335_4_459	BCL11a	Exon 4	-	chr2:60460837-60460862	UUUGCCUCCUCGUCGGAGCACUCCU	1012
53335_4_460	BCL11a	Exon 4	-	chr2:60460849-60460874	AGACAAUCGCCUUUUGCCUCCUCGU	1013
53335_4_461	BCL11a	Exon 4	-	chr2:60460884-60460909	AGCUCAAAGAUCCCUUCCUUAGCUU	1014
53335_4_462	BCL11a	Exon 4	-	chr2:60460913-60460938	GUGGCUCGCCGGCUACGCGGCCUCC	1015
53335_4_463	BCL11a	Exon 4	-	chr2:60460921-60460946	UACUCGCAGUGGCUCGCCGGCUACG	1016
53335_4_464	BCL11a	Exon 4	-	chr2:60460929-60460954	AGAACGUGUACUCGCAGUGGCUCGC	1017
53335_4_465	BCL11a	Exon 4	-	chr2:60460937-60460962	CAACACGGAGAACGUGUACUCGCAG	1018
53335_4_466	BCL11a	Exon 4	-	chr2:60460957-60460982	CUGCCCCCGGCCGCGAUGCCCAACA	1019
53335_4_467	BCL11a	Exon 4	-	chr2:60460975-60461000	CUCGAGAAGGAGUUCGACCUGCCCC	1020
53335_4_468	BCL11a	Exon 4	-	chr2:60460993-60461018	UUCUCUAAGCGCAUCAAGCUCGAGA	1021
53335_4_469	BCL11a	Exon 4	-	chr2:60461043-60461068	GGGGCCUGUCCAAAAAGCUGCUGCU	1022
53335_4_470	BCL11a	Exon 4	-	chr2:60461044-60461069	GGGGGCCUGUCCAAAAAGCUGCUGC	1023
53335_4_471	BCL11a	Exon 4	-	chr2:60461067-60461092	GCUCCCCGGGCGAGUCGGCCUCGGG	1024
53335_4_47	BCL11	Exon 4	-	chr2:60461068-	UGCUCCCCGGGCGAGUCGG	1025

2	a			60461093	CCUCGG	
53335_4_473	BCL11a	Exon 4	-	chr2:60461069-60461094	CUGCUCCCCGGGCGAGUCGGCCUCG	1026
53335_4_474	BCL11a	Exon 4	-	chr2:60461070-60461095	GCUGCUCCCCGGGCGAGUCGGCCUC	1027
53335_4_475	BCL11a	Exon 4	-	chr2:60461071-60461096	GGCUGCUCCCCGGGCGAGUCGGCCU	1028
53335_4_476	BCL11a	Exon 4	-	chr2:60461077-60461102	GGCCGCGGCUGCUCCCCGGGCGAGU	1029
53335_4_477	BCL11a	Exon 4	-	chr2:60461085-60461110	CUGUUAAUGGCCGCGGCUGCUCCCC	1030
53335_4_478	BCL11a	Exon 4	-	chr2:60461086-60461111	ACUGUUAAUGGCCGCGGCUGCUCCC	1031
53335_4_479	BCL11a	Exon 4	-	chr2:60461097-60461122	UAGACGAUGGCACUGUUAAUGGCCG	1032
53335_4_480	BCL11a	Exon 4	-	chr2:60461103-60461128	ACCGCAUAGACGAUGGCACUGUUAA	1033
53335_4_481	BCL11a	Exon 4	-	chr2:60461115-60461140	CCGGCGAGUCGGACCGCAUAGACGA	1034
53335_4_482	BCL11a	Exon 4	-	chr2:60461131-60461156	GACGAAGACUCGGUGGCCGGCGAGU	1035
53335_4_483	BCL11a	Exon 4	-	chr2:60461139-60461164	ACACUUGCGACGAAGACUCGGUGGC	1036
53335_4_484	BCL11a	Exon 4	-	chr2:60461143-60461168	AGGGACACUUGCGACGAAGACUCGG	1037
53335_4_485	BCL11a	Exon 4	-	chr2:60461146-60461171	CACAGGGACACUUGCGACGAAGACU	1038
53335_4_486	BCL11a	Exon 4	-	chr2:60461167-60461192	CACCUGGCCGAGGCCGAGGGCCACA	1039
53335_4_487	BCL11a	Exon 4	-	chr2:60461168-60461193	CCACCUGGCCGAGGCCGAGGGCCAC	1040
53335_4_488	BCL11a	Exon 4	-	chr2:60461175-60461200	AGCGCGGCCACCUGGCCGAGGCCGA	1041
53335_4_489	BCL11a	Exon 4	-	chr2:60461176-60461201	AAGCGCGGCCACCUGGCCGAGGCCG	1042
53335_4_49	BCL11	Exon 4	-	chr2:60461182-	AAGCAUAAGCGCGGCCACC	1043

0	a			60461207	UGGCCG	
53335_4_491	BCL11a	Exon 4	-	chr2:60461188-60461213	GGCGAGAAGCAUAAGCGCGGCCACC	1044
53335_4_492	BCL11a	Exon 4	-	chr2:60461196-60461221	AGGUCCUGGGCGAGAAGCAUAAGCG	1045
53335_4_493	BCL11a	Exon 4	-	chr2:60461214-60461239	UCAGCGAGGCCUUCCACCAGGUCCU	1046
53335_4_494	BCL11a	Exon 4	-	chr2:60461215-60461240	UUCAGCGAGGCCUUCCACCAGGUCC	1047
53335_4_495	BCL11a	Exon 4	-	chr2:60461221-60461246	CAGCACUUCAGCGAGGCCUUCCACC	1048
53335_4_496	BCL11a	Exon 4	-	chr2:60461233-60461258	CUCAGCUCCAUGCAGCACUUCAGCG	1049
53335_4_497	BCL11a	Exon 4	-	chr2:60461263-60461288	GCCCUGCCCGACGUCAUGCAGGGCA	1050
53335_4_498	BCL11a	Exon 4	-	chr2:60461268-60461293	GCCGCGCCCUGCCCGACGUCAUGCA	1051
53335_4_499	BCL11a	Exon 4	-	chr2:60461269-60461294	AGCCGCGCCCUGCCCGACGUCAUGC	1052
53335_4_500	BCL11a	Exon 4	-	chr2:60461304-60461329	GCUCGCGGGGCGCGGUCGUGGGCGU	1053
53335_4_501	BCL11a	Exon 4	-	chr2:60461305-60461330	AGCUCGCGGGGCGCGGUCGUGGGCG	1054
53335_4_502	BCL11a	Exon 4	-	chr2:60461310-60461335	AGAACAGCUCGCGGGGCGCGGUCGU	1055
53335_4_503	BCL11a	Exon 4	-	chr2:60461311-60461336	GAGAACAGCUCGCGGGGCGCGGUCG	1056
53335_4_504	BCL11a	Exon 4	-	chr2:60461317-60461342	CACCACGAGAACAGCUCGCGGGGCG	1057
53335_4_505	BCL11a	Exon 4	-	chr2:60461322-60461347	CGCGCCACCACGAGAACAGCUCGCG	1058
53335_4_506	BCL11a	Exon 4	-	chr2:60461323-60461348	GCGCGCCACCACGAGAACAGCUCGC	1059
53335_4_507	BCL11a	Exon 4	-	chr2:60461324-60461349	GGCGCGCCACCACGAGAACAGCUCG	1060
53335_4_50	BCL11	Exon 4	-	chr2:60461350-	UACGGCUUCGGGCUGAGCC	1061

8	a			60461375	UGGAGG	
53335_4_509	BCL11a	Exon 4	-	chr2:60461353-60461378	GACUACGGCUUCGGGCUGAGCCUGG	1062
53335_4_510	BCL11a	Exon 4	-	chr2:60461356-60461381	CUGGACUACGGCUUCGGGCUGAGCC	1063
53335_4_511	BCL11a	Exon 4	-	chr2:60461366-60461391	CUCGCUCUCCCUGGACUACGGCUUC	1064
53335_4_512	BCL11a	Exon 4	-	chr2:60461367-60461392	UCUCGCUCUCCCUGGACUACGGCUU	1065
53335_4_513	BCL11a	Exon 4	-	chr2:60461373-60461398	ACUGCCUCUCGCUCUCCCUGGACUA	1066
53335_4_514	BCL11a	Exon 4	-	chr2:60461380-60461405	CUCCUCGACUGCCUCUCGCUCUCCC	1067
53335_4_515	BCL11a	Exon 4	-	chr2:60461512-60461537	GCCAGCAGCGCGCUCAAGUCCGUGG	1068
53335_4_516	BCL11a	Exon 4	-	chr2:60461515-60461540	AGCGCCAGCAGCGCGCUCAAGUCCG	1069
53335_4_517	BCL11a	Exon 4	-	chr2:60461544-60461569	CGGAACCCGGCACCAGCGACUUGGU	1070
53335_4_518	BCL11a	Exon 4	-	chr2:60461545-60461570	CCGGAACCCGGCACCAGCGACUUGG	1071
53335_4_519	BCL11a	Exon 4	-	chr2:60461548-60461573	UCCCCGGAACCCGGCACCAGCGACU	1072
53335_4_520	BCL11a	Exon 4	-	chr2:60461562-60461587	UCUCCACCGCCAGCUCCCCGGAACC	1073
53335_4_521	BCL11a	Exon 4	-	chr2:60461569-60461594	GACGGUCUCUCCACCGCCAGCUCCC	1074
53335_4_522	BCL11a	Exon 4	-	chr2:60461592-60461617	CCCCCAUGACGGUCAAGUCCGACGA	1075
53335_4_523	BCL11a	Exon 4	-	chr2:60461608-60461633	CACAUGCACAAAUCGUCCCCCAUGA	1076
53335_4_524	BCL11a	Exon 4	-	chr2:60461665-60461690	AACCUGUGCGACCACGCGUGCACCC	1077
53335_4_525	BCL11a	Exon 4	-	chr2:60461712-60461737	UGGUGGUGCACCGGCGCAGCCACAC	1078
53335_4_52	BCL11	Exon 4	-	chr2:60461713-	CUGGUGGUGCACCGGCGCA	1079

6	a			60461738	GCCACA	
53335_4_527	BCL11a	Exon 4	-	chr2:60461726-60461751	AUUUCAGAGCAACCUGGUGGUGCAC	1080
53335_4_528	BCL11a	Exon 4	-	chr2:60461734-60461759	ACGUUCAAAUUUCAGAGCAACCUGG	1081
53335_4_529	BCL11a	Exon 4	-	chr2:60461737-60461762	AAGACGUUCAAAUUUCAGAGCAACC	1082
53335_4_530	BCL11a	Exon 4	-	chr2:60461766-60461791	UCAAGUCCAAGUCAUGCGAGUUCUG	1083
53335_4_531	BCL11a	Exon 4	-	chr2:60461794-60461819	UCCGCCCCUCCUCCCUCCCAGCCCC	1084
53335_4_532	BCL11a	Exon 4	-	chr2:60461848-60461873	CAGCCAGGUAGCAAGCCGCCCUUCC	1085
53335_4_533	BCL11a	Exon 4	-	chr2:60461868-60461893	AAAGGUUACUGCAACCAUUCCAGCC	1086
53335_4_534	BCL11a	Exon 4	-	chr2:60461891-60461916	CCCAGGCCGGCCCAGCCCUAUGCAA	1087
53335_4_535	BCL11a	Exon 4	-	chr2:60461909-60461934	GUCUAGCCCACCGCUGUCCCCAGGC	1088
53335_4_536	BCL11a	Exon 4	-	chr2:60461913-60461938	ACACGUCUAGCCCACCGCUGUCCCC	1089
53335_4_537	BCL11a	Exon 4	-	chr2:60461942-60461967	CUCUAGGAGACUUAGAGAGCUGGCA	1090
53335_4_538	BCL11a	Exon 4	-	chr2:60461943-60461968	UCUCUAGGAGACUUAGAGAGCUGGC	1091
53335_4_539	BCL11a	Exon 4	-	chr2:60461947-60461972	GAUUUCUCUAGGAGACUUAGAGAGC	1092
53335_4_540	BCL11a	Exon 4	-	chr2:60461963-60461988	GGAGCCUCCCGCCAUGGAUUUCUCU	1093
53335_4_541	BCL11a	Exon 4	-	chr2:60461974-60461999	CCAAUGGCUAUGGAGCCUCCCGCCA	1094
53335_4_542	BCL11a	Exon 4	-	chr2:60461989-60462014	GUGCUGCGGUUGAAUCCAAUGGCUA	1095
53335_4_543	BCL11a	Exon 4	-	chr2:60461995-60462020	GACAGGGUGCUGCGGUUGAAUCCAA	1096
53335_4_54	BCL11	Exon 4	-	chr2:60462008-	CCCGAGUGCCUUUGACAGG	1097

4	a			60462033	GUGCUG	
53335_4_545	BCL11a	Exon 4	-	chr2:60462016-60462041	ACCCAUCACCCGAGUGCCUUUGACA	1098
53335_4_546	BCL11a	Exon 4	-	chr2:60462017-60462042	CACCCAUCACCCGAGUGCCUUUGAC	1099
53335_4_547	BCL11a	Exon 4	-	chr2:60462046-60462071	CGCCUGGGGGCGGAAGAGAUGGCCC	1100
53335_4_548	BCL11a	Exon 4	-	chr2:60462052-60462077	AUAGAGCGCCUGGGGGCGGAAGAGA	1101
53335_4_549	BCL11a	Exon 4	-	chr2:60462061-60462086	CCCCACCGCAUAGAGCGCCUGGGGG	1102
53335_4_550	BCL11a	Exon 4	-	chr2:60462064-60462089	GACCCCCACCGCAUAGAGCGCCUGG	1103
53335_4_551	BCL11a	Exon 4	-	chr2:60462065-60462090	GGACCCCCACCGCAUAGAGCGCCUG	1104
53335_4_552	BCL11a	Exon 4	-	chr2:60462066-60462091	UGGACCCCCACCGCAUAGAGCGCCU	1105
53335_4_553	BCL11a	Exon 4	-	chr2:60462067-60462092	UUGGACCCCCACCGCAUAGAGCGCC	1106
53335_4_554	BCL11a	Exon 4	-	chr2:60462091-60462116	UUUAGUCCACCACCGAGACAUCACU	1107
53335_4_555	BCL11a	Exon 4	-	chr2:60462143-60462168	GAGAGAGGCUUCCGGCCUGGCAGAA	1108
53335_4_556	BCL11a	Exon 4	-	chr2:60462144-60462169	CGAGAGAGGCUUCCGGCCUGGCAGA	1109
53335_4_557	BCL11a	Exon 4	-	chr2:60462151-60462176	UCAGUAUCGAGAGAGGCUUCCGGCC	1110
53335_4_558	BCL11a	Exon 4	-	chr2:60462156-60462181	CAGGAUCAGUAUCGAGAGAGGCUUC	1111
53335_4_559	BCL11a	Exon 4	-	chr2:60462163-60462188	AGAAUACCAGGAUCAGUAUCGAGAG	1112
53335_4_560	BCL11a	Exon 4	-	chr2:60462180-60462205	ACCCCUUUAACCUGCUAAGAAUACC	1113
53335_4_561	BCL11a	Exon 4	-	chr2:60462227-60462252	AUGUCCUUCCCAGCCACCUCUCCAU	1114
53335_4_56	BCL11	Exon 4	-	chr2:60462228-	AAUGUCCUUCCCAGCCACC	1115

2	a			60462253	UCUCCA	
53335_4_563	BCL11a	Exon 4	-	chr2:60462261-60462286	CGCGGGUUGGUAUCCCUUCAGGACU	1116
53335_4_564	BCL11a	Exon 4	-	chr2:60462267-60462292	UGACCCCGCGGGUUGGUAUCCCUUC	1117
53335_4_565	BCL11a	Exon 4	-	chr2:60462279-60462304	ACGGAAGUCCCCUGACCCCGCGGGU	1118
53335_4_566	BCL11a	Exon 4	-	chr2:60462283-60462308	GAACACGGAAGUCCCCUGACCCCGC	1119
53335_4_567	BCL11a	Exon 4	-	chr2:60462284-60462309	CGAACACGGAAGUCCCCUGACCCCG	1120
53335_4_568	BCL11a	Exon 4	-	chr2:60462303-60462328	UAAGAAUCUACUUAGAAAGCGAACA	1121
53335_4_569	BCL11a	Exon 4	-	chr2:60462333-60462358	UCUUGCAACACGCACAGAACACUCA	1122
53335_4_570	BCL11a	Exon 4	-	chr2:60462365-60462390	UUGCAAACAGCCAUUCACCAGUGCA	1123
53335_3_1	BCL11a	Exon 3	+	chr2:60468716-60468741	UAAGGCUCAACUUACAAAUACCCUG	1124
53335_3_2	BCL11a	Exon 3	+	chr2:60468717-60468742	AAGGCUCAACUUACAAAUACCCUGC	1125
53335_3_3	BCL11a	Exon 3	+	chr2:60468718-60468743	AGGCUCAACUUACAAAUACCCUGCG	1126
53335_3_4	BCL11a	Exon 3	+	chr2:60468740-60468765	GCGGGGCAUAUUCUGCACUCAUCCC	1127
53335_3_5	BCL11a	Exon 3	+	chr2:60468745-60468770	GCAUAUUCUGCACUCAUCCCAGGCG	1128
53335_3_6	BCL11a	Exon 3	+	chr2:60468746-60468771	CAUAUUCUGCACUCAUCCCAGGCGU	1129
53335_3_7	BCL11a	Exon 3	+	chr2:60468747-60468772	AUAUUCUGCACUCAUCCCAGGCGUG	1130
53335_3_8	BCL11a	Exon 3	+	chr2:60468773-60468798	GGAUUAGAGCUCCAUGUGCAGAACG	1131
53335_3_9	BCL11a	Exon 3	+	chr2:60468774-60468799	GAUUAGAGCUCCAUGUGCAGAACGA	1132
53335_3_10	BCL11	Exon 3	+	chr2:60468775-	AUUAGAGCUCCAUGUGCAG	1133

	a			60468800	AACGAG	
53335_3_11	BCL11a	Exon 3	+	chr2:60468778-60468803	AGAGCUCCAUGUGCAGAACGAGGGG	1134
53335_3_12	BCL11a	Exon 3	+	chr2:60468783-60468808	UCCAUGUGCAGAACGAGGGGAGGAG	1135
53335_3_13	BCL11a	Exon 3	-	chr2:60468739-60468764	GGAUGAGUGCAGAAUAUGCCCCGCA	1136
53335_3_14	BCL11a	Exon 3	-	chr2:60468740-60468765	GGGAUGAGUGCAGAAUAUGCCCCGC	1137
53335_3_15	BCL11a	Exon 3	-	chr2:60468765-60468790	ACAUGGAGCUCUAAUCCCCACGCCU	1138
53335_3_16	BCL11a	Exon 3	-	chr2:60468766-60468791	CACAUGGAGCUCUAAUCCCCACGCC	1139
53335_3_17	BCL11a	Exon 3	-	chr2:60468787-60468812	GCCUCUCCUCCCCUCGUUCUGCACA	1140
53335_3_18	BCL11a	Exon 3	-	chr2:60468814-60468839	UCACAGAUAAACUUCUGCACUGGAG	1141
53335_3_19	BCL11a	Exon 3	-	chr2:60468815-60468840	UUCACAGAUAAACUUCUGCACUGGA	1142
53335_3_20	BCL11a	Exon 3	-	chr2:60468816-60468841	UUUCACAGAUAAACUUCUGCACUGG	1143
53335_3_21	BCL11a	Exon 3	-	chr2:60468819-60468844	UUCUUUCACAGAUAAACUUCUGCAC	1144
53335_2_1	BCL11a	Exon 2	+	chr2:60545963-60545988	CAUUUACCUGCUAUGUGUUCCUGUU	1145
53335_2_2	BCL11a	Exon 2	+	chr2:60545964-60545989	AUUUACCUGCUAUGUGUUCCUGUUU	1146
53335_2_3	BCL11a	Exon 2	+	chr2:60545965-60545990	UUUACCUGCUAUGUGUUCCUGUUUG	1147
53335_2_4	BCL11a	Exon 2	+	chr2:60546009-60546034	ACGUUGAUAAACAAUCGUCAUCCUC	1148
53335_2_5	BCL11a	Exon 2	+	chr2:60546019-60546044	ACAAUCGUCAUCCUCUGGCGUGACC	1149
53335_2_6	BCL11a	Exon 2	+	chr2:60546035-60546060	GGCGUGACCUGGAUGCCAACCUCCA	1150
53335_2_7	BCL11	Exon 2	+	chr2:60546036-	GCGUGACCUGGAUGCCAAC	1151

	a			60546061	CUCCAC	
53335_2_8	BCL11a	Exon 2	+	chr2:60546041-60546066	ACCUGGAUGCCAACCUCCACGGGAU	1152
53335_2_9	BCL11a	Exon 2	+	chr2:60546063-60546088	GAUUGGAUGCUUUUUUCAUCUCGAU	1153
53335_2_10	BCL11a	Exon 2	+	chr2:60546069-60546094	AUGCUUUUUUCAUCUCGAUUGGUGA	1154
53335_2_11	BCL11a	Exon 2	+	chr2:60546070-60546095	UGCUUUUUUCAUCUCGAUUGGUGAA	1155
53335_2_12	BCL11a	Exon 2	+	chr2:60546071-60546096	GCUUUUUUCAUCUCGAUUGGUGAAG	1156
53335_2_13	BCL11a	Exon 2	+	chr2:60546075-60546100	UUUUCAUCUCGAUUGGUGAAGGGGA	1157
53335_2_14	BCL11a	Exon 2	+	chr2:60546078-60546103	UCAUCUCGAUUGGUGAAGGGGAAGG	1158
53335_2_15	BCL11a	Exon 2	+	chr2:60546106-60546131	CUUAUCCACAGCUUUUUCUAAGCAG	1159
53335_2_16	BCL11a	Exon 2	+	chr2:60546162-60546187	CGAUAAAAAUAAGAAUGUCCCCCAA	1160
53335_2_17	BCL11a	Exon 2	+	chr2:60546163-60546188	GAUAAAAAUAAGAAUGUCCCCCAAU	1161
53335_2_18	BCL11a	Exon 2	+	chr2:60546175-60546200	AAUGUCCCCCAAUGGGAAGUUCAUC	1162
53335_2_19	BCL11a	Exon 2	+	chr2:60546188-60546213	GGGAAGUUCAUCUGGCACUGCCCAC	1163
53335_2_20	BCL11a	Exon 2	+	chr2:60546193-60546218	GUUCAUCUGGCACUGCCCACAGGUG	1164
53335_2_21	BCL11a	Exon 2	+	chr2:60546196-60546221	CAUCUGGCACUGCCCACAGGUGAGG	1165
53335_2_22	BCL11a	Exon 2	+	chr2:60546213-60546238	AGGUGAGGAGGUCAUGAUCCCCUUC	1166
53335_2_23	BCL11a	Exon 2	+	chr2:60546225-60546250	CAUGAUCCCCUUCUGGAGCUCCCAA	1167
53335_2_24	BCL11a	Exon 2	+	chr2:60546226-60546251	AUGAUCCCCUUCUGGAGCUCCCAAC	1168
53335_2_25	BCL11	Exon 2	+	chr2:60546232-	CCCUUCUGGAGCUCCCAAC	1169

	a			60546257	GGGCCG	
53335_2_26	BCL11a	Exon 2	+	chr2:60546237-60546262	CUGGAGCUCCCAACGGGCCGUGGUC	1170
53335_2_27	BCL11a	Exon 2	+	chr2:60546257-60546282	UGGUCUGGUUCAUCAUCUGUAAGAA	1171
53335_2_28	BCL11a	Exon 2	+	chr2:60546267-60546292	CAUCAUCUGUAAGAAUGGCUUCAAG	1172
53335_2_29	BCL11a	Exon 2	+	chr2:60546272-60546297	UCUGUAAGAAUGGCUUCAAGAGGCU	1173
53335_2_30	BCL11a	Exon 2	+	chr2:60546278-60546303	AGAAUGGCUUCAAGAGGCUCGGCUG	1174
53335_2_31	BCL11a	Exon 2	+	chr2:60546282-60546307	UGGCUUCAAGAGGCUCGGCUGUGGU	1175
53335_2_32	BCL11a	Exon 2	-	chr2:60545956-60545981	ACACAUAGCAGGUAAAUGAGAAGCA	1176
53335_2_33	BCL11a	Exon 2	-	chr2:60545972-60545997	UUUGCCCCAAACAGGAACACAUAGC	1177
53335_2_34	BCL11a	Exon 2	-	chr2:60545985-60546010	UCAUCUAGAGGAAUUUGCCCCAAAC	1178
53335_2_35	BCL11a	Exon 2	-	chr2:60546002-60546027	ACGAUUGUUUAUCAACGUCAUCUAG	1179
53335_2_36	BCL11a	Exon 2	-	chr2:60546033-60546058	GAGGUUGGCAUCCAGGUCACGCCAG	1180
53335_2_37	BCL11a	Exon 2	-	chr2:60546045-60546070	UCCAAUCCCGUGGAGGUUGGCAUCC	1181
53335_2_38	BCL11a	Exon 2	-	chr2:60546053-60546078	AAAAAGCAUCCAAUCCCGUGGAGGU	1182
53335_2_39	BCL11a	Exon 2	-	chr2:60546057-60546082	AUGAAAAAAGCAUCCAAUCCCGUGG	1183
53335_2_40	BCL11a	Exon 2	-	chr2:60546060-60546085	GAGAUGAAAAAAGCAUCCAAUCCCG	1184
53335_2_41	BCL11a	Exon 2	-	chr2:60546114-60546139	GGCAGCCUCUGCUUAGAAAAAGCUG	1185
53335_2_42	BCL11a	Exon 2	-	chr2:60546140-60546165	UCGAGCACAAACGGAAACAAUGCAA	1186
53335_2_43	BCL11	Exon 2	-	chr2:60546154-	CAUUCUUAUUUUUAUCGAG	1187

	a			60546179	CACAAA	
53335_2_44	BCL11a	Exon 2	-	chr2:60546183-60546208	CAGUGCCAGAUGAACUUCCCAUUGG	1188
53335_2_45	BCL11a	Exon 2	-	chr2:60546184-60546209	GCAGUGCCAGAUGAACUUCCCAUUG	1189
53335_2_46	BCL11a	Exon 2	-	chr2:60546185-60546210	GGCAGUGCCAGAUGAACUUCCCAUU	1190
53335_2_47	BCL11a	Exon 2	-	chr2:60546186-60546211	GGGCAGUGCCAGAUGAACUUCCCAU	1191
53335_2_48	BCL11a	Exon 2	-	chr2:60546211-60546236	AGGGGAUCAUGACCUCCUCACCUGU	1192
53335_2_49	BCL11a	Exon 2	-	chr2:60546212-60546237	AAGGGGAUCAUGACCUCCUCACCUG	1193
53335_2_50	BCL11a	Exon 2	-	chr2:60546234-60546259	CACGGCCCGUUGGGAGCUCCAGAAG	1194
53335_2_51	BCL11a	Exon 2	-	chr2:60546235-60546260	CCACGGCCCGUUGGGAGCUCCAGAA	1195
53335_2_52	BCL11a	Exon 2	-	chr2:60546236-60546261	ACCACGGCCCGUUGGGAGCUCCAGA	1196
53335_2_53	BCL11a	Exon 2	-	chr2:60546248-60546273	AUGAUGAACCAGACCACGGCCCGUU	1197
53335_2_54	BCL11a	Exon 2	-	chr2:60546249-60546274	GAUGAUGAACCAGACCACGGCCCGU	1198
53335_2_55	BCL11a	Exon 2	-	chr2:60546257-60546282	UUCUUACAGAUGAUGAACCAGACCA	1199
53335_1_1	BCL11a	Exon 1	+	chr2:60553216-60553241	CGAGAAUUCCCGUUUGCUUAAGUGC	1200
53335_1_2	BCL11a	Exon 1	+	chr2:60553217-60553242	GAGAAUUCCCGUUUGCUUAAGUGCU	1201
53335_1_3	BCL11a	Exon 1	+	chr2:60553218-60553243	AGAAUUCCCGUUUGCUUAAGUGCUG	1202
53335_1_4	BCL11a	Exon 1	+	chr2:60553234-60553259	UAAGUGCUGGGGUUUGCCUUGCUUG	1203
53335_1_5	BCL11a	Exon 1	+	chr2:60553244-60553269	GGUUUGCCUUGCUUGCGGCGAGACA	1204
53335_1_6	BCL11	Exon 1	+	chr2:60553247-	UUGCCUUGCUUGCGGCGAG	1205

	a			60553272	ACAUGG	
53335_1_7	BCL11a	Exon 1	+	chr2:60553248-60553273	UGCCUUGCUUGCGGCGAGACAUGGU	1206
53335_1_8	BCL11a	Exon 1	+	chr2:60553254-60553279	GCUUGCGGCGAGACAUGGUGGGCUG	1207
53335_1_9	BCL11a	Exon 1	+	chr2:60553255-60553280	CUUGCGGCGAGACAUGGUGGGCUGC	1208
53335_1_10	BCL11a	Exon 1	+	chr2:60553256-60553281	UUGCGGCGAGACAUGGUGGGCUGCG	1209
53335_1_11	BCL11a	Exon 1	+	chr2:60553291-60553316	CGGCGGCGGCGGCGGCGGCGGCGGG	1210
53335_1_12	BCL11a	Exon 1	+	chr2:60553298-60553323	GGCGGCGGCGGCGGCGGGCGGACGA	1211
53335_1_13	BCL11a	Exon 1	+	chr2:60553303-60553328	CGGCGGCGGCGGGCGGACGACGGCU	1212
53335_1_14	BCL11a	Exon 1	+	chr2:60553313-60553338	GGGCGGACGACGGCUCGGUUCACAU	1213
53335_1_15	BCL11a	Exon 1	+	chr2:60553314-60553339	GGCGGACGACGGCUCGGUUCACAUC	1214
53335_1_16	BCL11a	Exon 1	+	chr2:60553322-60553347	ACGGCUCGGUUCACAUCGGGAGAGC	1215
53335_1_17	BCL11a	Exon 1	+	chr2:60553323-60553348	CGGCUCGGUUCACAUCGGGAGAGCC	1216
53335_1_18	BCL11a	Exon 1	+	chr2:60553335-60553360	CAUCGGGAGAGCCGGGUUAGAAAGA	1217
53335_1_19	BCL11a	Exon 1	+	chr2:60553406-60553431	AAAUAAAUUAGAAAUAAUACAAAGA	1218
53335_1_20	BCL11a	Exon 1	+	chr2:60553412-60553437	AUUAGAAAUAAUACAAAGAUGGCGC	1219
53335_1_21	BCL11a	Exon 1	+	chr2:60553413-60553438	UUAGAAAUAAUACAAAGAUGGCGCA	1220
53335_1_22	BCL11a	Exon 1	+	chr2:60553427-60553452	AAGAUGGCGCAGGGAAGAUGAAUUG	1221
53335_1_23	BCL11a	Exon 1	+	chr2:60553428-60553453	AGAUGGCGCAGGGAAGAUGAAUUGU	1222
53335_1_24	BCL11	Exon 1	+	chr2:60553441-	AAGAUGAAUUGUGGGAGAG	1223

	a			60553466	CCGUCA	
53335_1_25	BCL11a	Exon 1	-	chr2:60553227-60553252	GGCAAACCCCAGCACUUAAGCAAAC	1224
53335_1_26	BCL11a	Exon 1	-	chr2:60553228-60553253	AGGCAAACCCCAGCACUUAAGCAAA	1225
53335_1_27	BCL11a	Exon 1	-	chr2:60553253-60553278	AGCCCACCAUGUCUCGCCGCAAGCA	1226
53335_1_28	BCL11a	Exon 1	-	chr2:60553349-60553374	CUCUGGAGUCUCCUUCUUUCUAACC	1227
53335_1_29	BCL11a	Exon 1	-	chr2:60553371-60553396	AAGGCACUGAUGAAGAUAUUUUCUC	1228
53335_1_30	BCL11a	Exon 1	-	chr2:60553395-60553420	UUUCUAAUUUAUUUUGGAUGUCAAA	1229
53335_1_31	BCL11a	Exon 1	-	chr2:60553406-60553431	UCUUUGUAUUAUUUCUAAUUUAUUU	1230
53335_1_32	BCL11a	Exon 1	-	chr2:60553463-60553488	AAAAAAGCUUAAAAAAAAGCCAUGA	1231

Table 2: gRNA targeting domains targeting BCL11a Intron 2 (e.g., to a BCL11a Enhancer)

Id.	Target	Target Region	Strand	Targeting Site (hg38)	gRNA Targeting Domain	SEQ ID NO:
53335_I2_1	BCL11a	Intron 2	+	chr2:60494277-60494302	GGGAGUUUGGCUUCUCAUCUGUGCA	1232
53335_I2_2	BCL11a	Intron 2	+	chr2:60494289-60494314	UCUCAUCUGUGCAUGGCCUCUAAAC	1233
53335_I2_3	BCL11a	Intron 2	+	chr2:60494290-60494315	CUCAUCUGUGCAUGGCCUCUAAACU	1234
53335_I2_4	BCL11a	Intron 2	+	chr2:60494302-60494327	UGGCCUCUAAACUGGGCAGUGACCA	1235
53335_I2_5	BCL11a	Intron 2	+	chr2:60494307-60494332	UCUAAACUGGGCAGUGACCAUGGCC	1236
53335_I2_6	BCL11a	Intron 2	+	chr2:60494324-60494349	CCAUGGCCUGGUCACCUCCCCACUC	1237
53335_I2_7	BCL11a	Intron 2	+	chr2:60494330-	CCUGGUCACCUCCCCACU	1238

				60494355	CUGGACC	
53335_I2_8	BCL11a	Intron 2	+	chr2:60494331-60494356	CUGGUCACCUCCCCACUCUGGACCU	1239
53335_I2_9	BCL11a	Intron 2	+	chr2:60494351-60494376	GACCUGGGUUGCCCCUCUGUAAACA	1240
53335_I2_10	BCL11a	Intron 2	+	chr2:60494354-60494379	CUGGGUUGCCCCUCUGUAAACAAGG	1241
53335_I2_11	BCL11a	Intron 2	+	chr2:60494418-60494443	AAAUCUUAUGCAAUUUUUGCCAAGA	1242
53335_I2_12	BCL11a	Intron 2	+	chr2:60494419-60494444	AAUCUUAUGCAAUUUUUGCCAAGAU	1243
53335_I2_13	BCL11a	Intron 2	+	chr2:60494426-60494451	UGCAAUUUUUGCCAAGAUGGGAGUA	1244
53335_I2_14	BCL11a	Intron 2	+	chr2:60494427-60494452	GCAAUUUUUGCCAAGAUGGGAGUAU	1245
53335_I2_15	BCL11a	Intron 2	+	chr2:60494428-60494453	CAAUUUUUGCCAAGAUGGGAGUAUG	1246
53335_I2_16	BCL11a	Intron 2	+	chr2:60494440-60494465	AGAUGGGAGUAUGGGGAGAGAAGAG	1247
53335_I2_17	BCL11a	Intron 2	+	chr2:60494446-60494471	GAGUAUGGGGAGAGAAGAGUGGAAA	1248
53335_I2_18	BCL11a	Intron 2	+	chr2:60494477-60494502	AGAGCUCAGUGAGAUGAGAUAUCAA	1249
53335_I2_19	BCL11a	Intron 2	+	chr2:60494478-60494503	GAGCUCAGUGAGAUGAGAUAUCAAA	1250
53335_I2_20	BCL11a	Intron 2	+	chr2:60494479-60494504	AGCUCAGUGAGAUGAGAUAUCAAAG	1251
53335_I2_21	BCL11a	Intron 2	+	chr2:60494518-60494543	UCAUUCCAUCUCCCUAAUCUCCAAU	1252
53335_I2_22	BCL11a	Intron 2	+	chr2:60494533-60494558	AAUCUCCAAUUGGCAAAGCCAGACU	1253
53335_I2_23	BCL11a	Intron 2	+	chr2:60494534-60494559	AUCUCCAAUUGGCAAAGCCAGACUU	1254
53335_I2_24	BCL11a	Intron 2	+	chr2:60494535-60494560	UCUCCAAUUGGCAAAGCCAGACUUG	1255
53335_I2_25	BCL11a	Intron 2	+	chr2:60494548-	AAGCCAGACUUGGGGCA	1256

				60494573	AUACAGAC	
53335_I2_26	BCL11a	Intron 2	+	chr2:60494617-60494642	UAUCACCAAAUGUUCUUUCUUCAGC	1257
53335_I2_27	BCL11a	Intron 2	+	chr2:60494631-60494656	CUUUCUUCAGCUGGAAUUUAAAAUA	1258
53335_I2_28	BCL11a	Intron 2	+	chr2:60494649-60494674	UAAAAUAUGGACUCAUCCGUAAAAU	1259
53335_I2_29	BCL11a	Intron 2	+	chr2:60494675-60494700	GGAAUAAUAAUAGUAUAUGCUUCAU	1260
53335_I2_30	BCL11a	Intron 2	+	chr2:60494676-60494701	GAAUAAUAAUAGUAUAUGCUUCAUA	1261
53335_I2_31	BCL11a	Intron 2	+	chr2:60494766-60494791	GCUUGUGAACUAAAAUGCUGCCUCC	1262
53335_I2_32	BCL11a	Intron 2	+	chr2:60494806-60494831	ACACCUCAGCAGAAACAAAGUUAUC	1263
53335_I2_33	BCL11a	Intron 2	+	chr2:60494830-60494855	CAGGCCCUUUCCCCAAUUCCUAGUU	1264
53335_I2_34	BCL11a	Intron 2	+	chr2:60494831-60494856	AGGCCCUUUCCCCAAUUCCUAGUUU	1265
53335_I2_35	BCL11a	Intron 2	+	chr2:60494844-60494869	AAUUCCUAGUUUGGGUCAGAAGAAA	1266
53335_I2_36	BCL11a	Intron 2	+	chr2:60494845-60494870	AUUCCUAGUUUGGGUCAGAAGAAAA	1267
53335_I2_37	BCL11a	Intron 2	+	chr2:60494851-60494876	AGUUUGGGUCAGAAGAAAAGGGAAA	1268
53335_I2_38	BCL11a	Intron 2	+	chr2:60494852-60494877	GUUUGGGUCAGAAGAAAAGGGAAAA	1269
53335_I2_39	BCL11a	Intron 2	+	chr2:60494857-60494882	GGUCAGAAGAAAAGGGAAAAGGGAG	1270
53335_I2_40	BCL11a	Intron 2	+	chr2:60494864-60494889	AGAAAAGGGAAAAGGGAGAGGAAAA	1271
53335_I2_41	BCL11a	Intron 2	+	chr2:60494883-60494908	GGAAAAAGGAAAAGAAUAUGACGUC	1272
53335_I2_42	BCL11a	Intron 2	+	chr2:60494884-60494909	GAAAAAGGAAAAGAAUAUGACGUCA	1273
53335_I2_43	BCL11a	Intron 2	+	chr2:60494885-	AAAAAGGAAAAGAAUAU	1274

				60494910	GACGUCAG	
53335_I2_44	BCL11a	Intron 2	+	chr2:60494886-60494911	AAAAGGAAAAGAAUAUGACGUCAGG	1275
53335_I2_45	BCL11a	Intron 2	+	chr2:60494889-60494914	AGGAAAAGAAUAUGACGUCAGGGGG	1276
53335_I2_46	BCL11a	Intron 2	+	chr2:60494901-60494926	UGACGUCAGGGGGAGGCAAGUCAGU	1277
53335_I2_47	BCL11a	Intron 2	+	chr2:60494902-60494927	GACGUCAGGGGGAGGCAAGUCAGUU	1278
53335_I2_48	BCL11a	Intron 2	+	chr2:60494928-60494953	GGAACACAGAUCCUAACACAGUAGC	1279
53335_I2_49	BCL11a	Intron 2	+	chr2:60494939-60494964	CCUAACACAGUAGCUGGUACCUGAU	1280
53335_I2_50	BCL11a	Intron 2	+	chr2:60494955-60494980	GUACCUGAUAGGUGCCUAUAUGUGA	1281
53335_I2_51	BCL11a	Intron 2	+	chr2:60494959-60494984	CUGAUAGGUGCCUAUAUGUGAUGGA	1282
53335_I2_52	BCL11a	Intron 2	+	chr2:60494960-60494985	UGAUAGGUGCCUAUAUGUGAUGGAU	1283
53335_I2_53	BCL11a	Intron 2	+	chr2:60494963-60494988	UAGGUGCCUAUAUGUGAUGGAUGGG	1284
53335_I2_54	BCL11a	Intron 2	+	chr2:60494986-60495011	GGUGGACAGCCCGACAGAUGAAAAA	1285
53335_I2_55	BCL11a	Intron 2	+	chr2:60494998-60495023	GACAGAUGAAAAAUGGACAAUUAUG	1286
53335_I2_56	BCL11a	Intron 2	+	chr2:60495001-60495026	AGAUGAAAAAUGGACAAUUAUGAGG	1287
53335_I2_57	BCL11a	Intron 2	+	chr2:60495002-60495027	GAUGAAAAAUGGACAAUUAUGAGGA	1288
53335_I2_58	BCL11a	Intron 2	+	chr2:60495003-60495028	AUGAAAAAUGGACAAUUAUGAGGAG	1289
53335_I2_59	BCL11a	Intron 2	+	chr2:60495017-60495042	AUUAUGAGGAGGGGAGAGUGCAGAC	1290
53335_I2_60	BCL11a	Intron 2	+	chr2:60495018-60495043	UUAUGAGGAGGGGAGAGUGCAGACA	1291
53335_I2_61	BCL11a	Intron 2	+	chr2:60495019-	UAUGAGGAGGGGAGAGU	1292

				60495044	GCAGACAG	
53335_I2_62	BCL11a	Intron 2	+	chr2:60495045-60495070	GGAAGCUUCACCUCCUUUACAAUUU	1293
53335_I2_63	BCL11a	Intron 2	+	chr2:60495046-60495071	GAAGCUUCACCUCCUUUACAAUUUU	1294
53335_I2_64	BCL11a	Intron 2	+	chr2:60495057-60495082	UCCUUUACAAUUUUGGGAGUCCACA	1295
53335_I2_65	BCL11a	Intron 2	+	chr2:60495062-60495087	UACAAUUUUGGGAGUCCACACGGCA	1296
53335_I2_66	BCL11a	Intron 2	+	chr2:60495135-60495160	CAUCACCAAGAGAGCCUUCCGAAAG	1297
53335_I2_67	BCL11a	Intron 2	+	chr2:60495144-60495169	GAGAGCCUUCCGAAAGAGGCCCCCC	1298
53335_I2_68	BCL11a	Intron 2	+	chr2:60495145-60495170	AGAGCCUUCCGAAAGAGGCCCCCCU	1299
53335_I2_69	BCL11a	Intron 2	+	chr2:60495152-60495177	UCCGAAAGAGGCCCCCCUGGGCAAA	1300
53335_I2_70	BCL11a	Intron 2	+	chr2:60495162-60495187	GCCCCCCUGGGCAAACGGCCACCGA	1301
53335_I2_71	BCL11a	Intron 2	+	chr2:60495167-60495192	CCUGGGCAAACGGCCACCGAUGGAG	1302
53335_I2_72	BCL11a	Intron 2	+	chr2:60495215-60495240	CCACCCACGCCCCCACCCUAAUCAG	1303
53335_I2_73	BCL11a	Intron 2	+	chr2:60495230-60495255	CCCUAAUCAGAGGCCAAACCCUUCC	1304
53335_I2_74	BCL11a	Intron 2	+	chr2:60495293-60495318	ACUAGCUUCAAAGUUGUAUUGACCC	1305
53335_I2_75	BCL11a	Intron 2	+	chr2:60495333-60495358	AAGAGUAGAUGCCAUAUCUCUUUUC	1306
53335_I2_76	BCL11a	Intron 2	+	chr2:60495354-60495379	UUUCUGGCCUAUGUUAUUACCUGUA	1307
53335_I2_77	BCL11a	Intron 2	+	chr2:60495366-60495391	GUUAUUACCUGUAUGGACUUUGCAC	1308
53335_I2_78	BCL11a	Intron 2	+	chr2:60495400-60495425	CUAUCUGCUCUUACUUAUGCACACC	1309
53335_I2_79	BCL11a	Intron 2	+	chr2:60495401-	UAUCUGCUCUUACUUAU	1310

				60495426	GCACACCU	
53335_I2_80	BCL11a	Intron 2	+	chr2:60495402-60495427	AUCUGCUCUUACUUAUGCACACCUG	1311
53335_I2_81	BCL11a	Intron 2	+	chr2:60495486-60495511	CCUGUCUAGCUGCCUUCCUUAUCAC	1312
53335_I2_82	BCL11a	Intron 2	+	chr2:60495500-60495525	UUCCUUAUCACAGGAAUAGCACCCA	1313
53335_I2_83	BCL11a	Intron 2	+	chr2:60495543-60495568	GAGUAGAACCCCCUAUAAACUAGUC	1314
53335_I2_84	BCL11a	Intron 2	+	chr2:60495554-60495579	CCUAUAAACUAGUCUGGUUUGCCCA	1315
53335_I2_85	BCL11a	Intron 2	+	chr2:60495555-60495580	CUAUAAACUAGUCUGGUUUGCCCAU	1316
53335_I2_86	BCL11a	Intron 2	+	chr2:60495556-60495581	UAUAAACUAGUCUGGUUUGCCCAUG	1317
53335_I2_87	BCL11a	Intron 2	+	chr2:60495566-60495591	UCUGGUUUGCCCAUGGGGCACAGUC	1318
53335_I2_88	BCL11a	Intron 2	+	chr2:60495578-60495603	AUGGGGCACAGUCAGGCUGUUUUCC	1319
53335_I2_89	BCL11a	Intron 2	+	chr2:60495579-60495604	UGGGGCACAGUCAGGCUGUUUUCCA	1320
53335_I2_90	BCL11a	Intron 2	+	chr2:60495582-60495607	GGCACAGUCAGGCUGUUUUCCAGGG	1321
53335_I2_91	BCL11a	Intron 2	+	chr2:60495583-60495608	GCACAGUCAGGCUGUUUUCCAGGGU	1322
53335_I2_92	BCL11a	Intron 2	+	chr2:60495584-60495609	CACAGUCAGGCUGUUUUCCAGGGUG	1323
53335_I2_93	BCL11a	Intron 2	+	chr2:60495661-60495686	ACACACGUAUGUGUUGUGAUCCCUG	1324
53335_I2_94	BCL11a	Intron 2	+	chr2:60495674-60495699	UUGUGAUCCCUGUGGUUUGAGAGUU	1325
53335_I2_95	BCL11a	Intron 2	+	chr2:60495706-60495731	UCCCUAAAAGUCAAAAUAUUCUCAA	1326
53335_I2_96	BCL11a	Intron 2	+	chr2:60495707-60495732	CCCUAAAAGUCAAAAUAUUCUCAAU	1327
53335_I2_97	BCL11a	Intron 2	+	chr2:60495735-	CCCUCAAUCAGCACAUA	1328

				60495760	CACACAAA	
53335_I2_98	BCL11a	Intron 2	+	chr2:60495742-60495767	UCAGCACAUACACACAAAAGGUACC	1329
53335_I2_99	BCL11a	Intron 2	+	chr2:60495775-60495800	UGUAAUUCUUUUCCUGCUCAAAGAC	1330
53335_I2_100	BCL11a	Intron 2	+	chr2:60495820-60495845	CCCCAACCAAAAACCCUUGCCACCA	1331
53335_I2_101	BCL11a	Intron 2	+	chr2:60495821-60495846	CCCAACCAAAAACCCUUGCCACCAU	1332
53335_I2_102	BCL11a	Intron 2	+	chr2:60495828-60495853	AAAAACCCUUGCCACCAUGGGAGCC	1333
53335_I2_103	BCL11a	Intron 2	+	chr2:60495829-60495854	AAAACCCUUGCCACCAUGGGAGCCU	1334
53335_I2_104	BCL11a	Intron 2	+	chr2:60495830-60495855	AAACCCUUGCCACCAUGGGAGCCUG	1335
53335_I2_105	BCL11a	Intron 2	+	chr2:60495839-60495864	CCACCAUGGGAGCCUGGGGCAGAGA	1336
53335_I2_106	BCL11a	Intron 2	+	chr2:60495867-60495892	CACAGUGAAGUCAAACUGUAAUUCC	1337
53335_I2_107	BCL11a	Intron 2	+	chr2:60495877-60495902	UCAAACUGUAAUUCCAGGCUCUAAA	1338
53335_I2_108	BCL11a	Intron 2	+	chr2:60495913-60495938	UUUUUCUGAGAGUCUCUAAAUUACA	1339
53335_I2_109	BCL11a	Intron 2	+	chr2:60495914-60495939	UUUUCUGAGAGUCUCUAAAUUACAA	1340
53335_I2_110	BCL11a	Intron 2	+	chr2:60495972-60495997	ACACCUAAGAAACAUACUGCAGCUC	1341
53335_I2_111	BCL11a	Intron 2	+	chr2:60496001-60496026	AAAGAGAACAAACAAACCAAAGAGA	1342
53335_I2_112	BCL11a	Intron 2	+	chr2:60496002-60496027	AAGAGAACAAACAAACCAAAGAGAA	1343
53335_I2_113	BCL11a	Intron 2	+	chr2:60496011-60496036	AACAAACCAAAGAGAAGGGAUCCAG	1344
53335_I2_114	BCL11a	Intron 2	+	chr2:60496048-60496073	UAUGUGAAAAGUCAAUUGAUAAUGA	1345
53335_I2_115	BCL11a	Intron 2	+	chr2:60496055-	AAAGUCAAUUGAUAAUG	1346

				60496080	AAGGCUUU	
53335_I2_116	BCL11a	Intron 2	+	chr2:60496063-60496088	UUGAUAAUGAAGGCUUUAGGAUAAC	1347
53335_I2_117	BCL11a	Intron 2	+	chr2:60496066-60496091	AUAAUGAAGGCUUUAGGAUAACCGG	1348
53335_I2_118	BCL11a	Intron 2	+	chr2:60496067-60496092	UAAUGAAGGCUUUAGGAUAACCGGA	1349
53335_I2_119	BCL11a	Intron 2	+	chr2:60496068-60496093	AAUGAAGGCUUUAGGAUAACCGGAG	1350
53335_I2_120	BCL11a	Intron 2	+	chr2:60496098-60496123	AUGAUUGAAAGCAAUGCACCUGUGC	1351
53335_I2_121	BCL11a	Intron 2	+	chr2:60496104-60496129	GAAAGCAAUGCACCUGUGCAGGAAA	1352
53335_I2_122	BCL11a	Intron 2	+	chr2:60496111-60496136	AUGCACCUGUGCAGGAAAUGGAUUA	1353
53335_I2_123	BCL11a	Intron 2	+	chr2:60496118-60496143	UGUGCAGGAAAUGGAUUACGGAAAC	1354
53335_I2_124	BCL11a	Intron 2	+	chr2:60496119-60496144	GUGCAGGAAAUGGAUUACGGAAACA	1355
53335_I2_125	BCL11a	Intron 2	+	chr2:60496153-60496178	UCAUGAAAUCCCAGAAAACCAGAAC	1356
53335_I2_126	BCL11a	Intron 2	+	chr2:60496154-60496179	CAUGAAAUCCCAGAAAACCAGAACC	1357
53335_I2_127	BCL11a	Intron 2	+	chr2:60496164-60496189	CAGAAAACCAGAACCGGGAAAGUUC	1358
53335_I2_128	BCL11a	Intron 2	+	chr2:60496171-60496196	CCAGAACCGGGAAAGUUCUGGAAGU	1359
53335_I2_129	BCL11a	Intron 2	+	chr2:60496198-60496223	GAAAAACAAAUCAUGACUUAAGCAA	1360
53335_I2_130	BCL11a	Intron 2	+	chr2:60496238-60496263	CGUUUACAGAAUGCCUUGUCCCACG	1361
53335_I2_131	BCL11a	Intron 2	-	chr2:60494308-60494333	AGGCCAUGGUCACUGCCCAGUUUAG	1362
53335_I2_132	BCL11a	Intron 2	-	chr2:60494327-60494352	CCAGAGUGGGGAGGUGACCAGGCCA	1363
53335_I2_133	BCL11a	Intron 2	-	chr2:60494333-	CCAGGUCCAGAGUGGGG	1364

				60494358	AGGUGACC	
53335_I2_134	BCL11a	Intron 2	-	chr2:60494341-60494366	GGGGCAACCCAGGUCCAGAGUGGGG	1365
53335_I2_135	BCL11a	Intron 2	-	chr2:60494344-60494369	AGAGGGGCAACCCAGGUCCAGAGUG	1366
53335_I2_136	BCL11a	Intron 2	-	chr2:60494345-60494370	CAGAGGGGCAACCCAGGUCCAGAGU	1367
53335_I2_137	BCL11a	Intron 2	-	chr2:60494346-60494371	ACAGAGGGGCAACCCAGGUCCAGAG	1368
53335_I2_138	BCL11a	Intron 2	-	chr2:60494356-60494381	CUCCUUGUUUACAGAGGGGCAACCC	1369
53335_I2_139	BCL11a	Intron 2	-	chr2:60494365-60494390	UAUUACAACCUCCUUGUUUACAGAG	1370
53335_I2_140	BCL11a	Intron 2	-	chr2:60494366-60494391	UUAUUACAACCUCCUUGUUUACAGA	1371
53335_I2_141	BCL11a	Intron 2	-	chr2:60494367-60494392	UUUAUUACAACCUCCUUGUUUACAG	1372
53335_I2_142	BCL11a	Intron 2	-	chr2:60494401-60494426	UAAGAUUUAUAAGACAUUAGGGUAU	1373
53335_I2_143	BCL11a	Intron 2	-	chr2:60494407-60494432	AUUGCAUAAGAUUUAUAAGACAUUA	1374
53335_I2_144	BCL11a	Intron 2	-	chr2:60494408-60494433	AAUUGCAUAAGAUUUAUAAGACAUU	1375
53335_I2_145	BCL11a	Intron 2	-	chr2:60494440-60494465	CUCUUCUCUCCCCAUACUCCCAUCU	1376
53335_I2_146	BCL11a	Intron 2	-	chr2:60494477-60494502	UUGAUAUCUCAUCUCACUGAGCUCU	1377
53335_I2_147	BCL11a	Intron 2	-	chr2:60494478-60494503	UUUGAUAUCUCAUCUCACUGAGCUC	1378
53335_I2_148	BCL11a	Intron 2	-	chr2:60494526-60494551	CUUUGCCAAUUGGAGAUUAGGGAGA	1379
53335_I2_149	BCL11a	Intron 2	-	chr2:60494532-60494557	GUCUGGCUUUGCCAAUUGGAGAUUA	1380
53335_I2_150	BCL11a	Intron 2	-	chr2:60494533-60494558	AGUCUGGCUUUGCCAAUUGGAGAUU	1381
53335_I2_151	BCL11a	Intron 2	-	chr2:60494541-	UUGCCCCAAGUCUGGCU	1382

				60494566	UUGCCAAU	
53335_I2_152	BCL11a	Intron 2	-	chr2:60494554-60494579	GAACCAGUCUGUAUUGCCCCAAGUC	1383
53335_I2_153	BCL11a	Intron 2	-	chr2:60494599-60494624	GGUGAUAAAUCAUUAGGAAUGAGCU	1384
53335_I2_154	BCL11a	Intron 2	-	chr2:60494610-60494635	AAAGAACAUUUGGUGAUAAAUCAUU	1385
53335_I2_155	BCL11a	Intron 2	-	chr2:60494625-60494650	AAAUUCCAGCUGAAGAAAGAACAUU	1386
53335_I2_156	BCL11a	Intron 2	-	chr2:60494668-60494693	AUAUACUAUUAUUAUUCCUAUUUUA	1387
53335_I2_157	BCL11a	Intron 2	-	chr2:60494745-60494770	AAGCUCGGAGCACUUACUCUGCUCU	1388
53335_I2_158	BCL11a	Intron 2	-	chr2:60494765-60494790	GAGGCAGCAUUUUAGUUCACAAGCU	1389
53335_I2_159	BCL11a	Intron 2	-	chr2:60494789-60494814	UGAGGUGUAACUAAUAAAUACCAGG	1390
53335_I2_160	BCL11a	Intron 2	-	chr2:60494792-60494817	UGCUGAGGUGUAACUAAUAAAUACC	1391
53335_I2_161	BCL11a	Intron 2	-	chr2:60494812-60494837	GGGCCUGAUAACUUUGUUUCUGCUG	1392
53335_I2_162	BCL11a	Intron 2	-	chr2:60494837-60494862	UGACCCAAACUAGGAAUUGGGGAAA	1393
53335_I2_163	BCL11a	Intron 2	-	chr2:60494838-60494863	CUGACCCAAACUAGGAAUUGGGGAA	1394
53335_I2_164	BCL11a	Intron 2	-	chr2:60494843-60494868	UUCUUCUGACCCAAACUAGGAAUUG	1395
53335_I2_165	BCL11a	Intron 2	-	chr2:60494844-60494869	UUUCUUCUGACCCAAACUAGGAAUU	1396
53335_I2_166	BCL11a	Intron 2	-	chr2:60494845-60494870	UUUUCUUCUGACCCAAACUAGGAAU	1397
53335_I2_167	BCL11a	Intron 2	-	chr2:60494851-60494876	UUUCCCUUUUCUUCUGACCCAAACU	1398
53335_I2_168	BCL11a	Intron 2	-	chr2:60494942-60494967	CCUAUCAGGUACCAGCUACUGUGUU	1399
53335_I2_169	BCL11a	Intron 2	-	chr2:60494961-	CAUCCAUCACAUAUAGG	1400

				60494986	CACCUAUC	
53335_I2_170	BCL11a	Intron 2	-	chr2:60494972-60494997	GGCUGUCCACCCAUCCAUCACAUAU	1401
53335_I2_171	BCL11a	Intron 2	-	chr2:60494998-60495023	CAUAAUUGUCCAUUUUUCAUCUGUC	1402
53335_I2_172	BCL11a	Intron 2	-	chr2:60494999-60495024	UCAUAAUUGUCCAUUUUUCAUCUGU	1403
53335_I2_173	BCL11a	Intron 2	-	chr2:60495058-60495083	GUGUGGACUCCCAAAAUUGUAAAGG	1404
53335_I2_174	BCL11a	Intron 2	-	chr2:60495061-60495086	GCCGUGUGGACUCCCAAAAUUGUAA	1405
53335_I2_175	BCL11a	Intron 2	-	chr2:60495080-60495105	GAAAUAAUUUGUAUGCCAUGCCGUG	1406
53335_I2_176	BCL11a	Intron 2	-	chr2:60495111-60495136	GGAGAAUUGGAUUUUAUUUCUCAAU	1407
53335_I2_177	BCL11a	Intron 2	-	chr2:60495112-60495137	UGGAGAAUUGGAUUUUAUUUCUCAA	1408
53335_I2_178	BCL11a	Intron 2	-	chr2:60495129-60495154	GAAGGCUCUCUUGGUGAUGGAGAAU	1409
53335_I2_179	BCL11a	Intron 2	-	chr2:60495137-60495162	CUCUUUCGGAAGGCUCUCUUGGUGA	1410
53335_I2_180	BCL11a	Intron 2	-	chr2:60495143-60495168	GGGGGCCUCUUUCGGAAGGCUCUCU	1411
53335_I2_181	BCL11a	Intron 2	-	chr2:60495152-60495177	UUUGCCCAGGGGGGCCUCUUUCGGA	1412
53335_I2_182	BCL11a	Intron 2	-	chr2:60495156-60495181	GCCGUUUGCCCAGGGGGGCCUCUUU	1413
53335_I2_183	BCL11a	Intron 2	-	chr2:60495166-60495191	UCCAUCGGUGGCCGUUUGCCCAGGG	1414
53335_I2_184	BCL11a	Intron 2	-	chr2:60495167-60495192	CUCCAUCGGUGGCCGUUUGCCCAGG	1415
53335_I2_185	BCL11a	Intron 2	-	chr2:60495168-60495193	UCUCCAUCGGUGGCCGUUUGCCCAG	1416
53335_I2_186	BCL11a	Intron 2	-	chr2:60495169-60495194	CUCUCCAUCGGUGGCCGUUUGCCCA	1417
53335_I2_187	BCL11a	Intron 2	-	chr2:60495170-	CCUCUCCAUCGGUGGCC	1418

				60495195	GUUUGCCC	
53335_I2_188	BCL11a	Intron 2	-	chr2:60495183-60495208	GAGGACUGGCAGACCUCUCCAUCGG	1419
53335_I2_189	BCL11a	Intron 2	-	chr2:60495186-60495211	GAAGAGGACUGGCAGACCUCUCCAU	1420
53335_I2_190	BCL11a	Intron 2	-	chr2:60495202-60495227	GGGCGUGGGUGGGGUAGAAGAGGAC	1421
53335_I2_191	BCL11a	Intron 2	-	chr2:60495207-60495232	GGUGGGGGCGUGGGUGGGGUAGAAG	1422
53335_I2_192	BCL11a	Intron 2	-	chr2:60495216-60495241	UCUGAUUAGGGUGGGGGCGUGGGUG	1423
53335_I2_193	BCL11a	Intron 2	-	chr2:60495217-60495242	CUCUGAUUAGGGUGGGGGCGUGGGU	1424
53335_I2_194	BCL11a	Intron 2	-	chr2:60495218-60495243	CCUCUGAUUAGGGUGGGGGCGUGGG	1425
53335_I2_195	BCL11a	Intron 2	-	chr2:60495221-60495246	UGGCCUCUGAUUAGGGUGGGGGCGU	1426
53335_I2_196	BCL11a	Intron 2	-	chr2:60495222-60495247	UUGGCCUCUGAUUAGGGUGGGGGCG	1427
53335_I2_197	BCL11a	Intron 2	-	chr2:60495227-60495252	AGGGUUUGGCCUCUGAUUAGGGUGG	1428
53335_I2_198	BCL11a	Intron 2	-	chr2:60495228-60495253	AAGGGUUUGGCCUCUGAUUAGGGUG	1429
53335_I2_199	BCL11a	Intron 2	-	chr2:60495229-60495254	GAAGGGUUUGGCCUCUGAUUAGGGU	1430
53335_I2_200	BCL11a	Intron 2	-	chr2:60495230-60495255	GGAAGGGUUUGGCCUCUGAUUAGGG	1431
53335_I2_201	BCL11a	Intron 2	-	chr2:60495233-60495258	CCAGGAAGGGUUUGGCCUCUGAUUA	1432
53335_I2_202	BCL11a	Intron 2	-	chr2:60495234-60495259	UCCAGGAAGGGUUUGGCCUCUGAUU	1433
53335_I2_203	BCL11a	Intron 2	-	chr2:60495246-60495271	UUUAUCACAGGCUCCAGGAAGGGUU	1434
53335_I2_204	BCL11a	Intron 2	-	chr2:60495251-60495276	UUGCUUUUAUCACAGGCUCCAGGAA	1435
53335_I2_205	BCL11a	Intron 2	-	chr2:60495252-	GUUGCUUUUAUCACAGG	1436

				60495277	CUCCAGGA	
53335_I2_206	BCL11a	Intron 2	-	chr2:60495256-60495281	AACAGUUGCUUUUAUCACAGGCUCC	1437
53335_I2_207	BCL11a	Intron 2	-	chr2:60495263-60495288	GCAAGCUAACAGUUGCUUUUAUCAC	1438
53335_I2_208	BCL11a	Intron 2	-	chr2:60495318-60495343	AUCUACUCUUAGACAUAACACACCA	1439
53335_I2_209	BCL11a	Intron 2	-	chr2:60495319-60495344	CAUCUACUCUUAGACAUAACACACC	1440
53335_I2_210	BCL11a	Intron 2	-	chr2:60495347-60495372	AAUAACAUAGGCCAGAAAAGAGAUA	1441
53335_I2_211	BCL11a	Intron 2	-	chr2:60495364-60495389	GCAAAGUCCAUACAGGUAAUAACAU	1442
53335_I2_212	BCL11a	Intron 2	-	chr2:60495376-60495401	GCUGAUUCCAGUGCAAAGUCCAUAC	1443
53335_I2_213	BCL11a	Intron 2	-	chr2:60495426-60495451	CGAUACAGGGCUGGCUCUAUGCCCC	1444
53335_I2_214	BCL11a	Intron 2	-	chr2:60495440-60495465	AGAUGGCUGAAAAGCGAUACAGGGC	1445
53335_I2_215	BCL11a	Intron 2	-	chr2:60495444-60495469	AGUGAGAUGGCUGAAAAGCGAUACA	1446
53335_I2_216	BCL11a	Intron 2	-	chr2:60495445-60495470	UAGUGAGAUGGCUGAAAAGCGAUAC	1447
53335_I2_217	BCL11a	Intron 2	-	chr2:60495462-60495487	GACUUGGGAGUUAUCUGUAGUGAGA	1448
53335_I2_218	BCL11a	Intron 2	-	chr2:60495482-60495507	UAAGGAAGGCAGCUAGACAGGACUU	1449
53335_I2_219	BCL11a	Intron 2	-	chr2:60495483-60495508	AUAAGGAAGGCAGCUAGACAGGACU	1450
53335_I2_220	BCL11a	Intron 2	-	chr2:60495489-60495514	CCUGUGAUAAGGAAGGCAGCUAGAC	1451
53335_I2_221	BCL11a	Intron 2	-	chr2:60495501-60495526	UUGGGUGCUAUUCCUGUGAUAAGGA	1452
53335_I2_222	BCL11a	Intron 2	-	chr2:60495505-60495530	GACCUUGGGUGCUAUUCCUGUGAUA	1453
53335_I2_223	BCL11a	Intron 2	-	chr2:60495524-	CUACUCUGAGGUACUGA	1454

				60495549	UGGACCUU	
53335_I2_224	BCL11a	Intron 2	-	chr2:60495525-60495550	UCUACUCUGAGGUACUGAUGGACCU	1455
53335_I2_225	BCL11a	Intron 2	-	chr2:60495532-60495557	AGGGGGUUCUACUCUGAGGUACUGA	1456
53335_I2_226	BCL11a	Intron 2	-	chr2:60495541-60495566	CUAGUUUAUAGGGGGUUCUACUCUG	1457
53335_I2_227	BCL11a	Intron 2	-	chr2:60495554-60495579	UGGGCAAACCAGACUAGUUUAUAGG	1458
53335_I2_228	BCL11a	Intron 2	-	chr2:60495555-60495580	AUGGGCAAACCAGACUAGUUUAUAG	1459
53335_I2_229	BCL11a	Intron 2	-	chr2:60495556-60495581	CAUGGGCAAACCAGACUAGUUUAUA	1460
53335_I2_230	BCL11a	Intron 2	-	chr2:60495557-60495582	CCAUGGGCAAACCAGACUAGUUUAU	1461
53335_I2_231	BCL11a	Intron 2	-	chr2:60495578-60495603	GGAAAACAGCCUGACUGUGCCCCAU	1462
53335_I2_232	BCL11a	Intron 2	-	chr2:60495579-60495604	UGGAAAACAGCCUGACUGUGCCCCA	1463
53335_I2_233	BCL11a	Intron 2	-	chr2:60495604-60495629	GGCAGAGAAUGUCUGCACCCCACCC	1464
53335_I2_234	BCL11a	Intron 2	-	chr2:60495630-60495655	UGACGUUAUAUGUAAGCAUCACAAC	1465
53335_I2_235	BCL11a	Intron 2	-	chr2:60495684-60495709	GGAAGCUCCAAACUCUCAAACCACA	1466
53335_I2_236	BCL11a	Intron 2	-	chr2:60495685-60495710	GGGAAGCUCCAAACUCUCAAACCAC	1467
53335_I2_237	BCL11a	Intron 2	-	chr2:60495710-60495735	CCCAUUGAGAAUAUUUUGACUUUUA	1468
53335_I2_238	BCL11a	Intron 2	-	chr2:60495711-60495736	GCCCAUUGAGAAUAUUUUGACUUUU	1469
53335_I2_239	BCL11a	Intron 2	-	chr2:60495738-60495763	CCUUUUGUGUGUAUGUGCUGAUUGA	1470
53335_I2_240	BCL11a	Intron 2	-	chr2:60495739-60495764	ACCUUUUGUGUGUAUGUGCUGAUUG	1471
53335_I2_241	BCL11a	Intron 2	-	chr2:60495768-	AGCAGGAAAAGAAUUAC	1472

				60495793	AGUUUUCC	
53335_I2_242	BCL11a	Intron 2	-	chr2:60495790-60495815	GGUAUUGAAUUGCCUGUCUUUGAGC	1473
53335_I2_243	BCL11a	Intron 2	-	chr2:60495816-60495841	GGCAAGGGUUUUUGGUUGGGGGAAG	1474
53335_I2_244	BCL11a	Intron 2	-	chr2:60495817-60495842	UGGCAAGGGUUUUUGGUUGGGGGAA	1475
53335_I2_245	BCL11a	Intron 2	-	chr2:60495818-60495843	GUGGCAAGGGUUUUUGGUUGGGGGA	1476
53335_I2_246	BCL11a	Intron 2	-	chr2:60495822-60495847	CAUGGUGGCAAGGGUUUUUGGUUGG	1477
53335_I2_247	BCL11a	Intron 2	-	chr2:60495823-60495848	CCAUGGUGGCAAGGGUUUUGGUUG	1478
53335_I2_248	BCL11a	Intron 2	-	chr2:60495824-60495849	CCCAUGGUGGCAAGGGUUUUGGUU	1479
53335_I2_249	BCL11a	Intron 2	-	chr2:60495825-60495850	UCCCAUGGUGGCAAGGGUUUUUGGU	1480
53335_I2_250	BCL11a	Intron 2	-	chr2:60495829-60495854	AGGCUCCCAUGGUGGCAAGGGUUUU	1481
53335_I2_251	BCL11a	Intron 2	-	chr2:60495836-60495861	CUGCCCCAGGCUCCCAUGGUGGCAA	1482
53335_I2_252	BCL11a	Intron 2	-	chr2:60495837-60495862	UCUGCCCCAGGCUCCCAUGGUGGCA	1483
53335_I2_253	BCL11a	Intron 2	-	chr2:60495842-60495867	CCUUCUCUGCCCCAGGCUCCCAUGG	1484
53335_I2_254	BCL11a	Intron 2	-	chr2:60495845-60495870	GUGCCUUCUCUGCCCCAGGCUCCCA	1485
53335_I2_255	BCL11a	Intron 2	-	chr2:60495854-60495879	GACUUCACUGUGCCUUCUCUGCCCC	1486
53335_I2_256	BCL11a	Intron 2	-	chr2:60495893-60495918	AAAAAUGACAGCACCAUUUAGAGCC	1487
53335_I2_257	BCL11a	Intron 2	-	chr2:60495978-60496003	UUUCCAGAGCUGCAGUAUGUUUCUU	1488
53335_I2_258	BCL11a	Intron 2	-	chr2:60496020-60496045	GGGUGACCUCUGGAUCCCUUCUCUU	1489
53335_I2_259	BCL11a	Intron 2	-	chr2:60496035-	ACUUUUCACAUAUGAGG	1490

				60496060	GUGACCUC	
53335_I2_260	BCL11a	Intron 2	-	chr2:60496045-60496070	UUAUCAAUUGACUUUUCACAUAUGA	1491
53335_I2_261	BCL11a	Intron 2	-	chr2:60496046-60496071	AUUAUCAAUUGACUUUUCACAUAUG	1492
53335_I2_262	BCL11a	Intron 2	-	chr2:60496090-60496115	GCAUUGCUUUCAAUCAUCUCCCCUC	1493
53335_I2_263	BCL11a	Intron 2	-	chr2:60496119-60496144	UGUUUCCGUAAUCCAUUUCCUGCAC	1494
53335_I2_264	BCL11a	Intron 2	-	chr2:60496165-60496190	AGAACUUUCCCGGUUCUGGUUUUCU	1495
53335_I2_265	BCL11a	Intron 2	-	chr2:60496166-60496191	CAGAACUUUCCCGGUUCUGGUUUUC	1496
53335_I2_266	BCL11a	Intron 2	-	chr2:60496174-60496199	CCGACUUCCAGAACUUUCCCGGUUC	1497
53335_I2_267	BCL11a	Intron 2	-	chr2:60496180-60496205	GUUUUUCCGACUUCCAGAACUUUCC	1498
53335_I2_268	BCL11a	Intron 2	-	chr2:60496233-60496258	GACAAGGCAUUCUGUAAACGUGUAU	1499

In embodiments, the gRNA targeting domain consists of the 20 3' nt of any one of the sequences in the table above.

Exemplary preferred gRNA tareting domains useful in the compositions and methods of the invention are described in the tables below.

Table 5. Preferred Guide RNA Targeting Domains Directed to Coding Regions of the BCL11a Gene

Id.	**Target**	**gRNA Targeting Domain**	**Targeting Site (Chr2)**	**SEQ ID NO:**
CR000044	BCL11a	ACAGGCCGUGAACCUAAGUG	60678414-60678436	1
CR000056	BCL11a	UAGAGGGGGGAAAUUAUAGG	60678685-60678707	2
CR000068	BCL11a	CGAGCGGUAAAUCCUAAAGA	60678840-60678862	3
CR000079	BCL11a	AGACAAAUUCAAAUCCUGCA	60678895-60678917	4
CR000091	BCL11a	GCUUUUGGUGGCUACCAUGC	60678909-60678931	5
CR000102	BCL11a	AAUUUAUGCCAUCUGAUAAG	60679112-60679134	6
CR000033	BCL11a	UGUUCCUCCUACCCACCCGA	60679178-60679200	7

CR000045	BCL11a	AUAAAUGUUGGAGCUUUAGG	60679288-60679310	8
CR000069	BCL11a	CAACCUAAUUACCUGUAUUG	60679389-60679411	9
CR000080	BCL11a	CGCUGUCAUGAGUGAUGCCC	60679428-60679450	10
CR000092	BCL11a	GGCAUCACUCAUGACAGCGA	60679432-60679454	11
CR000103	BCL11a	AGUCCCAUAGAGAGGGCCCG	60679456-60679478	12
CR000115	BCL11a	ACUGAUUCACUGUUCCAAUG	60679476-60679498	13
CR000034	BCL11a	AGGACUCUGUCUUCGCACAA	60679577-60679599	14
CR000058	BCL11a	CCACGCUGACGUCGACUGGG	60679650-60679672	15
CR000070	BCL11a	GUUCUUCACACACCCCCAUU	60679779-60679801	16
CR000081	BCL11a	GCGCUUCUCCACACCGCCCG	60687934-60687956	17
CR000093	BCL11a	GUCUGGAGUCUCCGAAGCUA	60688006-60688028	18
CR000116	BCL11a	AAAGAUCCCUUCCUUAGCUU	60688017-60688039	19
CR000035	BCL11a	UCGCCGGCUACGCGGCCUCC	60688046-60688068	20
CR000047	BCL11a	CGGAGAACGUGUACUCGCAG	60688070-60688092	21
CR000071	BCL11a	GAGCUUGAUGCGCUUAGAGA	60688133-60688155	22
CR000082	BCL11a	CCCCCCGAGGCCGACUCGCC	60688200-60688222	23
CR000094	BCL11a	CACCAUGCCCUGCAUGACGU	60688394-60688416	24
CR000105	BCL11a	GAGAGCGAGAGGGUGGACUA	60688506-60688528	25
CR000117	BCL11a	CACGGACUUGAGCGCGCUGC	60688649-60688671	26
CR000036	BCL11a	GCCCACCAAGUCGCUGGUGC	60688676-60688698	27
CR000048	BCL11a	CCCACCAAGUCGCUGGUGCC	60688677-60688699	28
CR000060	BCL11a	GGCGGUGGAGAGACCGUCGU	60688712-60688734	29
CR000072	BCL11a	GCCGCAGAACUCGCAUGACU	60688898-60688920	30
CR000083	BCL11a	CCGCCCCCAGGCGCUCUAUG	60689194-60689216	31
CR000095	BCL11a	UGGGGGUCCAAGUGAUGUCU	60689217-60689239	32
CR000106	BCL11a	CUCAACUUACAAAUACCCUG	60695857-60695879	33
CR000118	BCL11a	AGUGCAGAAUAUGCCCCGCA	60695872-60695894	34
CR000037	BCL11a	GCAUAUUCUGCACUCAUCCC	60695881-60695903	35
CR000049	BCL11a	GAGCUCUAAUCCCCACGCCU	60695898-60695920	36
CR000061	BCL11a	AGAGCUCCAUGUGCAGAACG	60695914-60695936	37
CR000084	BCL11a	GAUAAACUUCUGCACUGGAG	60695947-60695969	38
CR000096	BCL11a	UAGCUGUAGUGCUUGAUUUU	60695981-60696003	39
CR000107	BCL11a	UAUCCAAAUUCAUACAAUAG	60716451-60716473	40
CR000119	BCL11a	AUGCCCUGAGUAUCCCAACA	60717068-60717090	41
CR000038	BCL11a	UAGUAACAGACCCAUGUGCU	60717232-60717254	42

CR000050	BCL11a	AUACUUCAAGGCCUCAAUGA	60717661-60717683	43
CR000062	BCL11a	GACUAGGUAGACCUUCAUUG	60717672-60717694	44
CR000073	BCL11a	CUGAGCUAGUGGGGGCUCUU	60720773-60720795	45
CR000085	BCL11a	CUGAGCACAUUCUUACGCCU	60721291-60721313	46
CR000097	BCL11a	UUUAUAAGACAUUAGGGUAt	60721534-60721556	47
CR000108	BCL11a	UGAUAGGUGCCUAUAUGUGA	60722096-60722118	48
CR000120	BCL11a	UCCACCCAUCCAUCACAUAU	60722105-60722127	49
CR000039	BCL11a	CUUCAAAGUUGUAUUGACCC	60722434-60722456	50
CR000051	BCL11a	AAACCAGACUAGUUUAUAGG	60722687-60722709	51
CR000063	BCL11a	UUUGAGACAGUUACCCCUUC	60723706-60723728	52
CR000074	BCL11a	AACCUGAGGGCUAGUUUCUA	60724541-60724563	53
CR000086	BCL11a	GCCUGGACCCACCGCUUCAU	60725058-60725080	54
CR000109	BCL11a	AAACCAGUGAGGUCAUCUAU	60725857-60725879	55
CR000121	BCL11a	ACCUGCUAUGUGUUCCUGUU	60773104-60773126	56
CR000040	BCL11a	UAGAGGAAUUUGCCCCAAAC	60773118-60773140	57
CR000052	BCL11a	GAUAAACAAUCGUCAUCCUC	60773150-60773172	58
CR000064	BCL11a	UGGCAUCCAGGUCACGCCAG	60773166-60773188	59
CR000075	BCL11a	GACCUGGAUGCCAACCUCCA	60773176-60773198	60
CR000087	BCL11a	AAAAGCAUCCAAUCCCGUGG	60773190-60773212	61
CR000110	BCL11a	GAUGCUUUUUUCAUCUCGAU	60773204-60773226	62
CR000122	BCL11a	CCACAGCUUUUUCUAAGCAG	60773247-60773269	63
CR000041	BCL11a	CCCCCAAUGGGAAGUUCAUC	60773316-60773338	64
CR000053	BCL11a	AUCAUGACCUCCUCACCUGU	60773344-60773366	65
CR000065	BCL11a	AGGAGGUCAUGAUCCCCUUC	60773354-60773376	66
CR000088	BCL11a	CCCCUUCUGGAGCUCCCAAC	60773367-60773389	67
CR000099	BCL11a	GCUCCCAACGGGCCGUGGUC	60773378-60773400	68
CR000111	BCL11a	ACAGAUGAUGAACCAGACCA	60773390-60773412	69
CR000123	BCL11a	UCUGUAAGAAUGGCUUCAAG	60773408-60773430	70
CR000042	BCL11a	CAAUUAUUAGAGUGCCAGAG	60773459-60773481	71
CR000054	BCL11a	GCCUUGCUUGCGGCGAGACA	60780385-60780407	72
CR000066	BCL11a	ACCAUGUCUCGCCGCAAGCA	60780386-60780408	73
CR000077	BCL11a	GAGUCUCCUUCUUUCUAACC	60780482-60780504	74
CR000089	BCL11a	GAAUUGUGGGAGAGCCGUCA	60780582-60780604	75
CR000100	BCL11a	AAAAUAGAGCGAGAGUGCAC	60781166-60781188	76
CR000112	BCL11a	GCCCCUGGCGUCCACACGCG	60781306-60781328	77

CR000124	BCL11a	CUCCUCGUUCUUUAUUCCUC	60781716-60781738	78
CR000043	BCL11a	GACUGCCCGCGCUUUGUCCU	60781815-60781837	79
CR000055	BCL11a	UUCCCAGGGACUGGGACUCC	60781838-60781860	80
CR000078	BCL11a	UGGCUCCUGGGUGUGCGCCU	60782123-60782145	81
CR000090	BCL11a	UGAAGCCCGCUUUUUGACAG	60782254-60782276	82
CR000101	BCL11a	AGGGUGGAGACGGGUCGCCA	60782526-60782548	83
CR000113	BCL11a	GCUCAGGGUCUCGCGGGCCA	60782543-60782565	84
CR000059	BCL11a	UGAGUCCGAGCAGAAGAAGA	73160981-73161003	85

Table 6: Preferred Guide RNA Targeting Domains directed to the French HPFH (French HPFH; Sankaran VG et al. A functional element necessary for fetal hemoglobin silencing. NEJM (2011) 365:807-814.)

Id.	**Target Name**	**Strand**	**gRNA Targeting Domain**	**Genomic Target Location**	**SEQ ID NO:**
CR001016	HPFH	-	UCUUAAACCAACCUGCUCAC	chr11:5234538-5234558	86
CR001017	HPFH	+	CAGGUUGGUUUAAGAUAAGC	chr11:5234543-5234563	87
CR001018	HPFH	+	AGGUUGGUUUAAGAUAAGCA	chr11:5234544-5234564	88
CR001019	HPFH	-	UUAAGGGAAUAGUGGAAUGA	chr11:5234600-5234620	89
CR001020	HPFH	-	AGGGCAAGUUAAGGGAAUAG	chr11:5234608-5234628	90
CR001021	HPFH	+	CCCUUAACUUGCCCUGAGAU	chr11:5234613-5234633	91
CR001022	HPFH	-	CCAAUCUCAGGGCAAGUUAA	chr11:5234616-5234636	92
CR001023	HPFH	-	GCCAAUCUCAGGGCAAGUUA	chr11:5234617-5234637	93
CR001024	HPFH	-	UGACAGAACAGCCAAUCUCA	chr11:5234627-5234647	94
CR001025	HPFH	-	AUGACAGAACAGCCAAUCUC	chr11:5234628-5234648	95
CR001026	HPFH	-	GAGAUAUGUAGAGGAGAACA	chr11:5234670-5234690	96
CR001027	HPFH	-	GGAGAUAUGUAGAGGAGAAC	chr11:5234671-5234691	97
CR001028	HPFH	-	UGCGGUGGGGAGAUAUGUAG	chr11:5234679-5234699	98
CR001029	HPFH	-	CUGCUGAAAGAGAUGCGGUG	chr11:5234692-5234712	99
CR001030	HPFH	-	ACUGCUGAAAGAGAUGCGGU	chr11:5234693-5234713	100
CR001031	HPFH	-	AACUGCUGAAAGAGAUGCGG	chr11:5234694-5234714	101
CR001032	HPFH	-	AACAACUGCUGAAAGAGAUG	chr11:5234697-5234717	102

CR001033	HPFH	-	UCUGCAAAAAUGAAACUAGG	chr11:5234731-5234751	103
CR001034	HPFH	-	ACUUCUGCAAAAAUGAAACU	chr11:5234734-5234754	104
CR001035	HPFH	+	CAUUUUUGCAGAAGUGUUUU	chr11:5234739-5234759	105
CR001036	HPFH	+	AGUGUUUUAGGCUAAUAUAG	chr11:5234751-5234771	106
CR001037	HPFH	-	UUGGAGACAAAAAUCUCUAG	chr11:5234883-5234903	107
CR001038	HPFH	+	UCUAGAGAUUUUUGUCUCCA	chr11:5234882-5234902	108
CR001039	HPFH	+	CUAGAGAUUUUUGUCUCCAA	chr11:5234883-5234903	109
CR001040	HPFH	+	GUCUCCAAGGGAAUUUUGAG	chr11:5234895-5234915	110
CR001041	HPFH	+	CCAAGGGAAUUUUGAGAGGU	chr11:5234899-5234919	111
CR001042	HPFH	-	CCAACCUCUCAAAAUUCCCU	chr11:5234902-5234922	112
CR001043	HPFH	+	GGAAUUUUGAGAGGUUGGAA	chr11:5234904-5234924	113
CR001044	HPFH	+	UGCUUGCUUCCUCCUUCUUU	chr11:5234953-5234973	114
CR001045	HPFH	-	AAGAAUUUACCAAAAGAAGG	chr11:5234965-5234985	115
CR001046	HPFH	-	AGGAAGAAUUUACCAAAAGA	chr11:5234968-5234988	116
CR001047	HPFH	-	AAAAAUUAGAGUUUUAUUAU	chr11:5234988-5235008	117
CR001048	HPFH	-	UUUUUUAAAUAUUCUUUUAA	Chr11:5235023-5235045	118
CR001049	HPFH	+	UAUUUACCAGUUAUUGAAAU	chr11:5235062-5235082	119
CR001050	HPFH	+	CCAGUUAUUGAAAUAGGUUC	chr11:5235068-5235088	120
CR001051	HPFH	-	CCAGAACCUAUUUCAAUAAC	chr11:5235071-5235091	121
CR001052	HPFH	+	UUCUGGAAACAUGAAUUUUA	chr11:5235085-5235105	122
CR001053	HPFH	+	AUUUUGAAUGUUUAAAAUUA	chr11:5235151-5235171	123
CR001054	HPFH	-	AAAUUUAAUCUGGCUGAAUA	chr11:5235216-5235236	124
CR001055	HPFH	-	GAACUUCGUUAAAUUUAAUC	chr11:5235226-5235246	125
CR001056	HPFH	+	AUUAAAUUUAACGAAGUUCC	chr11:5235227-5235247	126
CR001057	HPFH	+	UUAAAUUUAACGAAGUUCCU	chr11:5235228-5235248	127
CR001058	HPFH	-	UUCUGUACUAGCAUAUUCCC	chr11:5235248-5235268	128
CR001059	HPFH	+	UGUGUUCUUAAAAAAAAAUG	Chr11:5235275-5235297	129
CR001060	HPFH	+	AAAAAUGUGGAAUUAGACCC	chr11:5235293-5235313	130
CR001061	HPFH	-	CUACUGGGAUCUUCAUUCCU	chr11:5235313-5235333	131
CR001062	HPFH	-	ACUACUGGGAUCUUCAUUCC	chr11:5235314-5235334	132

CR001063	HPFH	-	GAAAAGAGUGAAAAACUACU	chr11:5235328-5235348	133
CR001064	HPFH	-	AGAAAAGAGUGAAAAACUAC	chr11:5235329-5235349	134
CR001065	HPFH	+	GAAUUCAAAUAAUGCCACAA	chr11:5235349-5235369	135
CR001066	HPFH	-	UGUGUAUUUGUCUGCCAUUG	chr11:5235366-5235386	136
CR001067	HPFH	+	CACCCAUGAGCAUAUCCAAA	chr11:5235384-5235404	137
CR001068	HPFH	-	UUCCUUUUGGAUAUGCUCAU	chr11:5235389-5235409	138
CR001069	HPFH	-	CUUCCUUUUGGAUAUGCUCA	chr11:5235390-5235410	139
CR001070	HPFH	+	CAUGAGCAUAUCCAAAAGGA	chr11:5235388-5235408	140
CR001071	HPFH	+	UAUCCAAAAGGAAGGAUUGA	chr11:5235396-5235416	141
CR001072	HPFH	-	UUUCCUUCAAUCCUUCCUUU	chr11:5235402-5235422	142
CR001073	HPFH	+	AAGGAAGGAUUGAAGGAAAG	chr11:5235403-5235423	143
CR001074	HPFH	+	GAAGGAUUGAAGGAAAGAGG	chr11:5235406-5235426	144
CR001075	HPFH	+	GAGGAGGAAGAAAUGGAGAA	chr11:5235422-5235442	145
CR001076	HPFH	+	AGGAAGAAAUGGAGAAAGGA	chr11:5235426-5235446	146
CR001077	HPFH	+	GAAGGAAGAGGGGAAGAGAG	chr11:5235448-5235468	147
CR001078	HPFH	+	GAAGAGGGGAAGAGAGAGGA	chr11:5235452-5235472	148
CR001079	HPFH	+	AGGGGAAGAGAGAGGAUGGA	chr11:5235456-5235476	149
CR001080	HPFH	+	GGGGAAGAGAGAGGAUGGAA	chr11:5235457-5235477	150
CR001081	HPFH	+	AAGAGAGAGGAUGGAAGGGA	chr11:5235461-5235481	151
CR001082	HPFH	+	AGAGAGGAUGGAAGGGAUGG	chr11:5235464-5235484	152
CR001083	HPFH	+	GGAAGGGAUGGAGGAGAAGA	chr11:5235473-5235493	153
CR001084	HPFH	+	GAAGAAGGAAAAAUAAAUAA	Chr11:5235483-5235505	154
CR001085	HPFH	+	AGGAAAAAUAAAUAAUGGAG	Chr11:5235488-5235510	155
CR001086	HPFH	+	AAAUAAAUAAUGGAGAGGAG	chr11:5235498-5235518	156
CR001087	HPFH	+	UGGAGAGGAGAGGAGAAAAA	chr11:5235508-5235528	157
CR001088	HPFH	+	AGAGGAGAGGAGAAAAAAGG	chr11:5235511-5235531	158
CR001089	HPFH	+	GAGGAGAGGAGAAAAAAGGA	chr11:5235512-5235532	159
CR001090	HPFH	+	AGGAGAGGAGAAAAAAGGAG	chr11:5235513-5235533	160
CR001091	HPFH	+	AGGAGAAAAAAGGAGGGGAG	chr11:5235518-5235538	161
CR001092	HPFH	+	GAGAGGAGAGGAGAAGGGAU	chr11:5235535-5235555	162

CR001093	HPFH	+	AGAGGAGAGGAGAAGGGAUA	chr11:5235536-5235556	163
CR001094	HPFH	+	GAAGAGAAAGAGAAAGGGAA	Chr11:5235553-5235575	164
CR001095	HPFH	+	AAGAGAGGAAAGAAGAGAAG	chr11:5235581-5235601	165
CR001096	HPFH	+	GAGAGAAAAGAAACGAAGAG	Chr11:5235598-5235620	166
CR001097	HPFH	+	AGAGAAAAGAAACGAAGAGA	Chr11:5235599-5235621	167
CR001098	HPFH	+	GAGAAAAGAAACGAAGAGAG	Chr11:5235600-5235622	168
CR001099	HPFH	+	AAAGAAACGAAGAGAGGGGA	chr11:5235609-5235629	169
CR001100	HPFH	+	AAGAAACGAAGAGAGGGGAA	chr11:5235610-5235630	170
CR001101	HPFH	+	GGAAGGGAAGGAAAAAAAAG	chr11:5235626-5235646	171
CR001102	HPFH	+	AAGACUGACAGUUCAAAUUU	chr11:5235672-5235692	172
CR001103	HPFH	+	ACUGACAGUUCAAAUUUUGG	chr11:5235675-5235695	173
CR001104	HPFH	+	UUCAAAUUUUGGUGGUGAUA	chr11:5235683-5235703	174
CR001105	HPFH	+	AAUAGAAACUCAAACUCUGU	chr11:5235709-5235729	175
CR001106	HPFH	+	GUACAAUAGUAUAACCCCUU	chr11:5235739-5235759	176
CR001107	HPFH	-	CUAUUAAAGGUUUUCCAAAG	chr11:5235756-5235776	177
CR001108	HPFH	-	ACUAUUAAAGGUUUUCCAAA	chr11:5235757-5235777	178
CR001109	HPFH	-	UACUAUUAAAGGUUUUCCAA	chr11:5235758-5235778	179
CR001110	HPFH	-	GCAUUUGUGGAUACUAUUAA	chr11:5235769-5235789	180
CR001111	HPFH	+	UUAAUAGUAUCCACAAAUGC	chr11:5235769-5235789	181
CR001132	HPFH	-	UAUCAAGCAUCCAGCAUUUG	chr11:5235782-5235802	1500
CR001133	HPFH	-	UAUCUAAAAAUGUAAUUGCU	chr11:5235814-5235834	1501
CR001134	HPFH	-	AGCAUUUCUAUACAUGUCUU	chr11:5235862-5235882	1502
CR001135	HPFH	+	UAAUCAUAAAAACCUCAAAC	chr11:5235893-5235913	1503
CR001136	HPFH	-	UUUAAGUGGCUACCGGUUUG	chr11:5235908-5235928	1504
CR001137	HPFH	-	GUAAGCAUUUAAGUGGCUAC	chr11:5235915-5235935	1505
CR001138	HPFH	-	ACUGUUGGUAAGCAUUUAAG	chr11:5235922-5235942	1506
CR001139	HPFH	-	UAAUUUAUCAAUUCUACUGU	chr11:5235937-5235957	1507
CR001140	HPFH	+	ACAGUAGAAUUGAUAAAUUA	chr11:5235937-5235957	1508
CR001141	HPFH	+	CAAAUGCAUUUUACAGCAUU	chr11:5236027-5236047	1509
CR001142	HPFH	+	GGUUGAUUAAAAGUAACCAG	chr11:5236048-5236068	1510

CR001143	HPFH	-	AUAUAGUUUGAACUCACCUC	Chr11:5236059-5236081	1511
CR001144	HPFH	+	UUUAUUUGUAUAUAGAAAGA	chr11:5236090-5236110	1512
CR001145	HPFH	+	UGCCUGAGAUUCUGAUCACA	chr11:5236119-5236139	1513
CR001146	HPFH	+	GCCUGAGAUUCUGAUCACAA	chr11:5236120-5236140	1514
CR001147	HPFH	+	CCUGAGAUUCUGAUCACAAG	chr11:5236121-5236141	1515
CR001148	HPFH	-	CCCCUUGUGAUCAGAAUCUC	chr11:5236124-5236144	1516
CR001149	HPFH	+	AAGGGGAAAUGUUAUAAAAU	chr11:5236138-5236158	1517
CR001150	HPFH	+	AGGGGAAAUGUUAUAAAAUA	chr11:5236139-5236159	1518
CR001151	HPFH	+	UGUUAUAAAAUAGGGUAGAG	chr11:5236147-5236167	1519
CR001152	HPFH	-	CAAAGUUUAAAGGUCAUUCA	chr11:5236175-5236195	1520
CR001153	HPFH	-	UAACUUGUAACAAAGUUUAA	chr11:5236185-5236205	1521
CR001154	HPFH	+	CAAGUUAUUUUUCUGUAACC	chr11:5236198-5236218	1522
CR001155	HPFH	-	AAUAUCUUUCGUUGGCUUCC	chr11:5236219-5236239	1523
CR001156	HPFH	-	AAUUAUUCAAUAUCUUUCGU	chr11:5236227-5236247	1524
CR001157	HPFH	+	GAUAUUGAAUAAUUCAAGAA	chr11:5236233-5236253	1525
CR001158	HPFH	+	AUUGAAUAAUUCAAGAAAGG	chr11:5236236-5236256	1526
CR001159	HPFH	+	GAAUAAUUCAAGAAAGGUGG	chr11:5236239-5236259	1527
CR001160	HPFH	+	AUUCAAGAAAGGUGGUGGCA	chr11:5236244-5236264	1528
CR001161	HPFH	+	UAUUUUAGAAGUAGAGAAAA	chr11:5236313-5236333	1529
CR001162	HPFH	+	AUUUUAGAAGUAGAGAAAAU	chr11:5236314-5236334	1530
CR001163	HPFH	+	GAAAAUGGGAGACAAAUAGC	chr11:5236328-5236348	1531
CR001164	HPFH	+	AAAAUGGGAGACAAAUAGCU	chr11:5236329-5236349	1532
CR001165	HPFH	+	AGCUGGGCUUCUGUUGCAGU	chr11:5236345-5236365	1533
CR001166	HPFH	+	GCUGGGCUUCUGUUGCAGUA	chr11:5236346-5236366	1534
CR001167	HPFH	+	GCCAUUUCUAUUAUCAGACU	chr11:5236383-5236403	1535
CR001168	HPFH	-	UCCAAGUCUGAUAAUAGAAA	chr11:5236387-5236407	1536
CR001169	HPFH	+	UUAUCAGACUUGGACCAUGA	chr11:5236393-5236413	1537
CR001170	HPFH	-	CACGACUGACAUCACCGUCA	chr11:5236410-5236430	1538
CR001171	HPFH	+	UCAGUCGUGAACACAAGAAU	chr11:5236421-5236441	1539
CR001172	HPFH	+	CAGUCGUGAACACAAGAAUA	chr11:5236422-5236442	1540

CR001173	HPFH	+	GGCCACAUUUGUGAGUUUAG	chr11:5236443-5236463	1541
CR001174	HPFH	-	UACCACUAAACUCACAAAUG	chr11:5236448-5236468	1542
CR001175	HPFH	+	UAAAAUCAGAAAUACAGUCU	chr11:5236471-5236491	1543
CR001176	HPFH	+	AAAAGAUGUACUUAGAUAUG	chr11:5236528-5236548	1544
CR001177	HPFH	+	UGUACUUAGAUAUGUGGAUC	chr11:5236534-5236554	1545
CR001178	HPFH	+	AGCUCAGAAAGAAUACAACC	chr11:5236557-5236577	1546
CR001179	HPFH	+	ACCAGGUCAAGAAUACAGAA	chr11:5236574-5236594	1547
CR001180	HPFH	-	UCCAUUCUGUAUUCUUGACC	chr11:5236578-5236598	1548
CR001181	HPFH	-	CUGUCAUUUUUAACAGGUAG	chr11:5236646-5236666	1549
CR001182	HPFH	-	CAUCAUCUGUCAUUUUUAAC	chr11:5236652-5236672	1550
CR001183	HPFH	-	AAACACAUUCUAAGAUUUUA	chr11:5236691-5236711	1551
CR001184	HPFH	+	AAUCUUAGAAUGUGUUUGUG	chr11:5236694-5236714	1552
CR001185	HPFH	+	AUCUUAGAAUGUGUUUGUGA	chr11:5236695-5236715	1553
CR001186	HPFH	+	UUAGAAUGUGUUUGUGAGGG	chr11:5236698-5236718	1554
CR001187	HPFH	-	CAAUUUUCUUAUAUAUGAAU	chr11:5236734-5236754	1555
CR001188	HPFH	+	UUGAUUCUAAAAAAAAAUGUU	Chr11:5236746-5236768	1556
CR001189	HPFH	+	AAAUGUUAGGUAAAUUCUUA	chr11:5236764-5236784	1557
CR001190	HPFH	+	GGUAAAUUCUUAAGGCCAUG	chr11:5236772-5236792	1558
CR001191	HPFH	-	AGAUCAAAUAACAGUCCUCA	chr11:5236790-5236810	1559
CR001192	HPFH	+	GUCUGUUAAUUCCAAAGACU	chr11:5236812-5236832	1560
CR001193	HPFH	-	AAAGUGAAAAGCCAAGUCUU	chr11:5236826-5236846	1561
CR001194	HPFH	+	CCUGAAAUGAUUUUACACAU	chr11:5236858-5236878	1562
CR001195	HPFH	-	CCAAUGUGUAAAAUCAUUUC	chr11:5236861-5236881	1563
CR001196	HPFH	+	CUGAAAUGAUUUUACACAUU	chr11:5236859-5236879	1564
CR001197	HPFH	+	AUUUUACACAUUGGGAGAUC	chr11:5236867-5236887	1565
CR001198	HPFH	+	GGUUACAUGUUUAUUCUAUA	chr11:5236888-5236908	1566
CR001199	HPFH	+	UCUAUAUGGAUUGCAUUGAG	chr11:5236902-5236922	1567
CR001200	HPFH	+	AGGAUUUGUAUAACAGAAUA	chr11:5236922-5236942	1568
CR001201	HPFH	+	UUUUCUUUUCUCUUCUGAGA	Chr11:5236945-5236967	1569
CR001202	HPFH	-	GCACUCUAGCUUGGGCAAUA	chr11:5236984-5237004	1570

CR001203	HPFH	-	UGCACUCUAGCUUGGGCAAU	chr11:5236985-5237005	1571
CR001204	HPFH	-	UGCACCAUUGCACUCUAGCU	Chr11:5236985-5237007	1572
CR001205	HPFH	-	GCUAUUCAGGUGGCUGAGGC	chr11:5237061-5237081	1573
CR001206	HPFH	+	ACCUGAAUAGCUGGGACUGC	Chr11:5237065-5237087	1574
CR001207	HPFH	+	GCAGGCAUGCACCACACGCC	Chr11:5237083-5237105	1575
CR001208	HPFH	-	UACAAAAUCAGCCGGGCGUG	chr11:5237102-5237122	1576
CR001209	HPFH	-	GGCUUGUAAACCCAGCACUU	chr11:5237208-5237228	1577
CR001210	HPFH	-	CUGGCUGGAUGCGGUGGCUC	chr11:5237229-5237249	1578
CR001211	HPFH	+	CUGAGCCACCGCAUCCAGCC	chr11:5237227-5237247	1579
CR001212	HPFH	-	CUUAUCCUGGCUGGAUGCGG	chr11:5237235-5237255	1580
CR001213	HPFH	+	CACCGCAUCCAGCCAGGAUA	chr11:5237233-5237253	1581
CR001214	HPFH	-	GACCUUAUCCUGGCUGGAUG	chr11:5237238-5237258	1582
CR001215	HPFH	-	CUUUUAGACCUUAUCCUGGC	chr11:5237244-5237264	1583
CR001216	HPFH	+	GCCAGGAUAAGGUCUAAAAG	chr11:5237244-5237264	1584
CR001217	HPFH	-	UCCACUUUUAGACCUUAUCC	chr11:5237248-5237268	1585
CR001218	HPFH	+	AAUAGCAUCUACUCUUGUUC	chr11:5237271-5237291	1586
CR001219	HPFH	+	CUCUUGUUCAGGAAACAAUG	chr11:5237282-5237302	1587
CR001220	HPFH	+	GGAAACAAUGAGGACCUGAC	chr11:5237292-5237312	1588
CR001221	HPFH	+	GAAACAAUGAGGACCUGACU	chr11:5237293-5237313	1589
CR001222	HPFH	+	ACCUGACUGGGCAGUAAGAG	chr11:5237305-5237325	1590
CR001223	HPFH	-	ACCACUCUUACUGCCCAGUC	chr11:5237309-5237329	1591
CR001224	HPFH	+	AAGAGUGGUGAUUAAUAGAU	chr11:5237320-5237340	1592
CR001225	HPFH	+	AGAGUGGUGAUUAAUAGAUA	chr11:5237321-5237341	1593
CR001226	HPFH	+	AGAAUCGAACUGUUGAUUAG	chr11:5237356-5237376	1594
CR001227	HPFH	+	UCGAACUGUUGAUUAGAGGU	chr11:5237360-5237380	1595
CR003027	HPFH	+	CGAACUGUUGAUUAGAGGUA	chr11:5237361-5237381	1692
CR003028	HPFH	+	AUGAUUUUAAUCUGUGACCU	chr11:5237386-5237406	1693
CR003029	HPFH	+	UAAUCUGUGACCUUGGUGAA	chr11:5237393-5237413	1694
CR003030	HPFH	+	AAUCUGUGACCUUGGUGAAU	chr11:5237394-5237414	1695
CR003031	HPFH	-	AGCUACUUGCCCAUUCACCA	chr11:5237406-5237426	1696

CR003032	HPFH	+	UAGCUAUCUAAUGACUAAAA	chr11:5237421-5237441	1697
CR003033	HPFH	+	AUGACUAAAAUGGAAAACAC	chr11:5237431-5237451	1698
CR003034	HPFH	+	AAAUACCCAUGCUGAGUCUG	chr11:5237482-5237502	1699
CR003035	HPFH	-	AGGCACCUCAGACUCAGCAU	chr11:5237490-5237510	1700
CR003036	HPFH	-	UAGGCACCUCAGACUCAGCA	chr11:5237491-5237511	1701
CR003037	HPFH	+	GCUGAGUCUGAGGUGCCUAU	chr11:5237492-5237512	1702
CR003038	HPFH	-	UAUUUAUAUAGAUGUCCUAU	chr11:5237510-5237530	1703
CR003039	HPFH	-	CAUAUAUCAAACAAUGUACU	chr11:5237535-5237555	1704
CR003040	HPFH	+	CCAGUACAUUGUUUGAUAUA	chr11:5237533-5237553	1705
CR003041	HPFH	-	CCAUAUAUCAAACAAUGUAC	chr11:5237536-5237556	1706
CR003042	HPFH	+	CAGUACAUUGUUUGAUAUAU	chr11:5237534-5237554	1707
CR003043	HPFH	+	CAUUGUUUGAUAUAUGGGUU	chr11:5237539-5237559	1708
CR003044	HPFH	+	GAUAUAUGGGUUUGGCACUG	chr11:5237547-5237567	1709
CR003045	HPFH	+	UAUGGGUUUGGCACUGAGGU	chr11:5237551-5237571	1710
CR003046	HPFH	+	GGGUUUGGCACUGAGGUUGG	chr11:5237554-5237574	1711
CR003047	HPFH	+	GCACUGAGGUUGGAGGUCAG	chr11:5237561-5237581	1712
CR003048	HPFH	+	CAGAGGUUAGAAAUCAGAGU	chr11:5237578-5237598	1713
CR003049	HPFH	+	AGAGGUUAGAAAUCAGAGUU	chr11:5237579-5237599	1714
CR003050	HPFH	+	UAGAAAUCAGAGUUGGGAAU	chr11:5237585-5237605	1715
CR003051	HPFH	+	AGAAAUCAGAGUUGGGAAUU	chr11:5237586-5237606	1716
CR003052	HPFH	+	GUUGGGAAUUGGGAUUAUAC	chr11:5237596-5237616	1717
CR003053	HPFH	-	CUUUGUAUUCAUCACACUCU	chr11:5237654-5237674	1718
CR003054	HPFH	+	AUGAAUACAAAGUUAAAUGA	chr11:5237662-5237682	1719
CR003055	HPFH	-	UAAAUGUUGGUGUUCAUUAA	chr11:5237689-5237709	1720
CR003056	HPFH	-	UGAGAUUUCACAUUAAAUGU	chr11:5237702-5237722	1721
CR003057	HPFH	+	ACAUUUAAUGUGAAAUCUCA	chr11:5237702-5237722	1722
CR003058	HPFH	-	UAAAAUCAUCGGGGAUUUUG	chr11:5237749-5237769	1723
CR003059	HPFH	-	CUAAAAUCAUCGGGGAUUUU	chr11:5237750-5237770	1724
CR003060	HPFH	-	UCUAAAAUCAUCGGGGAUUU	chr11:5237751-5237771	1725
CR003061	HPFH	-	ACUGAGUUCUAAAAUCAUCG	chr11:5237758-5237778	1726

CR003062	HPFH	-	UACUGAGUUCUAAAAUCAUC	chr11:5237759-5237779	1727
CR003063	HPFH	-	AUACUGAGUUCUAAAAUCAU	chr11:5237760-5237780	1728
CR003064	HPFH	+	UAAUUAGUGUAAUGCCAAUG	chr11:5237786-5237806	1729
CR003065	HPFH	+	AAUUAGUGUAAUGCCAAUGU	chr11:5237787-5237807	1730
CR003066	HPFH	+	AAUGCCAAUGUGGGUUAGAA	chr11:5237796-5237816	1731
CR003067	HPFH	-	ACUUCCAUUCUAACCCACAU	chr11:5237803-5237823	1732
CR003068	HPFH	+	AAUGGAAGUCAACUUGCUGU	chr11:5237814-5237834	1733
CR003069	HPFH	+	CUUGCUGUUGGUUUCAGAGC	chr11:5237826-5237846	1734
CR003070	HPFH	+	CUGUUGGUUUCAGAGCAGGU	chr11:5237830-5237850	1735
CR003071	HPFH	+	UUCAGAGCAGGUAGGAGAUA	chr11:5237838-5237858	1736
CR003072	HPFH	+	AGUGAAAAGCUGAAACAAAA	chr11:5237877-5237897	1737
CR003073	HPFH	+	AAGCUGAAACAAAAAGGAAA	chr11:5237883-5237903	1738
CR003074	HPFH	+	UGAAACAAAAAGGAAAAGGU	chr11:5237887-5237907	1739
CR003075	HPFH	+	GAAACAAAAAGGAAAAGGUA	chr11:5237888-5237908	1740
CR003076	HPFH	+	GGAAAAGGUAGGGUGAAAGA	chr11:5237898-5237918	1741
CR003077	HPFH	+	GAAAAGGUAGGGUGAAAGAU	chr11:5237899-5237919	1742
CR003078	HPFH	+	AAAGAUGGGAAAUGUAUGUA	chr11:5237913-5237933	1743
CR003079	HPFH	+	GAUGGGAAAUGUAUGUAAGG	chr11:5237916-5237936	1744
CR003080	HPFH	+	UGUAAGGAGGAUGAGCCACA	chr11:5237929-5237949	1745
CR003081	HPFH	+	GGAGGAUGAGCCACAUGGUA	chr11:5237934-5237954	1746
CR003082	HPFH	+	GAGGAUGAGCCACAUGGUAU	chr11:5237935-5237955	1747
CR003083	HPFH	+	GAUGAGCCACAUGGUAUGGG	chr11:5237938-5237958	1748
CR003084	HPFH	-	AGUAUACCUCCCAUACCAUG	chr11:5237947-5237967	1749
CR003085	HPFH	+	AUGGUAUGGGAGGUAUACUA	chr11:5237948-5237968	1750
CR003086	HPFH	+	GGAGGUAUACUAAGGACUCU	chr11:5237956-5237976	1751
CR003087	HPFH	+	GAGGUAUACUAAGGACUCUA	chr11:5237957-5237977	1752
CR003088	HPFH	+	ACUCUAGGGUCAGAGAAAUA	chr11:5237971-5237991	1753
CR003089	HPFH	+	CUCUAGGGUCAGAGAAAUAU	chr11:5237972-5237992	1754
CR003090	HPFH	-	AAGAAUGUGAAUUUUGUAGA	chr11:5238004-5238024	1755
CR003091	HPFH	+	UUCUACAAAAUUCACAUUCU	chr11:5238003-5238023	1756

CR003092	HPFH	+	ACAAAAUUCACAUUCUUGGC	chr11:5238007-5238027	1757
CR003093	HPFH	+	CAAAAUUCACAUUCUUGGCU	chr11:5238008-5238028	1758
CR003094	HPFH	+	UUCACAUUCUUGGCUGGGUG	chr11:5238013-5238033	1759
CR003095	HPFH	+	AGGGUGGAUCACCUGAUGUU	chr11:5238071-5238093	1760
CR003096	HPFH	-	GAUCUCGAACUCCUAACAUC	chr11:5238090-5238110	1761

In some aspects of the invention, it is preferred that the gRNA molecule to an HPFH region comprise, e.g., consist of, a targeting domain of a gRNA capable of producing at least about a 20% increase in F cells relative to control, e.g., in an assay described in Example 4. In an aspect, the gRNA molecule includes a targeting domain comprising, e.g., consisting of, SEQ ID NO: 113. In an aspect, the gRNA molecule includes a targeting domain comprising, e.g., consisting of, SEQ ID NO: 99. In an aspect, the gRNA molecule includes a targeting domain comprising, e.g., consisting of, SEQ ID NO: 112. In an aspect, the gRNA molecule includes a targeting domain comprising, e.g., consisting of, SEQ ID NO: 98. In an aspect, the gRNA molecule includes a targeting domain comprising, e.g., consisting of, SEQ ID NO: 1580. In an aspect, the gRNA molecule includes a targeting domain comprising, e.g., consisting of, SEQ ID NO: 106. In an aspect, the gRNA molecule includes a targeting domain comprising, e.g., consisting of, SEQ ID NO: 1589. In an aspect, the gRNA molecule includes a targeting domain comprising, e.g., consisting of, SEQ ID NO: 1503. In an aspect, the gRNA molecule includes a targeting domain comprising, e.g., consisting of, SEQ ID NO: 160. In an aspect, the gRNA molecule includes a targeting domain comprising, e.g., consisting of, SEQ ID NO: 1537. In an aspect, the gRNA molecule includes a targeting domain comprising, e.g., consisting of, SEQ ID NO: 159. In an aspect, the gRNA molecule includes a targeting domain comprising, e.g., consisting of, SEQ ID NO: 101. In an aspect, the gRNA molecule includes a targeting domain comprising, e.g., consisting of, SEQ ID NO: 162. In an aspect, the gRNA molecule includes a targeting domain comprising, e.g., consisting of, SEQ ID NO: 104. In an aspect, the gRNA molecule includes a targeting domain comprising, e.g., consisting of, SEQ ID NO: 138. In an aspect, the gRNA molecule includes a targeting domain comprising, e.g., consisting of, SEQ ID NO: 1536. In an aspect, the gRNA molecule includes a targeting domain comprising, e.g., consisting of, SEQ ID NO: 1539. In an aspect, the gRNA molecule includes a targeting domain comprising, e.g., consisting of, SEQ ID NO: 1585.

In some aspects of the invention, e.g., as indicated herein, it may be beneficial to include gRNA molecules targeting more than one, e.g., two, target sites (e.g., a first gRNA molecule and a second gRNA molecule). In some embodiments, the two target sites are both located in an HPFH region. In such aspects, any combination of more than one, e.g., two, gRNA molecules (e.g., a first gRNA

molecule and a second gRNA molecule) comprising targeting domains listed in Table 6 may be used. In an aspect, the first gRNA molecule and the second gRNA molecule include targeting domains comprising, e.g., consisting of, SEQ ID NO: 100 and SEQ ID NO: 165, respectively. In an aspect, the first gRNA molecule and the second gRNA molecule include targeting domains comprising, e.g., consisting of, SEQ ID NO: 100 and SEQ ID NO: 113, respectively. In an aspect, the first gRNA molecule and the second gRNA molecule include targeting domains comprising, e.g., consisting of, SEQ ID NO: 100 and SEQ ID NO: 99, respectively. In an aspect, the first gRNA molecule and the second gRNA molecule include targeting domains comprising, e.g., consisting of, SEQ ID NO: 100 and SEQ ID NO: 112, respectively. In an aspect, the first gRNA molecule and the second gRNA molecule include targeting domains comprising, e.g., consisting of, SEQ ID NO: 100 and SEQ ID NO: 98, respectively. In an aspect, the first gRNA molecule and the second gRNA molecule include targeting domains comprising, e.g., consisting of, SEQ ID NO: 100 and SEQ ID NO: 1580, respectively. In an aspect, the first gRNA molecule and the second gRNA molecule include targeting domains comprising, e.g., consisting of, SEQ ID NO: 100 and SEQ ID NO: 106, respectively. In an aspect, the first gRNA molecule and the second gRNA molecule include targeting domains comprising, e.g., consisting of, SEQ ID NO: 100 and SEQ ID NO: 1503, respectively. In an aspect, the first gRNA molecule and the second gRNA molecule include targeting domains comprising, e.g., consisting of, SEQ ID NO: 100 and SEQ ID NO: 1589, respectively. In an aspect, the first gRNA molecule and the second gRNA molecule include targeting domains comprising, e.g., consisting of, SEQ ID NO: 100 and SEQ ID NO: 160, respectively. In an aspect, the first gRNA molecule and the second gRNA molecule include targeting domains comprising, e.g., consisting of, SEQ ID NO: 100 and SEQ ID NO: 1537, respectively. In an aspect, the first gRNA molecule and the second gRNA molecule include targeting domains comprising, e.g., consisting of, SEQ ID NO: 100 and SEQ ID NO: 159, respectively. In an aspect, the first gRNA molecule and the second gRNA molecule include targeting domains comprising, e.g., consisting of, SEQ ID NO: 100 and SEQ ID NO: 101, respectively. In an aspect, the first gRNA molecule and the second gRNA molecule include targeting domains comprising, e.g., consisting of, SEQ ID NO: 100 and SEQ ID NO: 162, respectively. In an aspect, the first gRNA molecule and the second gRNA molecule include targeting domains comprising, e.g., consisting of, SEQ ID NO: 100 and SEQ ID NO: 104, respectively. In an aspect, the first gRNA molecule and the second gRNA molecule include targeting domains comprising, e.g., consisting of, SEQ ID NO: 100 and SEQ ID NO: 138, respectively. In an aspect, the first gRNA molecule and the second gRNA molecule include targeting domains comprising, e.g., consisting of, SEQ ID NO: 100 and SEQ ID NO: 1536, respectively. In an aspect, the first gRNA molecule and the second gRNA molecule include targeting domains comprising, e.g., consisting of, SEQ ID NO: 100 and SEQ ID NO: 1539, respectively. In an aspect, the first gRNA molecule and the second gRNA molecule include targeting domains comprising, e.g., consisting of, SEQ ID NO: 100 and SEQ ID NO: 1585, respectively. In an aspect, the first gRNA molecule and the second gRNA

molecule include targeting domains comprising, e.g., consisting of, SEQ ID NO: 165 and SEQ ID NO: 113, respectively. In an aspect, the first gRNA molecule and the second gRNA molecule include targeting domains comprising, e.g., consisting of, SEQ ID NO: 165 and SEQ ID NO: 99, respectively. In an aspect, the first gRNA molecule and the second gRNA molecule include targeting domains comprising, e.g., consisting of, SEQ ID NO: 165 and SEQ ID NO: 112, respectively. In an aspect, the first gRNA molecule and the second gRNA molecule include targeting domains comprising, e.g., consisting of, SEQ ID NO: 165 and SEQ ID NO: 98, respectively. In an aspect, the first gRNA molecule and the second gRNA molecule include targeting domains comprising, e.g., consisting of, SEQ ID NO: 165 and SEQ ID NO: 1580, respectively. In an aspect, the first gRNA molecule and the second gRNA molecule include targeting domains comprising, e.g., consisting of, SEQ ID NO: 165 and SEQ ID NO: 106, respectively. In an aspect, the first gRNA molecule and the second gRNA molecule include targeting domains comprising, e.g., consisting of, SEQ ID NO: 165 and SEQ ID NO: 1503, respectively. In an aspect, the first gRNA molecule and the second gRNA molecule include targeting domains comprising, e.g., consisting of, SEQ ID NO: 165 and SEQ ID NO: 1589, respectively. In an aspect, the first gRNA molecule and the second gRNA molecule include targeting domains comprising, e.g., consisting of, SEQ ID NO: 165 and SEQ ID NO: 160, respectively. In an aspect, the first gRNA molecule and the second gRNA molecule include targeting domains comprising, e.g., consisting of, SEQ ID NO: 165 and SEQ ID NO: 1537, respectively. In an aspect, the first gRNA molecule and the second gRNA molecule include targeting domains comprising, e.g., consisting of, SEQ ID NO: 165 and SEQ ID NO: 159, respectively. In an aspect, the first gRNA molecule and the second gRNA molecule include targeting domains comprising, e.g., consisting of, SEQ ID NO: 165 and SEQ ID NO: 101, respectively. In an aspect, the first gRNA molecule and the second gRNA molecule include targeting domains comprising, e.g., consisting of, SEQ ID NO: 165 and SEQ ID NO: 162, respectively. In an aspect, the first gRNA molecule and the second gRNA molecule include targeting domains comprising, e.g., consisting of, SEQ ID NO: 165 and SEQ ID NO: 104, respectively. In an aspect, the first gRNA molecule and the second gRNA molecule include targeting domains comprising, e.g., consisting of, SEQ ID NO: 165 and SEQ ID NO: 138, respectively. In an aspect, the first gRNA molecule and the second gRNA molecule include targeting domains comprising, e.g., consisting of, SEQ ID NO: 165 and SEQ ID NO: 1536, respectively. In an aspect, the first gRNA molecule and the second gRNA molecule include targeting domains comprising, e.g., consisting of, SEQ ID NO: 165 and SEQ ID NO: 1539, respectively. In an aspect, the first gRNA molecule and the second gRNA molecule include targeting domains comprising, e.g., consisting of, SEQ ID NO: 165 and SEQ ID NO: 1585, respectively. In an aspect, the first gRNA molecule and the second gRNA molecule include targeting domains comprising, e.g., consisting of, SEQ ID NO: 113 and SEQ ID NO: 165, respectively. In an aspect, the first gRNA molecule and the second gRNA molecule include targeting domains comprising, e.g., consisting of, SEQ ID NO: 113 and SEQ ID NO: 99, respectively. In an aspect, the first gRNA molecule and the second gRNA

molecule include targeting domains comprising, e.g., consisting of, SEQ ID NO: 113 and SEQ ID NO: 112, respectively. In an aspect, the first gRNA molecule and the second gRNA molecule include targeting domains comprising, e.g., consisting of, SEQ ID NO: 113 and SEQ ID NO: 98, respectively. In an aspect, the first gRNA molecule and the second gRNA molecule include targeting domains comprising, e.g., consisting of, SEQ ID NO: 113 and SEQ ID NO: 1580, respectively. In an aspect, the first gRNA molecule and the second gRNA molecule include targeting domains comprising, e.g., consisting of, SEQ ID NO: 113 and SEQ ID NO: 106, respectively. In an aspect, the first gRNA molecule and the second gRNA molecule include targeting domains comprising, e.g., consisting of, SEQ ID NO: 113 and SEQ ID NO: 1503, respectively. In an aspect, the first gRNA molecule and the second gRNA molecule include targeting domains comprising, e.g., consisting of, SEQ ID NO: 113 and SEQ ID NO: 1589, respectively. In an aspect, the first gRNA molecule and the second gRNA molecule include targeting domains comprising, e.g., consisting of, SEQ ID NO: 113 and SEQ ID NO: 160, respectively. In an aspect, the first gRNA molecule and the second gRNA molecule include targeting domains comprising, e.g., consisting of, SEQ ID NO: 113 and SEQ ID NO: 1537, respectively. In an aspect, the first gRNA molecule and the second gRNA molecule include targeting domains comprising, e.g., consisting of, SEQ ID NO: 113 and SEQ ID NO: 159, respectively. In an aspect, the first gRNA molecule and the second gRNA molecule include targeting domains comprising, e.g., consisting of, SEQ ID NO: 113 and SEQ ID NO: 101, respectively. In an aspect, the first gRNA molecule and the second gRNA molecule include targeting domains comprising, e.g., consisting of, SEQ ID NO: 113 and SEQ ID NO: 162, respectively. In an aspect, the first gRNA molecule and the second gRNA molecule include targeting domains comprising, e.g., consisting of, SEQ ID NO: 113 and SEQ ID NO: 104, respectively. In an aspect, the first gRNA molecule and the second gRNA molecule include targeting domains comprising, e.g., consisting of, SEQ ID NO: 113 and SEQ ID NO: 138, respectively. In an aspect, the first gRNA molecule and the second gRNA molecule include targeting domains comprising, e.g., consisting of, SEQ ID NO: 113 and SEQ ID NO: 1536, respectively. In an aspect, the first gRNA molecule and the second gRNA molecule include targeting domains comprising, e.g., consisting of, SEQ ID NO: 113 and SEQ ID NO: 1539, respectively. In an aspect, the first gRNA molecule and the second gRNA molecule include targeting domains comprising, e.g., consisting of, SEQ ID NO: 113 and SEQ ID NO: 1585, respectively. In an aspect, the first gRNA molecule and the second gRNA molecule include targeting domains comprising, e.g., consisting of, SEQ ID NO: 99 and SEQ ID NO: 165, respectively. In an aspect, the first gRNA molecule and the second gRNA molecule include targeting domains comprising, e.g., consisting of, SEQ ID NO: 99 and SEQ ID NO: 113, respectively. In an aspect, the first gRNA molecule and the second gRNA molecule include targeting domains comprising, e.g., consisting of, SEQ ID NO: 99 and SEQ ID NO: 112, respectively. In an aspect, the first gRNA molecule and the second gRNA molecule include targeting domains comprising, e.g., consisting of, SEQ ID NO: 99 and SEQ ID NO: 98, respectively. In an aspect, the first gRNA molecule and the second gRNA

molecule include targeting domains comprising, e.g., consisting of, SEQ ID NO: 99 and SEQ ID NO: 1580, respectively. In an aspect, the first gRNA molecule and the second gRNA molecule include targeting domains comprising, e.g., consisting of, SEQ ID NO: 99 and SEQ ID NO: 106, respectively. In an aspect, the first gRNA molecule and the second gRNA molecule include targeting domains comprising, e.g., consisting of, SEQ ID NO: 99 and SEQ ID NO: 1503, respectively. In an aspect, the first gRNA molecule and the second gRNA molecule include targeting domains comprising, e.g., consisting of, SEQ ID NO: 99 and SEQ ID NO: 1589, respectively. In an aspect, the first gRNA molecule and the second gRNA molecule include targeting domains comprising, e.g., consisting of, SEQ ID NO: 99 and SEQ ID NO: 160, respectively. In an aspect, the first gRNA molecule and the second gRNA molecule include targeting domains comprising, e.g., consisting of, SEQ ID NO: 99 and SEQ ID NO: 1537, respectively. In an aspect, the first gRNA molecule and the second gRNA molecule include targeting domains comprising, e.g., consisting of, SEQ ID NO: 99 and SEQ ID NO: 159, respectively. In an aspect, the first gRNA molecule and the second gRNA molecule include targeting domains comprising, e.g., consisting of, SEQ ID NO: 99 and SEQ ID NO: 101, respectively. In an aspect, the first gRNA molecule and the second gRNA molecule include targeting domains comprising, e.g., consisting of, SEQ ID NO: 99 and SEQ ID NO: 162, respectively. In an aspect, the first gRNA molecule and the second gRNA molecule include targeting domains comprising, e.g., consisting of, SEQ ID NO: 99 and SEQ ID NO: 104, respectively. In an aspect, the first gRNA molecule and the second gRNA molecule include targeting domains comprising, e.g., consisting of, SEQ ID NO: 99 and SEQ ID NO: 138, respectively. In an aspect, the first gRNA molecule and the second gRNA molecule include targeting domains comprising, e.g., consisting of, SEQ ID NO: 99 and SEQ ID NO: 1536, respectively. In an aspect, the first gRNA molecule and the second gRNA molecule include targeting domains comprising, e.g., consisting of, SEQ ID NO: 99 and SEQ ID NO: 1539, respectively. In an aspect, the first gRNA molecule and the second gRNA molecule include targeting domains comprising, e.g., consisting of, SEQ ID NO: 99 and SEQ ID NO: 1585, respectively. In an aspect, the first gRNA molecule and the second gRNA molecule include targeting domains comprising, e.g., consisting of, SEQ ID NO: 112 and SEQ ID NO: 165, respectively. In an aspect, the first gRNA molecule and the second gRNA molecule include targeting domains comprising, e.g., consisting of, SEQ ID NO: 112 and SEQ ID NO: 113, respectively. In an aspect, the first gRNA molecule and the second gRNA molecule include targeting domains comprising, e.g., consisting of, SEQ ID NO: 112 and SEQ ID NO: 99, respectively. In an aspect, the first gRNA molecule and the second gRNA molecule include targeting domains comprising, e.g., consisting of, SEQ ID NO: 112 and SEQ ID NO: 98, respectively. In an aspect, the first gRNA molecule and the second gRNA molecule include targeting domains comprising, e.g., consisting of, SEQ ID NO: 112 and SEQ ID NO: 1580, respectively. In an aspect, the first gRNA molecule and the second gRNA molecule include targeting domains comprising, e.g., consisting of, SEQ ID NO: 112 and SEQ ID NO: 106, respectively. In an aspect, the first gRNA molecule and the second gRNA

molecule include targeting domains comprising, e.g., consisting of, SEQ ID NO: 112 and SEQ ID NO: 1503, respectively. In an aspect, the first gRNA molecule and the second gRNA molecule include targeting domains comprising, e.g., consisting of, SEQ ID NO: 112 and SEQ ID NO: 1589, respectively. In an aspect, the first gRNA molecule and the second gRNA molecule include targeting domains comprising, e.g., consisting of, SEQ ID NO: 112 and SEQ ID NO: 160, respectively. In an aspect, the first gRNA molecule and the second gRNA molecule include targeting domains comprising, e.g., consisting of, SEQ ID NO: 112 and SEQ ID NO: 1537, respectively. In an aspect, the first gRNA molecule and the second gRNA molecule include targeting domains comprising, e.g., consisting of, SEQ ID NO: 112 and SEQ ID NO: 159, respectively. In an aspect, the first gRNA molecule and the second gRNA molecule include targeting domains comprising, e.g., consisting of, SEQ ID NO: 112 and SEQ ID NO: 101, respectively. In an aspect, the first gRNA molecule and the second gRNA molecule include targeting domains comprising, e.g., consisting of, SEQ ID NO: 112 and SEQ ID NO: 162, respectively. In an aspect, the first gRNA molecule and the second gRNA molecule include targeting domains comprising, e.g., consisting of, SEQ ID NO: 112 and SEQ ID NO: 104, respectively. In an aspect, the first gRNA molecule and the second gRNA molecule include targeting domains comprising, e.g., consisting of, SEQ ID NO: 112 and SEQ ID NO: 138, respectively. In an aspect, the first gRNA molecule and the second gRNA molecule include targeting domains comprising, e.g., consisting of, SEQ ID NO: 112 and SEQ ID NO: 1536, respectively. In an aspect, the first gRNA molecule and the second gRNA molecule include targeting domains comprising, e.g., consisting of, SEQ ID NO: 112 and SEQ ID NO: 1539, respectively. In an aspect, the first gRNA molecule and the second gRNA molecule include targeting domains comprising, e.g., consisting of, SEQ ID NO: 112 and SEQ ID NO: 1585, respectively. In an aspect, the first gRNA molecule and the second gRNA molecule include targeting domains comprising, e.g., consisting of, SEQ ID NO: 98 and SEQ ID NO: 165, respectively. In an aspect, the first gRNA molecule and the second gRNA molecule include targeting domains comprising, e.g., consisting of, SEQ ID NO: 98 and SEQ ID NO: 113, respectively. In an aspect, the first gRNA molecule and the second gRNA molecule include targeting domains comprising, e.g., consisting of, SEQ ID NO: 98 and SEQ ID NO: 99, respectively. In an aspect, the first gRNA molecule and the second gRNA molecule include targeting domains comprising, e.g., consisting of, SEQ ID NO: 98 and SEQ ID NO: 112, respectively. In an aspect, the first gRNA molecule and the second gRNA molecule include targeting domains comprising, e.g., consisting of, SEQ ID NO: 98 and SEQ ID NO: 1580, respectively. In an aspect, the first gRNA molecule and the second gRNA molecule include targeting domains comprising, e.g., consisting of, SEQ ID NO: 98 and SEQ ID NO: 106, respectively. In an aspect, the first gRNA molecule and the second gRNA molecule include targeting domains comprising, e.g., consisting of, SEQ ID NO: 98 and SEQ ID NO: 1503, respectively. In an aspect, the first gRNA molecule and the second gRNA molecule include targeting domains comprising, e.g., consisting of, SEQ ID NO: 98 and SEQ ID NO: 1589, respectively. In an aspect, the first gRNA molecule and the second gRNA

molecule include targeting domains comprising, e.g., consisting of, SEQ ID NO: 98 and SEQ ID NO: 160, respectively. In an aspect, the first gRNA molecule and the second gRNA molecule include targeting domains comprising, e.g., consisting of, SEQ ID NO: 98 and SEQ ID NO: 1537, respectively. In an aspect, the first gRNA molecule and the second gRNA molecule include targeting domains comprising, e.g., consisting of, SEQ ID NO: 98 and SEQ ID NO: 159, respectively. In an aspect, the first gRNA molecule and the second gRNA molecule include targeting domains comprising, e.g., consisting of, SEQ ID NO: 98 and SEQ ID NO: 101, respectively. In an aspect, the first gRNA molecule and the second gRNA molecule include targeting domains comprising, e.g., consisting of, SEQ ID NO: 98 and SEQ ID NO: 162, respectively. In an aspect, the first gRNA molecule and the second gRNA molecule include targeting domains comprising, e.g., consisting of, SEQ ID NO: 98 and SEQ ID NO: 104, respectively. In an aspect, the first gRNA molecule and the second gRNA molecule include targeting domains comprising, e.g., consisting of, SEQ ID NO: 98 and SEQ ID NO: 138, respectively. In an aspect, the first gRNA molecule and the second gRNA molecule include targeting domains comprising, e.g., consisting of, SEQ ID NO: 98 and SEQ ID NO: 1536, respectively. In an aspect, the first gRNA molecule and the second gRNA molecule include targeting domains comprising, e.g., consisting of, SEQ ID NO: 98 and SEQ ID NO: 1539, respectively. In an aspect, the first gRNA molecule and the second gRNA molecule include targeting domains comprising, e.g., consisting of, SEQ ID NO: 98 and SEQ ID NO: 1585, respectively. In an aspect, the first gRNA molecule and the second gRNA molecule include targeting domains comprising, e.g., consisting of, SEQ ID NO: 1580 and SEQ ID NO: 165, respectively. In an aspect, the first gRNA molecule and the second gRNA molecule include targeting domains comprising, e.g., consisting of, SEQ ID NO: 1580 and SEQ ID NO: 113, respectively. In an aspect, the first gRNA molecule and the second gRNA molecule include targeting domains comprising, e.g., consisting of, SEQ ID NO: 1580 and SEQ ID NO: 99, respectively. In an aspect, the first gRNA molecule and the second gRNA molecule include targeting domains comprising, e.g., consisting of, SEQ ID NO: 1580 and SEQ ID NO: 112, respectively. In an aspect, the first gRNA molecule and the second gRNA molecule include targeting domains comprising, e.g., consisting of, SEQ ID NO: 1580 and SEQ ID NO: 98, respectively. In an aspect, the first gRNA molecule and the second gRNA molecule include targeting domains comprising, e.g., consisting of, SEQ ID NO: 1580 and SEQ ID NO: 106, respectively. In an aspect, the first gRNA molecule and the second gRNA molecule include targeting domains comprising, e.g., consisting of, SEQ ID NO: 1580 and SEQ ID NO: 1503, respectively. In an aspect, the first gRNA molecule and the second gRNA molecule include targeting domains comprising, e.g., consisting of, SEQ ID NO: 1580 and SEQ ID NO: 1589, respectively. In an aspect, the first gRNA molecule and the second gRNA molecule include targeting domains comprising, e.g., consisting of, SEQ ID NO: 1580 and SEQ ID NO: 160, respectively. In an aspect, the first gRNA molecule and the second gRNA molecule include targeting domains comprising, e.g., consisting of, SEQ ID NO: 1580 and SEQ ID NO: 1537, respectively. In an aspect, the first gRNA molecule and

the second gRNA molecule include targeting domains comprising, e.g., consisting of, SEQ ID NO: 1580 and SEQ ID NO: 159, respectively. In an aspect, the first gRNA molecule and the second gRNA molecule include targeting domains comprising, e.g., consisting of, SEQ ID NO: 1580 and SEQ ID NO: 101, respectively. In an aspect, the first gRNA molecule and the second gRNA molecule include targeting domains comprising, e.g., consisting of, SEQ ID NO: 1580 and SEQ ID NO: 162, respectively. In an aspect, the first gRNA molecule and the second gRNA molecule include targeting domains comprising, e.g., consisting of, SEQ ID NO: 1580 and SEQ ID NO: 104, respectively. In an aspect, the first gRNA molecule and the second gRNA molecule include targeting domains comprising, e.g., consisting of, SEQ ID NO: 1580 and SEQ ID NO: 138, respectively. In an aspect, the first gRNA molecule and the second gRNA molecule include targeting domains comprising, e.g., consisting of, SEQ ID NO: 1580 and SEQ ID NO: 1536, respectively. In an aspect, the first gRNA molecule and the second gRNA molecule include targeting domains comprising, e.g., consisting of, SEQ ID NO: 1580 and SEQ ID NO: 1539, respectively. In an aspect, the first gRNA molecule and the second gRNA molecule include targeting domains comprising, e.g., consisting of, SEQ ID NO: 1580 and SEQ ID NO: 1585, respectively. In an aspect, the first gRNA molecule and the second gRNA molecule include targeting domains comprising, e.g., consisting of, SEQ ID NO: 106 and SEQ ID NO: 165, respectively. In an aspect, the first gRNA molecule and the second gRNA molecule include targeting domains comprising, e.g., consisting of, SEQ ID NO: 106 and SEQ ID NO: 113, respectively. In an aspect, the first gRNA molecule and the second gRNA molecule include targeting domains comprising, e.g., consisting of, SEQ ID NO: 106 and SEQ ID NO: 99, respectively. In an aspect, the first gRNA molecule and the second gRNA molecule include targeting domains comprising, e.g., consisting of, SEQ ID NO: 106 and SEQ ID NO: 112, respectively. In an aspect, the first gRNA molecule and the second gRNA molecule include targeting domains comprising, e.g., consisting of, SEQ ID NO: 106 and SEQ ID NO: 98, respectively. In an aspect, the first gRNA molecule and the second gRNA molecule include targeting domains comprising, e.g., consisting of, SEQ ID NO: 106 and SEQ ID NO: 1580, respectively. In an aspect, the first gRNA molecule and the second gRNA molecule include targeting domains comprising, e.g., consisting of, SEQ ID NO: 106 and SEQ ID NO: 1503, respectively. In an aspect, the first gRNA molecule and the second gRNA molecule include targeting domains comprising, e.g., consisting of, SEQ ID NO: 106 and SEQ ID NO: 1589, respectively. In an aspect, the first gRNA molecule and the second gRNA molecule include targeting domains comprising, e.g., consisting of, SEQ ID NO: 106 and SEQ ID NO: 160, respectively. In an aspect, the first gRNA molecule and the second gRNA molecule include targeting domains comprising, e.g., consisting of, SEQ ID NO: 106 and SEQ ID NO: 1537, respectively. In an aspect, the first gRNA molecule and the second gRNA molecule include targeting domains comprising, e.g., consisting of, SEQ ID NO: 106 and SEQ ID NO: 159, respectively. In an aspect, the first gRNA molecule and the second gRNA molecule include targeting domains comprising, e.g., consisting of, SEQ ID NO: 106 and SEQ ID NO: 101, respectively. In an aspect, the first gRNA

molecule and the second gRNA molecule include targeting domains comprising, e.g., consisting of, SEQ ID NO: 106 and SEQ ID NO: 162, respectively. In an aspect, the first gRNA molecule and the second gRNA molecule include targeting domains comprising, e.g., consisting of, SEQ ID NO: 106 and SEQ ID NO: 104, respectively. In an aspect, the first gRNA molecule and the second gRNA molecule include targeting domains comprising, e.g., consisting of, SEQ ID NO: 106 and SEQ ID NO: 138, respectively. In an aspect, the first gRNA molecule and the second gRNA molecule include targeting domains comprising, e.g., consisting of, SEQ ID NO: 106 and SEQ ID NO: 1536, respectively. In an aspect, the first gRNA molecule and the second gRNA molecule include targeting domains comprising, e.g., consisting of, SEQ ID NO: 106 and SEQ ID NO: 1539, respectively. In an aspect, the first gRNA molecule and the second gRNA molecule include targeting domains comprising, e.g., consisting of, SEQ ID NO: 106 and SEQ ID NO: 1585, respectively. In an aspect, the first gRNA molecule and the second gRNA molecule include targeting domains comprising, e.g., consisting of, SEQ ID NO: 1503 and SEQ ID NO: 165, respectively. In an aspect, the first gRNA molecule and the second gRNA molecule include targeting domains comprising, e.g., consisting of, SEQ ID NO: 1503 and SEQ ID NO: 113, respectively. In an aspect, the first gRNA molecule and the second gRNA molecule include targeting domains comprising, e.g., consisting of, SEQ ID NO: 1503 and SEQ ID NO: 99, respectively. In an aspect, the first gRNA molecule and the second gRNA molecule include targeting domains comprising, e.g., consisting of, SEQ ID NO: 1503 and SEQ ID NO: 112, respectively. In an aspect, the first gRNA molecule and the second gRNA molecule include targeting domains comprising, e.g., consisting of, SEQ ID NO: 1503 and SEQ ID NO: 98, respectively. In an aspect, the first gRNA molecule and the second gRNA molecule include targeting domains comprising, e.g., consisting of, SEQ ID NO: 1503 and SEQ ID NO: 1580, respectively. In an aspect, the first gRNA molecule and the second gRNA molecule include targeting domains comprising, e.g., consisting of, SEQ ID NO: 1503 and SEQ ID NO: 106, respectively. In an aspect, the first gRNA molecule and the second gRNA molecule include targeting domains comprising, e.g., consisting of, SEQ ID NO: 1503 and SEQ ID NO: 1589, respectively. In an aspect, the first gRNA molecule and the second gRNA molecule include targeting domains comprising, e.g., consisting of, SEQ ID NO: 1503 and SEQ ID NO: 160, respectively. In an aspect, the first gRNA molecule and the second gRNA molecule include targeting domains comprising, e.g., consisting of, SEQ ID NO: 1503 and SEQ ID NO: 1537, respectively. In an aspect, the first gRNA molecule and the second gRNA molecule include targeting domains comprising, e.g., consisting of, SEQ ID NO: 1503 and SEQ ID NO: 159, respectively. In an aspect, the first gRNA molecule and the second gRNA molecule include targeting domains comprising, e.g., consisting of, SEQ ID NO: 1503 and SEQ ID NO: 101, respectively. In an aspect, the first gRNA molecule and the second gRNA molecule include targeting domains comprising, e.g., consisting of, SEQ ID NO: 1503 and SEQ ID NO: 162, respectively. In an aspect, the first gRNA molecule and the second gRNA molecule include targeting domains comprising, e.g., consisting of, SEQ ID NO: 1503 and SEQ ID NO: 104, respectively. In an aspect,

the first gRNA molecule and the second gRNA molecule include targeting domains comprising, e.g., consisting of, SEQ ID NO: 1503 and SEQ ID NO: 138, respectively. In an aspect, the first gRNA molecule and the second gRNA molecule include targeting domains comprising, e.g., consisting of, SEQ ID NO: 1503 and SEQ ID NO: 1536, respectively. In an aspect, the first gRNA molecule and the second gRNA molecule include targeting domains comprising, e.g., consisting of, SEQ ID NO: 1503 and SEQ ID NO: 1539, respectively. In an aspect, the first gRNA molecule and the second gRNA molecule include targeting domains comprising, e.g., consisting of, SEQ ID NO: 1503 and SEQ ID NO: 1585, respectively. In an aspect, the first gRNA molecule and the second gRNA molecule include targeting domains comprising, e.g., consisting of, SEQ ID NO: 1589 and SEQ ID NO: 165, respectively. In an aspect, the first gRNA molecule and the second gRNA molecule include targeting domains comprising, e.g., consisting of, SEQ ID NO: 1589 and SEQ ID NO: 113, respectively. In an aspect, the first gRNA molecule and the second gRNA molecule include targeting domains comprising, e.g., consisting of, SEQ ID NO: 1589 and SEQ ID NO: 99, respectively. In an aspect, the first gRNA molecule and the second gRNA molecule include targeting domains comprising, e.g., consisting of, SEQ ID NO: 1589 and SEQ ID NO: 112, respectively. In an aspect, the first gRNA molecule and the second gRNA molecule include targeting domains comprising, e.g., consisting of, SEQ ID NO: 1589 and SEQ ID NO: 98, respectively. In an aspect, the first gRNA molecule and the second gRNA molecule include targeting domains comprising, e.g., consisting of, SEQ ID NO: 1589 and SEQ ID NO: 1580, respectively. In an aspect, the first gRNA molecule and the second gRNA molecule include targeting domains comprising, e.g., consisting of, SEQ ID NO: 1589 and SEQ ID NO: 106, respectively. In an aspect, the first gRNA molecule and the second gRNA molecule include targeting domains comprising, e.g., consisting of, SEQ ID NO: 1589 and SEQ ID NO: 1503, respectively. In an aspect, the first gRNA molecule and the second gRNA molecule include targeting domains comprising, e.g., consisting of, SEQ ID NO: 1589 and SEQ ID NO: 160, respectively. In an aspect, the first gRNA molecule and the second gRNA molecule include targeting domains comprising, e.g., consisting of, SEQ ID NO: 1589 and SEQ ID NO: 1537, respectively. In an aspect, the first gRNA molecule and the second gRNA molecule include targeting domains comprising, e.g., consisting of, SEQ ID NO: 1589 and SEQ ID NO: 159, respectively. In an aspect, the first gRNA molecule and the second gRNA molecule include targeting domains comprising, e.g., consisting of, SEQ ID NO: 1589 and SEQ ID NO: 101, respectively. In an aspect, the first gRNA molecule and the second gRNA molecule include targeting domains comprising, e.g., consisting of, SEQ ID NO: 1589 and SEQ ID NO: 162, respectively. In an aspect, the first gRNA molecule and the second gRNA molecule include targeting domains comprising, e.g., consisting of, SEQ ID NO: 1589 and SEQ ID NO: 104, respectively. In an aspect, the first gRNA molecule and the second gRNA molecule include targeting domains comprising, e.g., consisting of, SEQ ID NO: 1589 and SEQ ID NO: 138, respectively. In an aspect, the first gRNA molecule and the second gRNA molecule include targeting domains comprising, e.g., consisting of, SEQ ID NO: 1589 and SEQ ID

NO: 1536, respectively. In an aspect, the first gRNA molecule and the second gRNA molecule include targeting domains comprising, e.g., consisting of, SEQ ID NO: 1589 and SEQ ID NO: 1539, respectively. In an aspect, the first gRNA molecule and the second gRNA molecule include targeting domains comprising, e.g., consisting of, SEQ ID NO: 1589 and SEQ ID NO: 1585, respectively. In an aspect, the first gRNA molecule and the second gRNA molecule include targeting domains comprising, e.g., consisting of, SEQ ID NO: 160 and SEQ ID NO: 165, respectively. In an aspect, the first gRNA molecule and the second gRNA molecule include targeting domains comprising, e.g., consisting of, SEQ ID NO: 160 and SEQ ID NO: 113, respectively. In an aspect, the first gRNA molecule and the second gRNA molecule include targeting domains comprising, e.g., consisting of, SEQ ID NO: 160 and SEQ ID NO: 99, respectively. In an aspect, the first gRNA molecule and the second gRNA molecule include targeting domains comprising, e.g., consisting of, SEQ ID NO: 160 and SEQ ID NO: 112, respectively. In an aspect, the first gRNA molecule and the second gRNA molecule include targeting domains comprising, e.g., consisting of, SEQ ID NO: 160 and SEQ ID NO: 98, respectively. In an aspect, the first gRNA molecule and the second gRNA molecule include targeting domains comprising, e.g., consisting of, SEQ ID NO: 160 and SEQ ID NO: 1580, respectively. In an aspect, the first gRNA molecule and the second gRNA molecule include targeting domains comprising, e.g., consisting of, SEQ ID NO: 160 and SEQ ID NO: 106, respectively. In an aspect, the first gRNA molecule and the second gRNA molecule include targeting domains comprising, e.g., consisting of, SEQ ID NO: 160 and SEQ ID NO: 1503, respectively. In an aspect, the first gRNA molecule and the second gRNA molecule include targeting domains comprising, e.g., consisting of, SEQ ID NO: 160 and SEQ ID NO: 1589, respectively. In an aspect, the first gRNA molecule and the second gRNA molecule include targeting domains comprising, e.g., consisting of, SEQ ID NO: 160 and SEQ ID NO: 1537, respectively. In an aspect, the first gRNA molecule and the second gRNA molecule include targeting domains comprising, e.g., consisting of, SEQ ID NO: 160 and SEQ ID NO: 159, respectively. In an aspect, the first gRNA molecule and the second gRNA molecule include targeting domains comprising, e.g., consisting of, SEQ ID NO: 160 and SEQ ID NO: 101, respectively. In an aspect, the first gRNA molecule and the second gRNA molecule include targeting domains comprising, e.g., consisting of, SEQ ID NO: 160 and SEQ ID NO: 162, respectively. In an aspect, the first gRNA molecule and the second gRNA molecule include targeting domains comprising, e.g., consisting of, SEQ ID NO: 160 and SEQ ID NO: 104, respectively. In an aspect, the first gRNA molecule and the second gRNA molecule include targeting domains comprising, e.g., consisting of, SEQ ID NO: 160 and SEQ ID NO: 138, respectively. In an aspect, the first gRNA molecule and the second gRNA molecule include targeting domains comprising, e.g., consisting of, SEQ ID NO: 160 and SEQ ID NO: 1536, respectively. In an aspect, the first gRNA molecule and the second gRNA molecule include targeting domains comprising, e.g., consisting of, SEQ ID NO: 160 and SEQ ID NO: 1539, respectively. In an aspect, the first gRNA molecule and the second gRNA molecule include targeting domains comprising, e.g., consisting of, SEQ ID NO: 160

and SEQ ID NO: 1585, respectively. In an aspect, the first gRNA molecule and the second gRNA molecule include targeting domains comprising, e.g., consisting of, SEQ ID NO: 1537 and SEQ ID NO: 165, respectively. In an aspect, the first gRNA molecule and the second gRNA molecule include targeting domains comprising, e.g., consisting of, SEQ ID NO: 1537 and SEQ ID NO: 113, respectively. In an aspect, the first gRNA molecule and the second gRNA molecule include targeting domains comprising, e.g., consisting of, SEQ ID NO: 1537 and SEQ ID NO: 99, respectively. In an aspect, the first gRNA molecule and the second gRNA molecule include targeting domains comprising, e.g., consisting of, SEQ ID NO: 1537 and SEQ ID NO: 112, respectively. In an aspect, the first gRNA molecule and the second gRNA molecule include targeting domains comprising, e.g., consisting of, SEQ ID NO: 1537 and SEQ ID NO: 98, respectively. In an aspect, the first gRNA molecule and the second gRNA molecule include targeting domains comprising, e.g., consisting of, SEQ ID NO: 1537 and SEQ ID NO: 1580, respectively. In an aspect, the first gRNA molecule and the second gRNA molecule include targeting domains comprising, e.g., consisting of, SEQ ID NO: 1537 and SEQ ID NO: 106, respectively. In an aspect, the first gRNA molecule and the second gRNA molecule include targeting domains comprising, e.g., consisting of, SEQ ID NO: 1537 and SEQ ID NO: 1503, respectively. In an aspect, the first gRNA molecule and the second gRNA molecule include targeting domains comprising, e.g., consisting of, SEQ ID NO: 1537 and SEQ ID NO: 1589, respectively. In an aspect, the first gRNA molecule and the second gRNA molecule include targeting domains comprising, e.g., consisting of, SEQ ID NO: 1537 and SEQ ID NO: 160, respectively. In an aspect, the first gRNA molecule and the second gRNA molecule include targeting domains comprising, e.g., consisting of, SEQ ID NO: 1537 and SEQ ID NO: 159, respectively. In an aspect, the first gRNA molecule and the second gRNA molecule include targeting domains comprising, e.g., consisting of, SEQ ID NO: 1537 and SEQ ID NO: 101, respectively. In an aspect, the first gRNA molecule and the second gRNA molecule include targeting domains comprising, e.g., consisting of, SEQ ID NO: 1537 and SEQ ID NO: 162, respectively. In an aspect, the first gRNA molecule and the second gRNA molecule include targeting domains comprising, e.g., consisting of, SEQ ID NO: 1537 and SEQ ID NO: 104, respectively. In an aspect, the first gRNA molecule and the second gRNA molecule include targeting domains comprising, e.g., consisting of, SEQ ID NO: 1537 and SEQ ID NO: 138, respectively. In an aspect, the first gRNA molecule and the second gRNA molecule include targeting domains comprising, e.g., consisting of, SEQ ID NO: 1537 and SEQ ID NO: 1536, respectively. In an aspect, the first gRNA molecule and the second gRNA molecule include targeting domains comprising, e.g., consisting of, SEQ ID NO: 1537 and SEQ ID NO: 1539, respectively. In an aspect, the first gRNA molecule and the second gRNA molecule include targeting domains comprising, e.g., consisting of, SEQ ID NO: 1537 and SEQ ID NO: 1585, respectively. In an aspect, the first gRNA molecule and the second gRNA molecule include targeting domains comprising, e.g., consisting of, SEQ ID NO: 159 and SEQ ID NO: 165, respectively. In an aspect, the first gRNA molecule and the second gRNA molecule include targeting domains comprising, e.g.,

consisting of, SEQ ID NO: 159 and SEQ ID NO: 113, respectively. In an aspect, the first gRNA molecule and the second gRNA molecule include targeting domains comprising, e.g., consisting of, SEQ ID NO: 159 and SEQ ID NO: 99, respectively. In an aspect, the first gRNA molecule and the second gRNA molecule include targeting domains comprising, e.g., consisting of, SEQ ID NO: 159 and SEQ ID NO: 112, respectively. In an aspect, the first gRNA molecule and the second gRNA molecule include targeting domains comprising, e.g., consisting of, SEQ ID NO: 159 and SEQ ID NO: 98, respectively. In an aspect, the first gRNA molecule and the second gRNA molecule include targeting domains comprising, e.g., consisting of, SEQ ID NO: 159 and SEQ ID NO: 1580, respectively. In an aspect, the first gRNA molecule and the second gRNA molecule include targeting domains comprising, e.g., consisting of, SEQ ID NO: 159 and SEQ ID NO: 106, respectively. In an aspect, the first gRNA molecule and the second gRNA molecule include targeting domains comprising, e.g., consisting of, SEQ ID NO: 159 and SEQ ID NO: 1503, respectively. In an aspect, the first gRNA molecule and the second gRNA molecule include targeting domains comprising, e.g., consisting of, SEQ ID NO: 159 and SEQ ID NO: 1589, respectively. In an aspect, the first gRNA molecule and the second gRNA molecule include targeting domains comprising, e.g., consisting of, SEQ ID NO: 159 and SEQ ID NO: 160, respectively. In an aspect, the first gRNA molecule and the second gRNA molecule include targeting domains comprising, e.g., consisting of, SEQ ID NO: 159 and SEQ ID NO: 1537, respectively. In an aspect, the first gRNA molecule and the second gRNA molecule include targeting domains comprising, e.g., consisting of, SEQ ID NO: 159 and SEQ ID NO: 101, respectively. In an aspect, the first gRNA molecule and the second gRNA molecule include targeting domains comprising, e.g., consisting of, SEQ ID NO: 159 and SEQ ID NO: 162, respectively. In an aspect, the first gRNA molecule and the second gRNA molecule include targeting domains comprising, e.g., consisting of, SEQ ID NO: 159 and SEQ ID NO: 104, respectively. In an aspect, the first gRNA molecule and the second gRNA molecule include targeting domains comprising, e.g., consisting of, SEQ ID NO: 159 and SEQ ID NO: 138, respectively. In an aspect, the first gRNA molecule and the second gRNA molecule include targeting domains comprising, e.g., consisting of, SEQ ID NO: 159 and SEQ ID NO: 1536, respectively. In an aspect, the first gRNA molecule and the second gRNA molecule include targeting domains comprising, e.g., consisting of, SEQ ID NO: 159 and SEQ ID NO: 1539, respectively. In an aspect, the first gRNA molecule and the second gRNA molecule include targeting domains comprising, e.g., consisting of, SEQ ID NO: 159 and SEQ ID NO: 1585, respectively. In an aspect, the first gRNA molecule and the second gRNA molecule include targeting domains comprising, e.g., consisting of, SEQ ID NO: 101 and SEQ ID NO: 165, respectively. In an aspect, the first gRNA molecule and the second gRNA molecule include targeting domains comprising, e.g., consisting of, SEQ ID NO: 101 and SEQ ID NO: 113, respectively. In an aspect, the first gRNA molecule and the second gRNA molecule include targeting domains comprising, e.g., consisting of, SEQ ID NO: 101 and SEQ ID NO: 99, respectively. In an aspect, the first gRNA molecule and the second gRNA molecule include targeting domains

comprising, e.g., consisting of, SEQ ID NO: 101 and SEQ ID NO: 112, respectively. In an aspect, the first gRNA molecule and the second gRNA molecule include targeting domains comprising, e.g., consisting of, SEQ ID NO: 101 and SEQ ID NO: 98, respectively. In an aspect, the first gRNA molecule and the second gRNA molecule include targeting domains comprising, e.g., consisting of, SEQ ID NO: 101 and SEQ ID NO: 1580, respectively. In an aspect, the first gRNA molecule and the second gRNA molecule include targeting domains comprising, e.g., consisting of, SEQ ID NO: 101 and SEQ ID NO: 106, respectively. In an aspect, the first gRNA molecule and the second gRNA molecule include targeting domains comprising, e.g., consisting of, SEQ ID NO: 101 and SEQ ID NO: 1503, respectively. In an aspect, the first gRNA molecule and the second gRNA molecule include targeting domains comprising, e.g., consisting of, SEQ ID NO: 101 and SEQ ID NO: 1589, respectively. In an aspect, the first gRNA molecule and the second gRNA molecule include targeting domains comprising, e.g., consisting of, SEQ ID NO: 101 and SEQ ID NO: 160, respectively. In an aspect, the first gRNA molecule and the second gRNA molecule include targeting domains comprising, e.g., consisting of, SEQ ID NO: 101 and SEQ ID NO: 1537, respectively. In an aspect, the first gRNA molecule and the second gRNA molecule include targeting domains comprising, e.g., consisting of, SEQ ID NO: 101 and SEQ ID NO: 159, respectively. In an aspect, the first gRNA molecule and the second gRNA molecule include targeting domains comprising, e.g., consisting of, SEQ ID NO: 101 and SEQ ID NO: 162, respectively. In an aspect, the first gRNA molecule and the second gRNA molecule include targeting domains comprising, e.g., consisting of, SEQ ID NO: 101 and SEQ ID NO: 104, respectively. In an aspect, the first gRNA molecule and the second gRNA molecule include targeting domains comprising, e.g., consisting of, SEQ ID NO: 101 and SEQ ID NO: 138, respectively. In an aspect, the first gRNA molecule and the second gRNA molecule include targeting domains comprising, e.g., consisting of, SEQ ID NO: 101 and SEQ ID NO: 1536, respectively. In an aspect, the first gRNA molecule and the second gRNA molecule include targeting domains comprising, e.g., consisting of, SEQ ID NO: 101 and SEQ ID NO: 1539, respectively. In an aspect, the first gRNA molecule and the second gRNA molecule include targeting domains comprising, e.g., consisting of, SEQ ID NO: 101 and SEQ ID NO: 1585, respectively. In an aspect, the first gRNA molecule and the second gRNA molecule include targeting domains comprising, e.g., consisting of, SEQ ID NO: 162 and SEQ ID NO: 165, respectively. In an aspect, the first gRNA molecule and the second gRNA molecule include targeting domains comprising, e.g., consisting of, SEQ ID NO: 162 and SEQ ID NO: 113, respectively. In an aspect, the first gRNA molecule and the second gRNA molecule include targeting domains comprising, e.g., consisting of, SEQ ID NO: 162 and SEQ ID NO: 99, respectively. In an aspect, the first gRNA molecule and the second gRNA molecule include targeting domains comprising, e.g., consisting of, SEQ ID NO: 162 and SEQ ID NO: 112, respectively. In an aspect, the first gRNA molecule and the second gRNA molecule include targeting domains comprising, e.g., consisting of, SEQ ID NO: 162 and SEQ ID NO: 98, respectively. In an aspect, the first gRNA molecule and the second gRNA molecule include targeting domains

comprising, e.g., consisting of, SEQ ID NO: 162 and SEQ ID NO: 1580, respectively. In an aspect, the first gRNA molecule and the second gRNA molecule include targeting domains comprising, e.g., consisting of, SEQ ID NO: 162 and SEQ ID NO: 106, respectively. In an aspect, the first gRNA molecule and the second gRNA molecule include targeting domains comprising, e.g., consisting of, SEQ ID NO: 162 and SEQ ID NO: 1503, respectively. In an aspect, the first gRNA molecule and the second gRNA molecule include targeting domains comprising, e.g., consisting of, SEQ ID NO: 162 and SEQ ID NO: 1589, respectively. In an aspect, the first gRNA molecule and the second gRNA molecule include targeting domains comprising, e.g., consisting of, SEQ ID NO: 162 and SEQ ID NO: 160, respectively. In an aspect, the first gRNA molecule and the second gRNA molecule include targeting domains comprising, e.g., consisting of, SEQ ID NO: 162 and SEQ ID NO: 1537, respectively. In an aspect, the first gRNA molecule and the second gRNA molecule include targeting domains comprising, e.g., consisting of, SEQ ID NO: 162 and SEQ ID NO: 159, respectively. In an aspect, the first gRNA molecule and the second gRNA molecule include targeting domains comprising, e.g., consisting of, SEQ ID NO: 162 and SEQ ID NO: 101, respectively. In an aspect, the first gRNA molecule and the second gRNA molecule include targeting domains comprising, e.g., consisting of, SEQ ID NO: 104 and SEQ ID NO: 165, respectively. In an aspect, the first gRNA molecule and the second gRNA molecule include targeting domains comprising, e.g., consisting of, SEQ ID NO: 104 and SEQ ID NO: 113, respectively. In an aspect, the first gRNA molecule and the second gRNA molecule include targeting domains comprising, e.g., consisting of, SEQ ID NO: 104 and SEQ ID NO: 99, respectively. In an aspect, the first gRNA molecule and the second gRNA molecule include targeting domains comprising, e.g., consisting of, SEQ ID NO: 104 and SEQ ID NO: 112, respectively. In an aspect, the first gRNA molecule and the second gRNA molecule include targeting domains comprising, e.g., consisting of, SEQ ID NO: 104 and SEQ ID NO: 98, respectively. In an aspect, the first gRNA molecule and the second gRNA molecule include targeting domains comprising, e.g., consisting of, SEQ ID NO: 104 and SEQ ID NO: 1580, respectively. In an aspect, the first gRNA molecule and the second gRNA molecule include targeting domains comprising, e.g., consisting of, SEQ ID NO: 104 and SEQ ID NO: 106, respectively. In an aspect, the first gRNA molecule and the second gRNA molecule include targeting domains comprising, e.g., consisting of, SEQ ID NO: 104 and SEQ ID NO: 1503, respectively. In an aspect, the first gRNA molecule and the second gRNA molecule include targeting domains comprising, e.g., consisting of, SEQ ID NO: 104 and SEQ ID NO: 1589, respectively. In an aspect, the first gRNA molecule and the second gRNA molecule include targeting domains comprising, e.g., consisting of, SEQ ID NO: 104 and SEQ ID NO: 160, respectively. In an aspect, the first gRNA molecule and the second gRNA molecule include targeting domains comprising, e.g., consisting of, SEQ ID NO: 104 and SEQ ID NO: 1537, respectively. In an aspect, the first gRNA molecule and the second gRNA molecule include targeting domains comprising, e.g., consisting of, SEQ ID NO: 104 and SEQ ID NO: 159, respectively. In an aspect, the first gRNA molecule and the second gRNA molecule include targeting domains

comprising, e.g., consisting of, SEQ ID NO: 104 and SEQ ID NO: 101, respectively. In an aspect, the first gRNA molecule and the second gRNA molecule include targeting domains comprising, e.g., consisting of, SEQ ID NO: 104 and SEQ ID NO: 162, respectively. In an aspect, the first gRNA molecule and the second gRNA molecule include targeting domains comprising, e.g., consisting of, SEQ ID NO: 104 and SEQ ID NO: 138, respectively. In an aspect, the first gRNA molecule and the second gRNA molecule include targeting domains comprising, e.g., consisting of, SEQ ID NO: 104 and SEQ ID NO: 1536, respectively. In an aspect, the first gRNA molecule and the second gRNA molecule include targeting domains comprising, e.g., consisting of, SEQ ID NO: 104 and SEQ ID NO: 1539, respectively. In an aspect, the first gRNA molecule and the second gRNA molecule include targeting domains comprising, e.g., consisting of, SEQ ID NO: 104 and SEQ ID NO: 1585, respectively. In an aspect, the first gRNA molecule and the second gRNA molecule include targeting domains comprising, e.g., consisting of, SEQ ID NO: 138 and SEQ ID NO: 165, respectively. In an aspect, the first gRNA molecule and the second gRNA molecule include targeting domains comprising, e.g., consisting of, SEQ ID NO: 138 and SEQ ID NO: 113, respectively. In an aspect, the first gRNA molecule and the second gRNA molecule include targeting domains comprising, e.g., consisting of, SEQ ID NO: 138 and SEQ ID NO: 99, respectively. In an aspect, the first gRNA molecule and the second gRNA molecule include targeting domains comprising, e.g., consisting of, SEQ ID NO: 138 and SEQ ID NO: 112, respectively. In an aspect, the first gRNA molecule and the second gRNA molecule include targeting domains comprising, e.g., consisting of, SEQ ID NO: 138 and SEQ ID NO: 98, respectively. In an aspect, the first gRNA molecule and the second gRNA molecule include targeting domains comprising, e.g., consisting of, SEQ ID NO: 138 and SEQ ID NO: 1580, respectively. In an aspect, the first gRNA molecule and the second gRNA molecule include targeting domains comprising, e.g., consisting of, SEQ ID NO: 138 and SEQ ID NO: 106, respectively. In an aspect, the first gRNA molecule and the second gRNA molecule include targeting domains comprising, e.g., consisting of, SEQ ID NO: 138 and SEQ ID NO: 1503, respectively. In an aspect, the first gRNA molecule and the second gRNA molecule include targeting domains comprising, e.g., consisting of, SEQ ID NO: 138 and SEQ ID NO: 1589, respectively. In an aspect, the first gRNA molecule and the second gRNA molecule include targeting domains comprising, e.g., consisting of, SEQ ID NO: 138 and SEQ ID NO: 160, respectively. In an aspect, the first gRNA molecule and the second gRNA molecule include targeting domains comprising, e.g., consisting of, SEQ ID NO: 138 and SEQ ID NO: 1537, respectively. In an aspect, the first gRNA molecule and the second gRNA molecule include targeting domains comprising, e.g., consisting of, SEQ ID NO: 138 and SEQ ID NO: 159, respectively. In an aspect, the first gRNA molecule and the second gRNA molecule include targeting domains comprising, e.g., consisting of, SEQ ID NO: 138 and SEQ ID NO: 101, respectively. In an aspect, the first gRNA molecule and the second gRNA molecule include targeting domains comprising, e.g., consisting of, SEQ ID NO: 138 and SEQ ID NO: 162, respectively. In an aspect, the first gRNA molecule and the second gRNA molecule include

targeting domains comprising, e.g., consisting of, SEQ ID NO: 138 and SEQ ID NO: 104, respectively. In an aspect, the first gRNA molecule and the second gRNA molecule include targeting domains comprising, e.g., consisting of, SEQ ID NO: 138 and SEQ ID NO: 1536, respectively. In an aspect, the first gRNA molecule and the second gRNA molecule include targeting domains comprising, e.g., consisting of, SEQ ID NO: 138 and SEQ ID NO: 1539, respectively. In an aspect, the first gRNA molecule and the second gRNA molecule include targeting domains comprising, e.g., consisting of, SEQ ID NO: 138 and SEQ ID NO: 1585, respectively. In an aspect, the first gRNA molecule and the second gRNA molecule include targeting domains comprising, e.g., consisting of, SEQ ID NO: 1536 and SEQ ID NO: 165, respectively. In an aspect, the first gRNA molecule and the second gRNA molecule include targeting domains comprising, e.g., consisting of, SEQ ID NO: 1536 and SEQ ID NO: 113, respectively. In an aspect, the first gRNA molecule and the second gRNA molecule include targeting domains comprising, e.g., consisting of, SEQ ID NO: 1536 and SEQ ID NO: 99, respectively. In an aspect, the first gRNA molecule and the second gRNA molecule include targeting domains comprising, e.g., consisting of, SEQ ID NO: 1536 and SEQ ID NO: 112, respectively. In an aspect, the first gRNA molecule and the second gRNA molecule include targeting domains comprising, e.g., consisting of, SEQ ID NO: 1536 and SEQ ID NO: 98, respectively. In an aspect, the first gRNA molecule and the second gRNA molecule include targeting domains comprising, e.g., consisting of, SEQ ID NO: 1536 and SEQ ID NO: 1580, respectively. In an aspect, the first gRNA molecule and the second gRNA molecule include targeting domains comprising, e.g., consisting of, SEQ ID NO: 1536 and SEQ ID NO: 106, respectively. In an aspect, the first gRNA molecule and the second gRNA molecule include targeting domains comprising, e.g., consisting of, SEQ ID NO: 1536 and SEQ ID NO: 1503, respectively. In an aspect, the first gRNA molecule and the second gRNA molecule include targeting domains comprising, e.g., consisting of, SEQ ID NO: 1536 and SEQ ID NO: 1589, respectively. In an aspect, the first gRNA molecule and the second gRNA molecule include targeting domains comprising, e.g., consisting of, SEQ ID NO: 1536 and SEQ ID NO: 160, respectively. In an aspect, the first gRNA molecule and the second gRNA molecule include targeting domains comprising, e.g., consisting of, SEQ ID NO: 1536 and SEQ ID NO: 1537, respectively. In an aspect, the first gRNA molecule and the second gRNA molecule include targeting domains comprising, e.g., consisting of, SEQ ID NO: 1536 and SEQ ID NO: 159, respectively. In an aspect, the first gRNA molecule and the second gRNA molecule include targeting domains comprising, e.g., consisting of, SEQ ID NO: 1536 and SEQ ID NO: 101, respectively. In an aspect, the first gRNA molecule and the second gRNA molecule include targeting domains comprising, e.g., consisting of, SEQ ID NO: 1536 and SEQ ID NO: 162, respectively. In an aspect, the first gRNA molecule and the second gRNA molecule include targeting domains comprising, e.g., consisting of, SEQ ID NO: 1536 and SEQ ID NO: 104, respectively. In an aspect, the first gRNA molecule and the second gRNA molecule include targeting domains comprising, e.g., consisting of, SEQ ID NO: 1536 and SEQ ID NO: 138, respectively. In an aspect, the first gRNA molecule and the

second gRNA molecule include targeting domains comprising, e.g., consisting of, SEQ ID NO: 1536 and SEQ ID NO: 1539, respectively. In an aspect, the first gRNA molecule and the second gRNA molecule include targeting domains comprising, e.g., consisting of, SEQ ID NO: 1536 and SEQ ID NO: 1585, respectively. In an aspect, the first gRNA molecule and the second gRNA molecule include targeting domains comprising, e.g., consisting of, SEQ ID NO: 1539 and SEQ ID NO: 165, respectively. In an aspect, the first gRNA molecule and the second gRNA molecule include targeting domains comprising, e.g., consisting of, SEQ ID NO: 1539 and SEQ ID NO: 113, respectively. In an aspect, the first gRNA molecule and the second gRNA molecule include targeting domains comprising, e.g., consisting of, SEQ ID NO: 1539 and SEQ ID NO: 99, respectively. In an aspect, the first gRNA molecule and the second gRNA molecule include targeting domains comprising, e.g., consisting of, SEQ ID NO: 1539 and SEQ ID NO: 112, respectively. In an aspect, the first gRNA molecule and the second gRNA molecule include targeting domains comprising, e.g., consisting of, SEQ ID NO: 1539 and SEQ ID NO: 98, respectively. In an aspect, the first gRNA molecule and the second gRNA molecule include targeting domains comprising, e.g., consisting of, SEQ ID NO: 1539 and SEQ ID NO: 1580, respectively. In an aspect, the first gRNA molecule and the second gRNA molecule include targeting domains comprising, e.g., consisting of, SEQ ID NO: 1539 and SEQ ID NO: 106, respectively. In an aspect, the first gRNA molecule and the second gRNA molecule include targeting domains comprising, e.g., consisting of, SEQ ID NO: 1539 and SEQ ID NO: 1503, respectively. In an aspect, the first gRNA molecule and the second gRNA molecule include targeting domains comprising, e.g., consisting of, SEQ ID NO: 1539 and SEQ ID NO: 1589, respectively. In an aspect, the first gRNA molecule and the second gRNA molecule include targeting domains comprising, e.g., consisting of, SEQ ID NO: 1539 and SEQ ID NO: 160, respectively. In an aspect, the first gRNA molecule and the second gRNA molecule include targeting domains comprising, e.g., consisting of, SEQ ID NO: 1539 and SEQ ID NO: 1537, respectively. In an aspect, the first gRNA molecule and the second gRNA molecule include targeting domains comprising, e.g., consisting of, SEQ ID NO: 1539 and SEQ ID NO: 159, respectively. In an aspect, the first gRNA molecule and the second gRNA molecule include targeting domains comprising, e.g., consisting of, SEQ ID NO: 1539 and SEQ ID NO: 101, respectively. In an aspect, the first gRNA molecule and the second gRNA molecule include targeting domains comprising, e.g., consisting of, SEQ ID NO: 1539 and SEQ ID NO: 162, respectively. In an aspect, the first gRNA molecule and the second gRNA molecule include targeting domains comprising, e.g., consisting of, SEQ ID NO: 1539 and SEQ ID NO: 104, respectively. In an aspect, the first gRNA molecule and the second gRNA molecule include targeting domains comprising, e.g., consisting of, SEQ ID NO: 1539 and SEQ ID NO: 138, respectively. In an aspect, the first gRNA molecule and the second gRNA molecule include targeting domains comprising, e.g., consisting of, SEQ ID NO: 1539 and SEQ ID NO: 1536, respectively. In an aspect, the first gRNA molecule and the second gRNA molecule include targeting domains comprising, e.g., consisting of, SEQ ID NO: 1539 and SEQ ID NO: 1585, respectively. In

an aspect, the first gRNA molecule and the second gRNA molecule include targeting domains comprising, e.g., consisting of, SEQ ID NO: 1585 and SEQ ID NO: 165, respectively. In an aspect, the first gRNA molecule and the second gRNA molecule include targeting domains comprising, e.g., consisting of, SEQ ID NO: 1585 and SEQ ID NO: 113, respectively. In an aspect, the first gRNA molecule and the second gRNA molecule include targeting domains comprising, e.g., consisting of, SEQ ID NO: 1585 and SEQ ID NO: 99, respectively. In an aspect, the first gRNA molecule and the second gRNA molecule include targeting domains comprising, e.g., consisting of, SEQ ID NO: 1585 and SEQ ID NO: 112, respectively. In an aspect, the first gRNA molecule and the second gRNA molecule include targeting domains comprising, e.g., consisting of, SEQ ID NO: 1585 and SEQ ID NO: 98, respectively. In an aspect, the first gRNA molecule and the second gRNA molecule include targeting domains comprising, e.g., consisting of, SEQ ID NO: 1585 and SEQ ID NO: 1580, respectively. In an aspect, the first gRNA molecule and the second gRNA molecule include targeting domains comprising, e.g., consisting of, SEQ ID NO: 1585 and SEQ ID NO: 106, respectively. In an aspect, the first gRNA molecule and the second gRNA molecule include targeting domains comprising, e.g., consisting of, SEQ ID NO: 1585 and SEQ ID NO: 1503, respectively. In an aspect, the first gRNA molecule and the second gRNA molecule include targeting domains comprising, e.g., consisting of, SEQ ID NO: 1585 and SEQ ID NO: 1589, respectively. In an aspect, the first gRNA molecule and the second gRNA molecule include targeting domains comprising, e.g., consisting of, SEQ ID NO: 1585 and SEQ ID NO: 160, respectively. In an aspect, the first gRNA molecule and the second gRNA molecule include targeting domains comprising, e.g., consisting of, SEQ ID NO: 1585 and SEQ ID NO: 1537, respectively. In an aspect, the first gRNA molecule and the second gRNA molecule include targeting domains comprising, e.g., consisting of, SEQ ID NO: 1585 and SEQ ID NO: 159, respectively. In an aspect, the first gRNA molecule and the second gRNA molecule include targeting domains comprising, e.g., consisting of, SEQ ID NO: 1585 and SEQ ID NO: 101, respectively. In an aspect, the first gRNA molecule and the second gRNA molecule include targeting domains comprising, e.g., consisting of, SEQ ID NO: 1585 and SEQ ID NO: 162, respectively. In an aspect, the first gRNA molecule and the second gRNA molecule include targeting domains comprising, e.g., consisting of, SEQ ID NO: 1585 and SEQ ID NO: 104, respectively. In an aspect, the first gRNA molecule and the second gRNA molecule include targeting domains comprising, e.g., consisting of, SEQ ID NO: 1585 and SEQ ID NO: 138, respectively. In an aspect, the first gRNA molecule and the second gRNA molecule include targeting domains comprising, e.g., consisting of, SEQ ID NO: 1585 and SEQ ID NO: 1536, respectively. In an aspect, the first gRNA molecule and the second gRNA molecule include targeting domains comprising, e.g., consisting of, SEQ ID NO: 1585 and SEQ ID NO: 1539, respectively.

Table 7: Preferred Guide RNA Targeting Domains directed to the +58 Enhancer Region of the BCL11a Gene (i.e., to a BCL11a Enhancer)

Id.	Exon/ Feature	Strand	Targeting domain	Locations	SEQ ID NO:
CR00242	58	+	UAUGCAAUUUUUGCCAAGAU	Chr2:60494419-60494441	182
CR00243	58	+	UUUUGCCAAGAUGGGAGUAU	Chr2:60494427-60494449	183
CR00244	58	+	UUUGCCAAGAUGGGAGUAUG	Chr2:60494428-60494450	184
CR00245	58	+	UCAGUGAGAUGAGAUAUCAA	Chr2:60494477-60494499	185
CR00246	58	+	CAGUGAGAUGAGAUAUCAAA	Chr2:60494478-60494500	186
CR00247	58	+	CCAUCUCCCUAAUCUCCAAU	Chr2:60494518-60494540	187
CR00248	58	-	CCAAUUGGAGAUUAGGGAGA	Chr2:60494518-60494540	188
CR00249	58	-	GCUUUGCCAAUUGGAGAUUA	Chr2:60494524-60494546	189
CR00250	58	-	GGCUUUGCCAAUUGGAGAUU	Chr2:60494525-60494547	190
CR00251	58	+	AAUUGGCAAAGCCAGACUUG	Chr2:60494535-60494557	191
CR00252	58	-	AGUCUGUAUUGCCCCAAGUC	Chr2:60494546-60494568	192
CR00253	58	+	AGACUUGGGGCAAUACAGAC	Chr2:60494548-60494570	193
CR00255	58	-	ACAUUUGGUGAUAAAUCAUU	Chr2:60494602-60494624	194
CR00256	58	+	CCAAAUGUUCUUUCUUCAGC	Chr2:60494617-60494639	195
CR00257	58	+	AUAAUAGUAUAUGCUUCAUA	Chr2:60494676-60494698	196
CR00258	58	-	CGGAGCACUUACUCUGCUCU	Chr2:60494737-60494759	197
CR00259	58	-	AGCAUUUUAGUUCACAAGCU	Chr2:60494757-60494779	198
CR00260	58	-	UGUAACUAAUAAAUACCAGG	Chr2:60494781-60494803	199
CR00261	58	-	AGGUGUAACUAAUAAAUACC	Chr2:60494784-60494806	200
CR00264	58	-	UCUGACCCAAACUAGGAAUU	Chr2:60494836-60494858	201
CR00266	58	+	AAGGAAAAGAAUAUGACGUC	Chr2:60494883-60494905	202
CR00267	58	+	AGGAAAAGAAUAUGACGUCA	Chr2:60494884-60494906	203
CR00268	58	+	GGAAAAGAAUAUGACGUCAG	Chr2:60494885-60494907	204
CR00269	58	+	GAAAAGAAUAUGACGUCAGG	Chr2:60494886-60494908	205
CR00270	58	+	UCAGGGGGAGGCAAGUCAGU	Chr2:60494901-60494923	206
CR00271	58	+	CAGGGGGAGGCAAGUCAGUU	Chr2:60494902-60494924	207
CR00272	58		AUCACAUAUAGGCACCUAUC	Chr2:60494939-60494961	208
CR00273	58		CAGGUACCAGCUACUGUGUU	Chr2:60494939-60494961	209
CR00274	58		ACUAUCCACGGAUAUACACU	Chr2:60494939-60494961	210
CR00275	58	+	CACAGUAGCUGGUACCUGAU	Chr2:60494939-60494961	211
CR00276	58	-	AUCACAUAUAGGCACCUAUC	Chr2:60494953-60494975	212
CR00277	58	+	UGAUAGGUGCCUAUAUGUGA	Chr2:60494955-60494977	213
CR00278	58	+	AGGUGCCUAUAUGUGAUGGA	Chr2:60494959-60494981	214

CR00279	58	+	GGUGCCUAUAUGUGAUGGAU	Chr2:60494960-60494982	215
CR00280	58	-	UCCACCCAUCCAUCACAUAU	Chr2:60494964-60494986	216
CR00281	58	+	ACAGCCCGACAGAUGAAAAA	Chr2:60494986-60495008	217
CR00282	58	+	AUGAAAAAUGGACAAUUAUG	Chr2:60494998-60495020	218
CR00283	58	+	AAAAAUGGACAAUUAUGAGG	Chr2:60495001-60495023	219
CR00284	58	+	AAAAUGGACAAUUAUGAGGA	Chr2:60495002-60495024	220
CR00285	58	+	AAAUGGACAAUUAUGAGGAG	Chr2:60495003-60495025	221
CR00286	58	+	GAGGAGGGGAGAGUGCAGAC	Chr2:60495017-60495039	222
CR00287	58	+	AGGAGGGGAGAGUGCAGACA	Chr2:60495018-60495040	223
CR00288	58	+	CUUCACCUCCUUUACAAUUU	Chr2:60495045-60495067	224
CR00289	58	+	UUCACCUCCUUUACAAUUUU	Chr2:60495046-60495068	225
CR00290	58	-	GACUCCCAAAAUUGUAAAGG	Chr2:60495050-60495072	226
CR00291	58	-	GUGGACUCCCAAAAUUGUAA	Chr2:60495053-60495075	227
CR00292	58	+	UUUUGGGAGUCCACACGGCA	Chr2:60495062-60495084	228
CR00293	58	-	AAUUUGUAUGCCAUGCCGUG	Chr2:60495072-60495094	229
CR00294	58	+	CCAAGAGAGCCUUCCGAAAG	Chr2:60495135-60495157	230
CR00295	58	-	CCAGGGGGGCCUCUUUCGGA	Chr2:60495144-60495166	231
CR00296	58	+	CCUUCCGAAAGAGGCCCCCC	Chr2:60495144-60495166	232
CR00297	58	+	CUUCCGAAAGAGGCCCCCCU	Chr2:60495145-60495167	233
CR00298	58	+	AAGAGGCCCCCCUGGGCAAA	Chr2:60495152-60495174	234
CR00299	58	-	CGGUGGCCGUUUGCCCAGGG	Chr2:60495158-60495180	235
CR00300	58	-	UCGGUGGCCGUUUGCCCAGG	Chr2:60495159-60495181	236
CR00301	58	-	AUCGGUGGCCGUUUGCCCAG	Chr2:60495160-60495182	237
CR00302	58	-	CAUCGGUGGCCGUUUGCCCA	Chr2:60495161-60495183	238
CR00303	58	+	CCUGGGCAAACGGCCACCGA	Chr2:60495162-60495184	239
CR00304	58	-	CCAUCGGUGGCCGUUUGCCC	Chr2:60495162-60495184	240
CR00305	58	+	GCAAACGGCCACCGAUGGAG	Chr2:60495167-60495189	241
CR00306	58	-	CUGGCAGACCUCUCCAUCGG	Chr2:60495175-60495197	242
CR00307	58	-	GGACUGGCAGACCUCUCCAU	Chr2:60495178-60495200	243
CR00308	58	-	UCUGAUUAGGGUGGGGGCGU	Chr2:60495213-60495235	244
CR00309	58	+	CACGCCCCCACCCUAAUCAG	Chr2:60495215-60495237	245
CR00310	58	-	UUGGCCUCUGAUUAGGGUGG	Chr2:60495219-60495241	246
CR00311	58	-	UUUGGCCUCUGAUUAGGGUG	Chr2:60495220-60495242	247
CR00312	58	-	GUUUGGCCUCUGAUUAGGGU	Chr2:60495221-60495243	248
CR00313	58	-	GGUUUGGCCUCUGAUUAGGG	Chr2:60495222-60495244	249

CR00314	58	-	AAGGGUUUGGCCUCUGAUUA	Chr2:60495225-60495247	250
CR00315	58	-	GAAGGGUUUGGCCUCUGAUU	Chr2:60495226-60495248	251
CR00316	58	-	UUGCUUUUAUCACAGGCUCC	Chr2:60495248-60495270	252
CR00317	58	-	CUAACAGUUGCUUUUAUCAC	Chr2:60495255-60495277	253
CR00318	58	+	CUUCAAAGUUGUAUUGACCC	Chr2:60495293-60495315	254
CR00319	58	-	ACUCUUAGACAUAACACACC	Chr2:60495311-60495333	255
CR00320	58	+	UAGAUGCCAUAUCUCUUUUC	Chr2:60495333-60495355	256
CR00321	58	-	CAUAGGCCAGAAAAGAGAUA	Chr2:60495339-60495361	257
CR00322	58	+	GGCCUAUGUUAUUACCUGUA	Chr2:60495354-60495376	258
CR00323	58	-	GUCCAUACAGGUAAUAACAU	Chr2:60495356-60495378	259
CR00324	58	+	UACCUGUAUGGACUUUGCAC	Chr2:60495366-60495388	260
CR00325	58	-	UUCCAGUGCAAAGUCCAUAC	Chr2:60495368-60495390	261
CR00326	58	+	UGCUCUUACUUAUGCACACC	Chr2:60495400-60495422	262
CR00327	58	+	GCUCUUACUUAUGCACACCU	Chr2:60495401-60495423	263
CR00328	58	+	CUCUUACUUAUGCACACCUG	Chr2:60495402-60495424	264
CR00329	58	-	CAGGGCUGGCUCUAUGCCCC	Chr2:60495418-60495440	265
CR00330	58	-	GCUGAAAAGCGAUACAGGGC	Chr2:60495432-60495454	266
CR00331	58	-	GAUGGCUGAAAAGCGAUACA	Chr2:60495436-60495458	267
CR00332	58	-	AGAUGGCUGAAAAGCGAUAC	Chr2:60495437-60495459	268
CR00333	58	-	GGGAGUUAUCUGUAGUGAGA	Chr2:60495454-60495476	269
CR00334	58	-	AAGGCAGCUAGACAGGACUU	Chr2:60495474-60495496	270
CR00335	58	-	GAAGGCAGCUAGACAGGACU	Chr2:60495475-60495497	271
CR00336	58	-	GAUAAGGAAGGCAGCUAGAC	Chr2:60495481-60495503	272
CR00337	58	+	CUAGCUGCCUUCCUUAUCAC	Chr2:60495486-60495508	273
CR00338	58	-	UGGGUGCUAUUCCUGUGAUA	Chr2:60495497-60495519	274
CR00339	58	+	UAUCACAGGAAUAGCACCCA	Chr2:60495500-60495522	275
CR00340	58	-	CUGAGGUACUGAUGGACCUU	Chr2:60495516-60495538	276
CR00341	58	-	UCUGAGGUACUGAUGGACCU	Chr2:60495517-60495539	277
CR001124	58	-	UUAGGGUGGGGGCGUGGGUG	Chr2:60495214-60495236	334
CR001125	58	-	UUUUAUCACAGGCUCCAGGA	Chr2:60495215-60495237	335
CR001126	58	-	UUUAUCACAGGCUCCAGGAA	Chr2:60495216-60495238	336
CR001127	58	-	CACAGGCUCCAGGAAGGGUU	Chr2:60495220-60495242	337
CR001128	58	+	AUCAGAGGCCAAACCCUUCC	Chr2:60495236-60495258	338
CR001129	58	-	CUCUGAUUAGGGUGGGGGCG	Chr2:60495244-60495266	339
CR001130	58	-	GAUUAGGGUGGGGGCGUGGG	Chr2:60495249-60495271	340

CR001131	58	-	AUUAGGGUGGGGGCGUGGGU	Chr2:60495250-60495272	341

In some aspects of the invention, it is preferred that the gRNA molecule to the +58 Enhancer region of BCL11a comprise a targeting domain of a gRNA listed in Figure 11. In an aspect, the gRNA molecule includes a targeting domain comprising, e.g., consisting of, SEQ ID NO: 341. In an aspect, the gRNA molecule includes a targeting domain comprising, e.g., consisting of, SEQ ID NO: 246. In an aspect, the gRNA molecule includes a targeting domain comprising, e.g., consisting of, SEQ ID NO: 248. In an aspect, the gRNA molecule includes a targeting domain comprising, e.g., consisting of, SEQ ID NO: 247. In an aspect, the gRNA molecule includes a targeting domain comprising, e.g., consisting of, SEQ ID NO: 245. In an aspect, the gRNA molecule includes a targeting domain comprising, e.g., consisting of, SEQ ID NO: 249. In an aspect, the gRNA molecule includes a targeting domain comprising, e.g., consisting of, SEQ ID NO: 244. In an aspect, the gRNA molecule includes a targeting domain comprising, e.g., consisting of, SEQ ID NO: 199. In an aspect, the gRNA molecule includes a targeting domain comprising, e.g., consisting of, SEQ ID NO: 251. In an aspect, the gRNA molecule includes a targeting domain comprising, e.g., consisting of, SEQ ID NO: 250. In an aspect, the gRNA molecule includes a targeting domain comprising, e.g., consisting of, SEQ ID NO: 334. In an aspect, the gRNA molecule includes a targeting domain comprising, e.g., consisting of, SEQ ID NO: 185. In an aspect, the gRNA molecule includes a targeting domain comprising, e.g., consisting of, SEQ ID NO: 186. In an aspect, the gRNA molecule includes a targeting domain comprising, e.g., consisting of, SEQ ID NO: 336. In an aspect, the gRNA molecule includes a targeting domain comprising, e.g., consisting of, SEQ ID NO: 337.

In some aspects of the invention, e.g., as indicated herein, it may be beneficial to include gRNA moleucles targeting more than one, e.g., two, target sites (e.g., a first gRNA molecule and a second gRNA molecule). In some embodiments, the two target sites are both located in the +58 BCL11a enhancer region. In such aspects, any combination of more than one, e.g., two, gRNA molecules (e.g., a first gRNA molecule and a second gRNA molecule) comprising targeting domains listed in Table 7 may be used. In an aspect, the first gRNA molecule and the second gRNA molecule include targeting domains comprising, e.g., consisting of, SEQ ID NO: 341 and SEQ ID NO: 244, respectively. In an aspect, the first gRNA molecule and the second gRNA molecule include targeting domains comprising, e.g., consisting of, SEQ ID NO: 341 and SEQ ID NO: 199, respectively. In an aspect, the first gRNA molecule and the second gRNA molecule include targeting domains comprising, e.g., consisting of, SEQ ID NO: 341 and SEQ ID NO: 251, respectively. In an aspect, the first gRNA molecule and the second gRNA molecule include targeting domains comprising, e.g., consisting of, SEQ ID NO: 341 and SEQ ID NO: 250, respectively. In an aspect, the first gRNA molecule and the second gRNA molecule include targeting domains comprising, e.g., consisting of, SEQ ID NO: 341 and SEQ ID NO: 334, respectively. In an aspect, the first gRNA molecule and the

second gRNA molecule include targeting domains comprising, e.g., consisting of, SEQ ID NO: 341 and SEQ ID NO: 185, respectively. In an aspect, the first gRNA molecule and the second gRNA molecule include targeting domains comprising, e.g., consisting of, SEQ ID NO: 341 and SEQ ID NO: 186, respectively. In an aspect, the first gRNA molecule and the second gRNA molecule include targeting domains comprising, e.g., consisting of, SEQ ID NO: 341 and SEQ ID NO: 336, respectively. In an aspect, the first gRNA molecule and the second gRNA molecule include targeting domains comprising, e.g., consisting of, SEQ ID NO: 341 and SEQ ID NO: 337, respectively. In an aspect, the first gRNA molecule and the second gRNA molecule include targeting domains comprising, e.g., consisting of, SEQ ID NO: 341 and SEQ ID NO: 246, respectively. In an aspect, the first gRNA molecule and the second gRNA molecule include targeting domains comprising, e.g., consisting of, SEQ ID NO: 341 and SEQ ID NO: 248, respectively. In an aspect, the first gRNA molecule and the second gRNA molecule include targeting domains comprising, e.g., consisting of, SEQ ID NO: 341 and SEQ ID NO: 247, respectively. In an aspect, the first gRNA molecule and the second gRNA molecule include targeting domains comprising, e.g., consisting of, SEQ ID NO: 341 and SEQ ID NO: 245, respectively. In an aspect, the first gRNA molecule and the second gRNA molecule include targeting domains comprising, e.g., consisting of, SEQ ID NO: 341 and SEQ ID NO: 249, respectively. In an aspect, the first gRNA molecule and the second gRNA molecule include targeting domains comprising, e.g., consisting of, SEQ ID NO: 341 and SEQ ID NO: 244, respectively. In an aspect, the first gRNA molecule and the second gRNA molecule include targeting domains comprising, e.g., consisting of, SEQ ID NO: 341 and SEQ ID NO: 199, respectively. In an aspect, the first gRNA molecule and the second gRNA molecule include targeting domains comprising, e.g., consisting of, SEQ ID NO: 341 and SEQ ID NO: 251, respectively. In an aspect, the first gRNA molecule and the second gRNA molecule include targeting domains comprising, e.g., consisting of, SEQ ID NO: 341 and SEQ ID NO: 250, respectively. In an aspect, the first gRNA molecule and the second gRNA molecule include targeting domains comprising, e.g., consisting of, SEQ ID NO: 341 and SEQ ID NO: 334, respectively. In an aspect, the first gRNA molecule and the second gRNA molecule include targeting domains comprising, e.g., consisting of, SEQ ID NO: 341 and SEQ ID NO: 185, respectively. In an aspect, the first gRNA molecule and the second gRNA molecule include targeting domains comprising, e.g., consisting of, SEQ ID NO: 341 and SEQ ID NO: 186, respectively. In an aspect, the first gRNA molecule and the second gRNA molecule include targeting domains comprising, e.g., consisting of, SEQ ID NO: 341 and SEQ ID NO: 336, respectively. In an aspect, the first gRNA molecule and the second gRNA molecule include targeting domains comprising, e.g., consisting of, SEQ ID NO: 341 and SEQ ID NO: 337, respectively. In an aspect, the first gRNA molecule and the second gRNA molecule include targeting domains comprising, e.g., consisting of, SEQ ID NO: 246 and SEQ ID NO: 244, respectively. In an aspect, the first gRNA molecule and the second gRNA molecule include targeting domains comprising, e.g., consisting of, SEQ ID NO: 246 and SEQ ID NO: 199, respectively. In an aspect, the first gRNA

molecule and the second gRNA molecule include targeting domains comprising, e.g., consisting of, SEQ ID NO: 246 and SEQ ID NO: 251, respectively. In an aspect, the first gRNA molecule and the second gRNA molecule include targeting domains comprising, e.g., consisting of, SEQ ID NO: 246 and SEQ ID NO: 250, respectively. In an aspect, the first gRNA molecule and the second gRNA molecule include targeting domains comprising, e.g., consisting of, SEQ ID NO: 246 and SEQ ID NO: 334, respectively. In an aspect, the first gRNA molecule and the second gRNA molecule include targeting domains comprising, e.g., consisting of, SEQ ID NO: 246 and SEQ ID NO: 185, respectively. In an aspect, the first gRNA molecule and the second gRNA molecule include targeting domains comprising, e.g., consisting of, SEQ ID NO: 246 and SEQ ID NO: 186, respectively. In an aspect, the first gRNA molecule and the second gRNA molecule include targeting domains comprising, e.g., consisting of, SEQ ID NO: 246 and SEQ ID NO: 336, respectively. In an aspect, the first gRNA molecule and the second gRNA molecule include targeting domains comprising, e.g., consisting of, SEQ ID NO: 246 and SEQ ID NO: 337, respectively. In an aspect, the first gRNA molecule and the second gRNA molecule include targeting domains comprising, e.g., consisting of, SEQ ID NO: 246 and SEQ ID NO: 248, respectively. In an aspect, the first gRNA molecule and the second gRNA molecule include targeting domains comprising, e.g., consisting of, SEQ ID NO: 246 and SEQ ID NO: 247, respectively. In an aspect, the first gRNA molecule and the second gRNA molecule include targeting domains comprising, e.g., consisting of, SEQ ID NO: 246 and SEQ ID NO: 245, respectively. In an aspect, the first gRNA molecule and the second gRNA molecule include targeting domains comprising, e.g., consisting of, SEQ ID NO: 246 and SEQ ID NO: 249, respectively. In an aspect, the first gRNA molecule and the second gRNA molecule include targeting domains comprising, e.g., consisting of, SEQ ID NO: 246 and SEQ ID NO: 244, respectively. In an aspect, the first gRNA molecule and the second gRNA molecule include targeting domains comprising, e.g., consisting of, SEQ ID NO: 246 and SEQ ID NO: 199, respectively. In an aspect, the first gRNA molecule and the second gRNA molecule include targeting domains comprising, e.g., consisting of, SEQ ID NO: 246 and SEQ ID NO: 251, respectively. In an aspect, the first gRNA molecule and the second gRNA molecule include targeting domains comprising, e.g., consisting of, SEQ ID NO: 246 and SEQ ID NO: 250, respectively. In an aspect, the first gRNA molecule and the second gRNA molecule include targeting domains comprising, e.g., consisting of, SEQ ID NO: 246 and SEQ ID NO: 334, respectively. In an aspect, the first gRNA molecule and the second gRNA molecule include targeting domains comprising, e.g., consisting of, SEQ ID NO: 246 and SEQ ID NO: 185, respectively. In an aspect, the first gRNA molecule and the second gRNA molecule include targeting domains comprising, e.g., consisting of, SEQ ID NO: 246 and SEQ ID NO: 186, respectively. In an aspect, the first gRNA molecule and the second gRNA molecule include targeting domains comprising, e.g., consisting of, SEQ ID NO: 246 and SEQ ID NO: 336, respectively. In an aspect, the first gRNA molecule and the second gRNA molecule include targeting domains comprising, e.g., consisting of, SEQ ID NO: 246 and SEQ ID NO: 337, respectively. In an aspect,

the first gRNA molecule and the second gRNA molecule include targeting domains comprising, e.g., consisting of, SEQ ID NO: 248 and SEQ ID NO: 244, respectively. In an aspect, the first gRNA molecule and the second gRNA molecule include targeting domains comprising, e.g., consisting of, SEQ ID NO: 248 and SEQ ID NO: 199, respectively. In an aspect, the first gRNA molecule and the second gRNA molecule include targeting domains comprising, e.g., consisting of, SEQ ID NO: 248 and SEQ ID NO: 251, respectively. In an aspect, the first gRNA molecule and the second gRNA molecule include targeting domains comprising, e.g., consisting of, SEQ ID NO: 248 and SEQ ID NO: 250, respectively. In an aspect, the first gRNA molecule and the second gRNA molecule include targeting domains comprising, e.g., consisting of, SEQ ID NO: 248 and SEQ ID NO: 334, respectively. In an aspect, the first gRNA molecule and the second gRNA molecule include targeting domains comprising, e.g., consisting of, SEQ ID NO: 248 and SEQ ID NO: 185, respectively. In an aspect, the first gRNA molecule and the second gRNA molecule include targeting domains comprising, e.g., consisting of, SEQ ID NO: 248 and SEQ ID NO: 186, respectively. In an aspect, the first gRNA molecule and the second gRNA molecule include targeting domains comprising, e.g., consisting of, SEQ ID NO: 248 and SEQ ID NO: 336, respectively. In an aspect, the first gRNA molecule and the second gRNA molecule include targeting domains comprising, e.g., consisting of, SEQ ID NO: 248 and SEQ ID NO: 337, respectively. In an aspect, the first gRNA molecule and the second gRNA molecule include targeting domains comprising, e.g., consisting of, SEQ ID NO: 248 and SEQ ID NO: 246, respectively. In an aspect, the first gRNA molecule and the second gRNA molecule include targeting domains comprising, e.g., consisting of, SEQ ID NO: 248 and SEQ ID NO: 247, respectively. In an aspect, the first gRNA molecule and the second gRNA molecule include targeting domains comprising, e.g., consisting of, SEQ ID NO: 248 and SEQ ID NO: 245, respectively. In an aspect, the first gRNA molecule and the second gRNA molecule include targeting domains comprising, e.g., consisting of, SEQ ID NO: 248 and SEQ ID NO: 249, respectively. In an aspect, the first gRNA molecule and the second gRNA molecule include targeting domains comprising, e.g., consisting of, SEQ ID NO: 248 and SEQ ID NO: 244, respectively. In an aspect, the first gRNA molecule and the second gRNA molecule include targeting domains comprising, e.g., consisting of, SEQ ID NO: 248 and SEQ ID NO: 199, respectively. In an aspect, the first gRNA molecule and the second gRNA molecule include targeting domains comprising, e.g., consisting of, SEQ ID NO: 248 and SEQ ID NO: 251, respectively. In an aspect, the first gRNA molecule and the second gRNA molecule include targeting domains comprising, e.g., consisting of, SEQ ID NO: 248 and SEQ ID NO: 250, respectively. In an aspect, the first gRNA molecule and the second gRNA molecule include targeting domains comprising, e.g., consisting of, SEQ ID NO: 248 and SEQ ID NO: 334, respectively. In an aspect, the first gRNA molecule and the second gRNA molecule include targeting domains comprising, e.g., consisting of, SEQ ID NO: 248 and SEQ ID NO: 185, respectively. In an aspect, the first gRNA molecule and the second gRNA molecule include targeting domains comprising, e.g., consisting of, SEQ ID NO: 248 and SEQ ID NO: 186, respectively. In an

aspect, the first gRNA molecule and the second gRNA molecule include targeting domains comprising, e.g., consisting of, SEQ ID NO: 248 and SEQ ID NO: 336, respectively. In an aspect, the first gRNA molecule and the second gRNA molecule include targeting domains comprising, e.g., consisting of, SEQ ID NO: 248 and SEQ ID NO: 337, respectively. In an aspect, the first gRNA molecule and the second gRNA molecule include targeting domains comprising, e.g., consisting of, SEQ ID NO: 247 and SEQ ID NO: 244, respectively. In an aspect, the first gRNA molecule and the second gRNA molecule include targeting domains comprising, e.g., consisting of, SEQ ID NO: 247 and SEQ ID NO: 199, respectively. In an aspect, the first gRNA molecule and the second gRNA molecule include targeting domains comprising, e.g., consisting of, SEQ ID NO: 247 and SEQ ID NO: 251, respectively. In an aspect, the first gRNA molecule and the second gRNA molecule include targeting domains comprising, e.g., consisting of, SEQ ID NO: 247 and SEQ ID NO: 250, respectively. In an aspect, the first gRNA molecule and the second gRNA molecule include targeting domains comprising, e.g., consisting of, SEQ ID NO: 247 and SEQ ID NO: 334, respectively. In an aspect, the first gRNA molecule and the second gRNA molecule include targeting domains comprising, e.g., consisting of, SEQ ID NO: 247 and SEQ ID NO: 185, respectively. In an aspect, the first gRNA molecule and the second gRNA molecule include targeting domains comprising, e.g., consisting of, SEQ ID NO: 247 and SEQ ID NO: 186, respectively. In an aspect, the first gRNA molecule and the second gRNA molecule include targeting domains comprising, e.g., consisting of, SEQ ID NO: 247 and SEQ ID NO: 336, respectively. In an aspect, the first gRNA molecule and the second gRNA molecule include targeting domains comprising, e.g., consisting of, SEQ ID NO: 247 and SEQ ID NO: 337, respectively. In an aspect, the first gRNA molecule and the second gRNA molecule include targeting domains comprising, e.g., consisting of, SEQ ID NO: 247 and SEQ ID NO: 246, respectively. In an aspect, the first gRNA molecule and the second gRNA molecule include targeting domains comprising, e.g., consisting of, SEQ ID NO: 247 and SEQ ID NO: 248, respectively. In an aspect, the first gRNA molecule and the second gRNA molecule include targeting domains comprising, e.g., consisting of, SEQ ID NO: 247 and SEQ ID NO: 245, respectively. In an aspect, the first gRNA molecule and the second gRNA molecule include targeting domains comprising, e.g., consisting of, SEQ ID NO: 247 and SEQ ID NO: 249, respectively. In an aspect, the first gRNA molecule and the second gRNA molecule include targeting domains comprising, e.g., consisting of, SEQ ID NO: 247 and SEQ ID NO: 244, respectively. In an aspect, the first gRNA molecule and the second gRNA molecule include targeting domains comprising, e.g., consisting of, SEQ ID NO: 247 and SEQ ID NO: 199, respectively. In an aspect, the first gRNA molecule and the second gRNA molecule include targeting domains comprising, e.g., consisting of, SEQ ID NO: 247 and SEQ ID NO: 251, respectively. In an aspect, the first gRNA molecule and the second gRNA molecule include targeting domains comprising, e.g., consisting of, SEQ ID NO: 247 and SEQ ID NO: 250, respectively. In an aspect, the first gRNA molecule and the second gRNA molecule include targeting domains comprising, e.g., consisting of, SEQ ID NO: 247 and SEQ ID NO: 334,

respectively. In an aspect, the first gRNA molecule and the second gRNA molecule include targeting domains comprising, e.g., consisting of, SEQ ID NO: 247 and SEQ ID NO: 185, respectively. In an aspect, the first gRNA molecule and the second gRNA molecule include targeting domains comprising, e.g., consisting of, SEQ ID NO: 247 and SEQ ID NO: 186, respectively. In an aspect, the first gRNA molecule and the second gRNA molecule include targeting domains comprising, e.g., consisting of, SEQ ID NO: 247 and SEQ ID NO: 336, respectively. In an aspect, the first gRNA molecule and the second gRNA molecule include targeting domains comprising, e.g., consisting of, SEQ ID NO: 247 and SEQ ID NO: 337, respectively. In an aspect, the first gRNA molecule and the second gRNA molecule include targeting domains comprising, e.g., consisting of, SEQ ID NO: 245 and SEQ ID NO: 244, respectively. In an aspect, the first gRNA molecule and the second gRNA molecule include targeting domains comprising, e.g., consisting of, SEQ ID NO: 245 and SEQ ID NO: 199, respectively. In an aspect, the first gRNA molecule and the second gRNA molecule include targeting domains comprising, e.g., consisting of, SEQ ID NO: 245 and SEQ ID NO: 251, respectively. In an aspect, the first gRNA molecule and the second gRNA molecule include targeting domains comprising, e.g., consisting of, SEQ ID NO: 245 and SEQ ID NO: 250, respectively. In an aspect, the first gRNA molecule and the second gRNA molecule include targeting domains comprising, e.g., consisting of, SEQ ID NO: 245 and SEQ ID NO: 334, respectively. In an aspect, the first gRNA molecule and the second gRNA molecule include targeting domains comprising, e.g., consisting of, SEQ ID NO: 245 and SEQ ID NO: 185, respectively. In an aspect, the first gRNA molecule and the second gRNA molecule include targeting domains comprising, e.g., consisting of, SEQ ID NO: 245 and SEQ ID NO: 186, respectively. In an aspect, the first gRNA molecule and the second gRNA molecule include targeting domains comprising, e.g., consisting of, SEQ ID NO: 245 and SEQ ID NO: 336, respectively. In an aspect, the first gRNA molecule and the second gRNA molecule include targeting domains comprising, e.g., consisting of, SEQ ID NO: 245 and SEQ ID NO: 337, respectively. In an aspect, the first gRNA molecule and the second gRNA molecule include targeting domains comprising, e.g., consisting of, SEQ ID NO: 245 and SEQ ID NO: 246, respectively. In an aspect, the first gRNA molecule and the second gRNA molecule include targeting domains comprising, e.g., consisting of, SEQ ID NO: 245 and SEQ ID NO: 248, respectively. In an aspect, the first gRNA molecule and the second gRNA molecule include targeting domains comprising, e.g., consisting of, SEQ ID NO: 245 and SEQ ID NO: 247, respectively. In an aspect, the first gRNA molecule and the second gRNA molecule include targeting domains comprising, e.g., consisting of, SEQ ID NO: 245 and SEQ ID NO: 249, respectively. In an aspect, the first gRNA molecule and the second gRNA molecule include targeting domains comprising, e.g., consisting of, SEQ ID NO: 245 and SEQ ID NO: 244, respectively. In an aspect, the first gRNA molecule and the second gRNA molecule include targeting domains comprising, e.g., consisting of, SEQ ID NO: 245 and SEQ ID NO: 199, respectively. In an aspect, the first gRNA molecule and the second gRNA molecule include targeting domains comprising, e.g., consisting of, SEQ ID NO: 245 and SEQ ID

NO: 251, respectively. In an aspect, the first gRNA molecule and the second gRNA molecule include targeting domains comprising, e.g., consisting of, SEQ ID NO: 245 and SEQ ID NO: 250, respectively. In an aspect, the first gRNA molecule and the second gRNA molecule include targeting domains comprising, e.g., consisting of, SEQ ID NO: 245 and SEQ ID NO: 334, respectively. In an aspect, the first gRNA molecule and the second gRNA molecule include targeting domains comprising, e.g., consisting of, SEQ ID NO: 245 and SEQ ID NO: 185, respectively. In an aspect, the first gRNA molecule and the second gRNA molecule include targeting domains comprising, e.g., consisting of, SEQ ID NO: 245 and SEQ ID NO: 186, respectively. In an aspect, the first gRNA molecule and the second gRNA molecule include targeting domains comprising, e.g., consisting of, SEQ ID NO: 245 and SEQ ID NO: 336, respectively. In an aspect, the first gRNA molecule and the second gRNA molecule include targeting domains comprising, e.g., consisting of, SEQ ID NO: 245 and SEQ ID NO: 337, respectively. In an aspect, the first gRNA molecule and the second gRNA molecule include targeting domains comprising, e.g., consisting of, SEQ ID NO: 249 and SEQ ID NO: 244, respectively. In an aspect, the first gRNA molecule and the second gRNA molecule include targeting domains comprising, e.g., consisting of, SEQ ID NO: 249 and SEQ ID NO: 199, respectively. In an aspect, the first gRNA molecule and the second gRNA molecule include targeting domains comprising, e.g., consisting of, SEQ ID NO: 249 and SEQ ID NO: 251, respectively. In an aspect, the first gRNA molecule and the second gRNA molecule include targeting domains comprising, e.g., consisting of, SEQ ID NO: 249 and SEQ ID NO: 250, respectively. In an aspect, the first gRNA molecule and the second gRNA molecule include targeting domains comprising, e.g., consisting of, SEQ ID NO: 249 and SEQ ID NO: 334, respectively. In an aspect, the first gRNA molecule and the second gRNA molecule include targeting domains comprising, e.g., consisting of, SEQ ID NO: 249 and SEQ ID NO: 185, respectively. In an aspect, the first gRNA molecule and the second gRNA molecule include targeting domains comprising, e.g., consisting of, SEQ ID NO: 249 and SEQ ID NO: 186, respectively. In an aspect, the first gRNA molecule and the second gRNA molecule include targeting domains comprising, e.g., consisting of, SEQ ID NO: 249 and SEQ ID NO: 336, respectively. In an aspect, the first gRNA molecule and the second gRNA molecule include targeting domains comprising, e.g., consisting of, SEQ ID NO: 249 and SEQ ID NO: 337, respectively. In an aspect, the first gRNA molecule and the second gRNA molecule include targeting domains comprising, e.g., consisting of, SEQ ID NO: 249 and SEQ ID NO: 246, respectively. In an aspect, the first gRNA molecule and the second gRNA molecule include targeting domains comprising, e.g., consisting of, SEQ ID NO: 249 and SEQ ID NO: 248, respectively. In an aspect, the first gRNA molecule and the second gRNA molecule include targeting domains comprising, e.g., consisting of, SEQ ID NO: 249 and SEQ ID NO: 247, respectively. In an aspect, the first gRNA molecule and the second gRNA molecule include targeting domains comprising, e.g., consisting of, SEQ ID NO: 249 and SEQ ID NO: 245, respectively. In an aspect, the first gRNA molecule and the second gRNA molecule include targeting domains comprising, e.g., consisting of, SEQ ID NO: 249

and SEQ ID NO: 244, respectively. In an aspect, the first gRNA molecule and the second gRNA molecule include targeting domains comprising, e.g., consisting of, SEQ ID NO: 249 and SEQ ID NO: 199, respectively. In an aspect, the first gRNA molecule and the second gRNA molecule include targeting domains comprising, e.g., consisting of, SEQ ID NO: 249 and SEQ ID NO: 251, respectively. In an aspect, the first gRNA molecule and the second gRNA molecule include targeting domains comprising, e.g., consisting of, SEQ ID NO: 249 and SEQ ID NO: 250, respectively. In an aspect, the first gRNA molecule and the second gRNA molecule include targeting domains comprising, e.g., consisting of, SEQ ID NO: 249 and SEQ ID NO: 334, respectively. In an aspect, the first gRNA molecule and the second gRNA molecule include targeting domains comprising, e.g., consisting of, SEQ ID NO: 249 and SEQ ID NO: 185, respectively. In an aspect, the first gRNA molecule and the second gRNA molecule include targeting domains comprising, e.g., consisting of, SEQ ID NO: 249 and SEQ ID NO: 186, respectively. In an aspect, the first gRNA molecule and the second gRNA molecule include targeting domains comprising, e.g., consisting of, SEQ ID NO: 249 and SEQ ID NO: 336, respectively. In an aspect, the first gRNA molecule and the second gRNA molecule include targeting domains comprising, e.g., consisting of, SEQ ID NO: 249 and SEQ ID NO: 337, respectively. In an aspect, the first gRNA molecule and the second gRNA molecule include targeting domains comprising, e.g., consisting of, SEQ ID NO: 244 and SEQ ID NO: 199, respectively. In an aspect, the first gRNA molecule and the second gRNA molecule include targeting domains comprising, e.g., consisting of, SEQ ID NO: 244 and SEQ ID NO: 251, respectively. In an aspect, the first gRNA molecule and the second gRNA molecule include targeting domains comprising, e.g., consisting of, SEQ ID NO: 244 and SEQ ID NO: 250, respectively. In an aspect, the first gRNA molecule and the second gRNA molecule include targeting domains comprising, e.g., consisting of, SEQ ID NO: 244 and SEQ ID NO: 334, respectively. In an aspect, the first gRNA molecule and the second gRNA molecule include targeting domains comprising, e.g., consisting of, SEQ ID NO: 244 and SEQ ID NO: 185, respectively. In an aspect, the first gRNA molecule and the second gRNA molecule include targeting domains comprising, e.g., consisting of, SEQ ID NO: 244 and SEQ ID NO: 186, respectively. In an aspect, the first gRNA molecule and the second gRNA molecule include targeting domains comprising, e.g., consisting of, SEQ ID NO: 244 and SEQ ID NO: 336, respectively. In an aspect, the first gRNA molecule and the second gRNA molecule include targeting domains comprising, e.g., consisting of, SEQ ID NO: 244 and SEQ ID NO: 337, respectively. In an aspect, the first gRNA molecule and the second gRNA molecule include targeting domains comprising, e.g., consisting of, SEQ ID NO: 244 and SEQ ID NO: 246, respectively. In an aspect, the first gRNA molecule and the second gRNA molecule include targeting domains comprising, e.g., consisting of, SEQ ID NO: 244 and SEQ ID NO: 248, respectively. In an aspect, the first gRNA molecule and the second gRNA molecule include targeting domains comprising, e.g., consisting of, SEQ ID NO: 244 and SEQ ID NO: 247, respectively. In an aspect, the first gRNA molecule and the second gRNA molecule include targeting domains comprising, e.g., consisting of,

SEQ ID NO: 244 and SEQ ID NO: 245, respectively. In an aspect, the first gRNA molecule and the second gRNA molecule include targeting domains comprising, e.g., consisting of, SEQ ID NO: 244 and SEQ ID NO: 249, respectively. In an aspect, the first gRNA molecule and the second gRNA molecule include targeting domains comprising, e.g., consisting of, SEQ ID NO: 244 and SEQ ID NO: 199, respectively. In an aspect, the first gRNA molecule and the second gRNA molecule include targeting domains comprising, e.g., consisting of, SEQ ID NO: 244 and SEQ ID NO: 251, respectively. In an aspect, the first gRNA molecule and the second gRNA molecule include targeting domains comprising, e.g., consisting of, SEQ ID NO: 244 and SEQ ID NO: 250, respectively. In an aspect, the first gRNA molecule and the second gRNA molecule include targeting domains comprising, e.g., consisting of, SEQ ID NO: 244 and SEQ ID NO: 334, respectively. In an aspect, the first gRNA molecule and the second gRNA molecule include targeting domains comprising, e.g., consisting of, SEQ ID NO: 244 and SEQ ID NO: 185, respectively. In an aspect, the first gRNA molecule and the second gRNA molecule include targeting domains comprising, e.g., consisting of, SEQ ID NO: 244 and SEQ ID NO: 186, respectively. In an aspect, the first gRNA molecule and the second gRNA molecule include targeting domains comprising, e.g., consisting of, SEQ ID NO: 244 and SEQ ID NO: 336, respectively. In an aspect, the first gRNA molecule and the second gRNA molecule include targeting domains comprising, e.g., consisting of, SEQ ID NO: 244 and SEQ ID NO: 337, respectively. In an aspect, the first gRNA molecule and the second gRNA molecule include targeting domains comprising, e.g., consisting of, SEQ ID NO: 199 and SEQ ID NO: 244, respectively. In an aspect, the first gRNA molecule and the second gRNA molecule include targeting domains comprising, e.g., consisting of, SEQ ID NO: 199 and SEQ ID NO: 251, respectively. In an aspect, the first gRNA molecule and the second gRNA molecule include targeting domains comprising, e.g., consisting of, SEQ ID NO: 199 and SEQ ID NO: 250, respectively. In an aspect, the first gRNA molecule and the second gRNA molecule include targeting domains comprising, e.g., consisting of, SEQ ID NO: 199 and SEQ ID NO: 334, respectively. In an aspect, the first gRNA molecule and the second gRNA molecule include targeting domains comprising, e.g., consisting of, SEQ ID NO: 199 and SEQ ID NO: 185, respectively. In an aspect, the first gRNA molecule and the second gRNA molecule include targeting domains comprising, e.g., consisting of, SEQ ID NO: 199 and SEQ ID NO: 186, respectively. In an aspect, the first gRNA molecule and the second gRNA molecule include targeting domains comprising, e.g., consisting of, SEQ ID NO: 199 and SEQ ID NO: 336, respectively. In an aspect, the first gRNA molecule and the second gRNA molecule include targeting domains comprising, e.g., consisting of, SEQ ID NO: 199 and SEQ ID NO: 337, respectively. In an aspect, the first gRNA molecule and the second gRNA molecule include targeting domains comprising, e.g., consisting of, SEQ ID NO: 199 and SEQ ID NO: 246, respectively. In an aspect, the first gRNA molecule and the second gRNA molecule include targeting domains comprising, e.g., consisting of, SEQ ID NO: 199 and SEQ ID NO: 248, respectively. In an aspect, the first gRNA molecule and the second gRNA molecule include targeting domains comprising, e.g.,

consisting of, SEQ ID NO: 199 and SEQ ID NO: 247, respectively. In an aspect, the first gRNA molecule and the second gRNA molecule include targeting domains comprising, e.g., consisting of, SEQ ID NO: 199 and SEQ ID NO: 245, respectively. In an aspect, the first gRNA molecule and the second gRNA molecule include targeting domains comprising, e.g., consisting of, SEQ ID NO: 199 and SEQ ID NO: 249, respectively. In an aspect, the first gRNA molecule and the second gRNA molecule include targeting domains comprising, e.g., consisting of, SEQ ID NO: 199 and SEQ ID NO: 244, respectively. In an aspect, the first gRNA molecule and the second gRNA molecule include targeting domains comprising, e.g., consisting of, SEQ ID NO: 199 and SEQ ID NO: 251, respectively. In an aspect, the first gRNA molecule and the second gRNA molecule include targeting domains comprising, e.g., consisting of, SEQ ID NO: 199 and SEQ ID NO: 250, respectively. In an aspect, the first gRNA molecule and the second gRNA molecule include targeting domains comprising, e.g., consisting of, SEQ ID NO: 199 and SEQ ID NO: 334, respectively. In an aspect, the first gRNA molecule and the second gRNA molecule include targeting domains comprising, e.g., consisting of, SEQ ID NO: 199 and SEQ ID NO: 185, respectively. In an aspect, the first gRNA molecule and the second gRNA molecule include targeting domains comprising, e.g., consisting of, SEQ ID NO: 199 and SEQ ID NO: 186, respectively. In an aspect, the first gRNA molecule and the second gRNA molecule include targeting domains comprising, e.g., consisting of, SEQ ID NO: 199 and SEQ ID NO: 336, respectively. In an aspect, the first gRNA molecule and the second gRNA molecule include targeting domains comprising, e.g., consisting of, SEQ ID NO: 199 and SEQ ID NO: 337, respectively. In an aspect, the first gRNA molecule and the second gRNA molecule include targeting domains comprising, e.g., consisting of, SEQ ID NO: 251 and SEQ ID NO: 244, respectively. In an aspect, the first gRNA molecule and the second gRNA molecule include targeting domains comprising, e.g., consisting of, SEQ ID NO: 251 and SEQ ID NO: 199, respectively. In an aspect, the first gRNA molecule and the second gRNA molecule include targeting domains comprising, e.g., consisting of, SEQ ID NO: 251 and SEQ ID NO: 250, respectively. In an aspect, the first gRNA molecule and the second gRNA molecule include targeting domains comprising, e.g., consisting of, SEQ ID NO: 251 and SEQ ID NO: 334, respectively. In an aspect, the first gRNA molecule and the second gRNA molecule include targeting domains comprising, e.g., consisting of, SEQ ID NO: 251 and SEQ ID NO: 185, respectively. In an aspect, the first gRNA molecule and the second gRNA molecule include targeting domains comprising, e.g., consisting of, SEQ ID NO: 251 and SEQ ID NO: 186, respectively. In an aspect, the first gRNA molecule and the second gRNA molecule include targeting domains comprising, e.g., consisting of, SEQ ID NO: 251 and SEQ ID NO: 336, respectively. In an aspect, the first gRNA molecule and the second gRNA molecule include targeting domains comprising, e.g., consisting of, SEQ ID NO: 251 and SEQ ID NO: 337, respectively. In an aspect, the first gRNA molecule and the second gRNA molecule include targeting domains comprising, e.g., consisting of, SEQ ID NO: 251 and SEQ ID NO: 246, respectively. In an aspect, the first gRNA molecule and the second gRNA molecule include targeting domains

comprising, e.g., consisting of, SEQ ID NO: 251 and SEQ ID NO: 248, respectively. In an aspect, the first gRNA molecule and the second gRNA molecule include targeting domains comprising, e.g., consisting of, SEQ ID NO: 251 and SEQ ID NO: 247, respectively. In an aspect, the first gRNA molecule and the second gRNA molecule include targeting domains comprising, e.g., consisting of, SEQ ID NO: 251 and SEQ ID NO: 245, respectively. In an aspect, the first gRNA molecule and the second gRNA molecule include targeting domains comprising, e.g., consisting of, SEQ ID NO: 251 and SEQ ID NO: 249, respectively. In an aspect, the first gRNA molecule and the second gRNA molecule include targeting domains comprising, e.g., consisting of, SEQ ID NO: 251 and SEQ ID NO: 244, respectively. In an aspect, the first gRNA molecule and the second gRNA molecule include targeting domains comprising, e.g., consisting of, SEQ ID NO: 251 and SEQ ID NO: 199, respectively. In an aspect, the first gRNA molecule and the second gRNA molecule include targeting domains comprising, e.g., consisting of, SEQ ID NO: 251 and SEQ ID NO: 250, respectively. In an aspect, the first gRNA molecule and the second gRNA molecule include targeting domains comprising, e.g., consisting of, SEQ ID NO: 251 and SEQ ID NO: 334, respectively. In an aspect, the first gRNA molecule and the second gRNA molecule include targeting domains comprising, e.g., consisting of, SEQ ID NO: 251 and SEQ ID NO: 185, respectively. In an aspect, the first gRNA molecule and the second gRNA molecule include targeting domains comprising, e.g., consisting of, SEQ ID NO: 251 and SEQ ID NO: 186, respectively. In an aspect, the first gRNA molecule and the second gRNA molecule include targeting domains comprising, e.g., consisting of, SEQ ID NO: 251 and SEQ ID NO: 336, respectively. In an aspect, the first gRNA molecule and the second gRNA molecule include targeting domains comprising, e.g., consisting of, SEQ ID NO: 251 and SEQ ID NO: 337, respectively. In an aspect, the first gRNA molecule and the second gRNA molecule include targeting domains comprising, e.g., consisting of, SEQ ID NO: 250 and SEQ ID NO: 244, respectively. In an aspect, the first gRNA molecule and the second gRNA molecule include targeting domains comprising, e.g., consisting of, SEQ ID NO: 250 and SEQ ID NO: 199, respectively. In an aspect, the first gRNA molecule and the second gRNA molecule include targeting domains comprising, e.g., consisting of, SEQ ID NO: 250 and SEQ ID NO: 251, respectively. In an aspect, the first gRNA molecule and the second gRNA molecule include targeting domains comprising, e.g., consisting of, SEQ ID NO: 250 and SEQ ID NO: 334, respectively. In an aspect, the first gRNA molecule and the second gRNA molecule include targeting domains comprising, e.g., consisting of, SEQ ID NO: 250 and SEQ ID NO: 185, respectively. In an aspect, the first gRNA molecule and the second gRNA molecule include targeting domains comprising, e.g., consisting of, SEQ ID NO: 250 and SEQ ID NO: 186, respectively. In an aspect, the first gRNA molecule and the second gRNA molecule include targeting domains comprising, e.g., consisting of, SEQ ID NO: 250 and SEQ ID NO: 336, respectively. In an aspect, the first gRNA molecule and the second gRNA molecule include targeting domains comprising, e.g., consisting of, SEQ ID NO: 250 and SEQ ID NO: 337, respectively. In an aspect, the first gRNA molecule and the second gRNA molecule include targeting

domains comprising, e.g., consisting of, SEQ ID NO: 250 and SEQ ID NO: 246, respectively. In an aspect, the first gRNA molecule and the second gRNA molecule include targeting domains comprising, e.g., consisting of, SEQ ID NO: 250 and SEQ ID NO: 248, respectively. In an aspect, the first gRNA molecule and the second gRNA molecule include targeting domains comprising, e.g., consisting of, SEQ ID NO: 250 and SEQ ID NO: 247, respectively. In an aspect, the first gRNA molecule and the second gRNA molecule include targeting domains comprising, e.g., consisting of, SEQ ID NO: 250 and SEQ ID NO: 245, respectively. In an aspect, the first gRNA molecule and the second gRNA molecule include targeting domains comprising, e.g., consisting of, SEQ ID NO: 250 and SEQ ID NO: 249, respectively. In an aspect, the first gRNA molecule and the second gRNA molecule include targeting domains comprising, e.g., consisting of, SEQ ID NO: 250 and SEQ ID NO: 244, respectively. In an aspect, the first gRNA molecule and the second gRNA molecule include targeting domains comprising, e.g., consisting of, SEQ ID NO: 250 and SEQ ID NO: 199, respectively. In an aspect, the first gRNA molecule and the second gRNA molecule include targeting domains comprising, e.g., consisting of, SEQ ID NO: 250 and SEQ ID NO: 251, respectively. In an aspect, the first gRNA molecule and the second gRNA molecule include targeting domains comprising, e.g., consisting of, SEQ ID NO: 250 and SEQ ID NO: 334, respectively. In an aspect, the first gRNA molecule and the second gRNA molecule include targeting domains comprising, e.g., consisting of, SEQ ID NO: 250 and SEQ ID NO: 185, respectively. In an aspect, the first gRNA molecule and the second gRNA molecule include targeting domains comprising, e.g., consisting of, SEQ ID NO: 250 and SEQ ID NO: 186, respectively. In an aspect, the first gRNA molecule and the second gRNA molecule include targeting domains comprising, e.g., consisting of, SEQ ID NO: 250 and SEQ ID NO: 336, respectively. In an aspect, the first gRNA molecule and the second gRNA molecule include targeting domains comprising, e.g., consisting of, SEQ ID NO: 250 and SEQ ID NO: 337, respectively. In an aspect, the first gRNA molecule and the second gRNA molecule include targeting domains comprising, e.g., consisting of, SEQ ID NO: 334 and SEQ ID NO: 244, respectively. In an aspect, the first gRNA molecule and the second gRNA molecule include targeting domains comprising, e.g., consisting of, SEQ ID NO: 334 and SEQ ID NO: 199, respectively. In an aspect, the first gRNA molecule and the second gRNA molecule include targeting domains comprising, e.g., consisting of, SEQ ID NO: 334 and SEQ ID NO: 251, respectively. In an aspect, the first gRNA molecule and the second gRNA molecule include targeting domains comprising, e.g., consisting of, SEQ ID NO: 334 and SEQ ID NO: 250, respectively. In an aspect, the first gRNA molecule and the second gRNA molecule include targeting domains comprising, e.g., consisting of, SEQ ID NO: 334 and SEQ ID NO: 185, respectively. In an aspect, the first gRNA molecule and the second gRNA molecule include targeting domains comprising, e.g., consisting of, SEQ ID NO: 334 and SEQ ID NO: 186, respectively. In an aspect, the first gRNA molecule and the second gRNA molecule include targeting domains comprising, e.g., consisting of, SEQ ID NO: 334 and SEQ ID NO: 336, respectively. In an aspect, the first gRNA molecule and the second gRNA molecule include

targeting domains comprising, e.g., consisting of, SEQ ID NO: 334 and SEQ ID NO: 337, respectively. In an aspect, the first gRNA molecule and the second gRNA molecule include targeting domains comprising, e.g., consisting of, SEQ ID NO: 334 and SEQ ID NO: 246, respectively. In an aspect, the first gRNA molecule and the second gRNA molecule include targeting domains comprising, e.g., consisting of, SEQ ID NO: 334 and SEQ ID NO: 248, respectively. In an aspect, the first gRNA molecule and the second gRNA molecule include targeting domains comprising, e.g., consisting of, SEQ ID NO: 334 and SEQ ID NO: 247, respectively. In an aspect, the first gRNA molecule and the second gRNA molecule include targeting domains comprising, e.g., consisting of, SEQ ID NO: 334 and SEQ ID NO: 245, respectively. In an aspect, the first gRNA molecule and the second gRNA molecule include targeting domains comprising, e.g., consisting of, SEQ ID NO: 334 and SEQ ID NO: 249, respectively. In an aspect, the first gRNA molecule and the second gRNA molecule include targeting domains comprising, e.g., consisting of, SEQ ID NO: 334 and SEQ ID NO: 244, respectively. In an aspect, the first gRNA molecule and the second gRNA molecule include targeting domains comprising, e.g., consisting of, SEQ ID NO: 334 and SEQ ID NO: 199, respectively. In an aspect, the first gRNA molecule and the second gRNA molecule include targeting domains comprising, e.g., consisting of, SEQ ID NO: 334 and SEQ ID NO: 251, respectively. In an aspect, the first gRNA molecule and the second gRNA molecule include targeting domains comprising, e.g., consisting of, SEQ ID NO: 334 and SEQ ID NO: 250, respectively. In an aspect, the first gRNA molecule and the second gRNA molecule include targeting domains comprising, e.g., consisting of, SEQ ID NO: 334 and SEQ ID NO: 185, respectively. In an aspect, the first gRNA molecule and the second gRNA molecule include targeting domains comprising, e.g., consisting of, SEQ ID NO: 334 and SEQ ID NO: 186, respectively. In an aspect, the first gRNA molecule and the second gRNA molecule include targeting domains comprising, e.g., consisting of, SEQ ID NO: 334 and SEQ ID NO: 336, respectively. In an aspect, the first gRNA molecule and the second gRNA molecule include targeting domains comprising, e.g., consisting of, SEQ ID NO: 334 and SEQ ID NO: 337, respectively. In an aspect, the first gRNA molecule and the second gRNA molecule include targeting domains comprising, e.g., consisting of, SEQ ID NO: 185 and SEQ ID NO: 244, respectively. In an aspect, the first gRNA molecule and the second gRNA molecule include targeting domains comprising, e.g., consisting of, SEQ ID NO: 185 and SEQ ID NO: 199, respectively. In an aspect, the first gRNA molecule and the second gRNA molecule include targeting domains comprising, e.g., consisting of, SEQ ID NO: 185 and SEQ ID NO: 251, respectively. In an aspect, the first gRNA molecule and the second gRNA molecule include targeting domains comprising, e.g., consisting of, SEQ ID NO: 185 and SEQ ID NO: 250, respectively. In an aspect, the first gRNA molecule and the second gRNA molecule include targeting domains comprising, e.g., consisting of, SEQ ID NO: 185 and SEQ ID NO: 334, respectively. In an aspect, the first gRNA molecule and the second gRNA molecule include targeting domains comprising, e.g., consisting of, SEQ ID NO: 185 and SEQ ID NO: 186, respectively. In an aspect, the first gRNA molecule and the second gRNA

molecule include targeting domains comprising, e.g., consisting of, SEQ ID NO: 185 and SEQ ID NO: 336, respectively. In an aspect, the first gRNA molecule and the second gRNA molecule include targeting domains comprising, e.g., consisting of, SEQ ID NO: 185 and SEQ ID NO: 337, respectively. In an aspect, the first gRNA molecule and the second gRNA molecule include targeting domains comprising, e.g., consisting of, SEQ ID NO: 185 and SEQ ID NO: 246, respectively. In an aspect, the first gRNA molecule and the second gRNA molecule include targeting domains comprising, e.g., consisting of, SEQ ID NO: 185 and SEQ ID NO: 248, respectively. In an aspect, the first gRNA molecule and the second gRNA molecule include targeting domains comprising, e.g., consisting of, SEQ ID NO: 185 and SEQ ID NO: 247, respectively. In an aspect, the first gRNA molecule and the second gRNA molecule include targeting domains comprising, e.g., consisting of, SEQ ID NO: 185 and SEQ ID NO: 245, respectively. In an aspect, the first gRNA molecule and the second gRNA molecule include targeting domains comprising, e.g., consisting of, SEQ ID NO: 185 and SEQ ID NO: 249, respectively. In an aspect, the first gRNA molecule and the second gRNA molecule include targeting domains comprising, e.g., consisting of, SEQ ID NO: 185 and SEQ ID NO: 244, respectively. In an aspect, the first gRNA molecule and the second gRNA molecule include targeting domains comprising, e.g., consisting of, SEQ ID NO: 185 and SEQ ID NO: 199, respectively. In an aspect, the first gRNA molecule and the second gRNA molecule include targeting domains comprising, e.g., consisting of, SEQ ID NO: 185 and SEQ ID NO: 251, respectively. In an aspect, the first gRNA molecule and the second gRNA molecule include targeting domains comprising, e.g., consisting of, SEQ ID NO: 185 and SEQ ID NO: 250, respectively. In an aspect, the first gRNA molecule and the second gRNA molecule include targeting domains comprising, e.g., consisting of, SEQ ID NO: 185 and SEQ ID NO: 334, respectively. In an aspect, the first gRNA molecule and the second gRNA molecule include targeting domains comprising, e.g., consisting of, SEQ ID NO: 185 and SEQ ID NO: 186, respectively. In an aspect, the first gRNA molecule and the second gRNA molecule include targeting domains comprising, e.g., consisting of, SEQ ID NO: 185 and SEQ ID NO: 336, respectively. In an aspect, the first gRNA molecule and the second gRNA molecule include targeting domains comprising, e.g., consisting of, SEQ ID NO: 185 and SEQ ID NO: 337, respectively. In an aspect, the first gRNA molecule and the second gRNA molecule include targeting domains comprising, e.g., consisting of, SEQ ID NO: 186 and SEQ ID NO: 244, respectively. In an aspect, the first gRNA molecule and the second gRNA molecule include targeting domains comprising, e.g., consisting of, SEQ ID NO: 186 and SEQ ID NO: 199, respectively. In an aspect, the first gRNA molecule and the second gRNA molecule include targeting domains comprising, e.g., consisting of, SEQ ID NO: 186 and SEQ ID NO: 251, respectively. In an aspect, the first gRNA molecule and the second gRNA molecule include targeting domains comprising, e.g., consisting of, SEQ ID NO: 186 and SEQ ID NO: 250, respectively. In an aspect, the first gRNA molecule and the second gRNA molecule include targeting domains comprising, e.g., consisting of, SEQ ID NO: 186 and SEQ ID NO: 334, respectively. In an aspect, the first gRNA molecule and the

second gRNA molecule include targeting domains comprising, e.g., consisting of, SEQ ID NO: 186 and SEQ ID NO: 185, respectively. In an aspect, the first gRNA molecule and the second gRNA molecule include targeting domains comprising, e.g., consisting of, SEQ ID NO: 186 and SEQ ID NO: 336, respectively. In an aspect, the first gRNA molecule and the second gRNA molecule include targeting domains comprising, e.g., consisting of, SEQ ID NO: 186 and SEQ ID NO: 337, respectively. In an aspect, the first gRNA molecule and the second gRNA molecule include targeting domains comprising, e.g., consisting of, SEQ ID NO: 186 and SEQ ID NO: 246, respectively. In an aspect, the first gRNA molecule and the second gRNA molecule include targeting domains comprising, e.g., consisting of, SEQ ID NO: 186 and SEQ ID NO: 248, respectively. In an aspect, the first gRNA molecule and the second gRNA molecule include targeting domains comprising, e.g., consisting of, SEQ ID NO: 186 and SEQ ID NO: 247, respectively. In an aspect, the first gRNA molecule and the second gRNA molecule include targeting domains comprising, e.g., consisting of, SEQ ID NO: 186 and SEQ ID NO: 245, respectively. In an aspect, the first gRNA molecule and the second gRNA molecule include targeting domains comprising, e.g., consisting of, SEQ ID NO: 186 and SEQ ID NO: 249, respectively. In an aspect, the first gRNA molecule and the second gRNA molecule include targeting domains comprising, e.g., consisting of, SEQ ID NO: 186 and SEQ ID NO: 244, respectively. In an aspect, the first gRNA molecule and the second gRNA molecule include targeting domains comprising, e.g., consisting of, SEQ ID NO: 186 and SEQ ID NO: 199, respectively. In an aspect, the first gRNA molecule and the second gRNA molecule include targeting domains comprising, e.g., consisting of, SEQ ID NO: 186 and SEQ ID NO: 251, respectively. In an aspect, the first gRNA molecule and the second gRNA molecule include targeting domains comprising, e.g., consisting of, SEQ ID NO: 186 and SEQ ID NO: 250, respectively. In an aspect, the first gRNA molecule and the second gRNA molecule include targeting domains comprising, e.g., consisting of, SEQ ID NO: 186 and SEQ ID NO: 334, respectively. In an aspect, the first gRNA molecule and the second gRNA molecule include targeting domains comprising, e.g., consisting of, SEQ ID NO: 186 and SEQ ID NO: 185, respectively. In an aspect, the first gRNA molecule and the second gRNA molecule include targeting domains comprising, e.g., consisting of, SEQ ID NO: 186 and SEQ ID NO: 336, respectively. In an aspect, the first gRNA molecule and the second gRNA molecule include targeting domains comprising, e.g., consisting of, SEQ ID NO: 186 and SEQ ID NO: 337, respectively. In an aspect, the first gRNA molecule and the second gRNA molecule include targeting domains comprising, e.g., consisting of, SEQ ID NO: 336 and SEQ ID NO: 244, respectively. In an aspect, the first gRNA molecule and the second gRNA molecule include targeting domains comprising, e.g., consisting of, SEQ ID NO: 336 and SEQ ID NO: 199, respectively. In an aspect, the first gRNA molecule and the second gRNA molecule include targeting domains comprising, e.g., consisting of, SEQ ID NO: 336 and SEQ ID NO: 251, respectively. In an aspect, the first gRNA molecule and the second gRNA molecule include targeting domains comprising, e.g., consisting of, SEQ ID NO: 336 and SEQ ID NO: 250, respectively. In an aspect, the first gRNA

molecule and the second gRNA molecule include targeting domains comprising, e.g., consisting of, SEQ ID NO: 336 and SEQ ID NO: 334, respectively. In an aspect, the first gRNA molecule and the second gRNA molecule include targeting domains comprising, e.g., consisting of, SEQ ID NO: 336 and SEQ ID NO: 185, respectively. In an aspect, the first gRNA molecule and the second gRNA molecule include targeting domains comprising, e.g., consisting of, SEQ ID NO: 336 and SEQ ID NO: 186, respectively. In an aspect, the first gRNA molecule and the second gRNA molecule include targeting domains comprising, e.g., consisting of, SEQ ID NO: 336 and SEQ ID NO: 337, respectively. In an aspect, the first gRNA molecule and the second gRNA molecule include targeting domains comprising, e.g., consisting of, SEQ ID NO: 336 and SEQ ID NO: 246, respectively. In an aspect, the first gRNA molecule and the second gRNA molecule include targeting domains comprising, e.g., consisting of, SEQ ID NO: 336 and SEQ ID NO: 248, respectively. In an aspect, the first gRNA molecule and the second gRNA molecule include targeting domains comprising, e.g., consisting of, SEQ ID NO: 336 and SEQ ID NO: 247, respectively. In an aspect, the first gRNA molecule and the second gRNA molecule include targeting domains comprising, e.g., consisting of, SEQ ID NO: 336 and SEQ ID NO: 245, respectively. In an aspect, the first gRNA molecule and the second gRNA molecule include targeting domains comprising, e.g., consisting of, SEQ ID NO: 336 and SEQ ID NO: 249, respectively. In an aspect, the first gRNA molecule and the second gRNA molecule include targeting domains comprising, e.g., consisting of, SEQ ID NO: 336 and SEQ ID NO: 244, respectively. In an aspect, the first gRNA molecule and the second gRNA molecule include targeting domains comprising, e.g., consisting of, SEQ ID NO: 336 and SEQ ID NO: 199, respectively. In an aspect, the first gRNA molecule and the second gRNA molecule include targeting domains comprising, e.g., consisting of, SEQ ID NO: 336 and SEQ ID NO: 251, respectively. In an aspect, the first gRNA molecule and the second gRNA molecule include targeting domains comprising, e.g., consisting of, SEQ ID NO: 336 and SEQ ID NO: 250, respectively. In an aspect, the first gRNA molecule and the second gRNA molecule include targeting domains comprising, e.g., consisting of, SEQ ID NO: 336 and SEQ ID NO: 334, respectively. In an aspect, the first gRNA molecule and the second gRNA molecule include targeting domains comprising, e.g., consisting of, SEQ ID NO: 336 and SEQ ID NO: 185, respectively. In an aspect, the first gRNA molecule and the second gRNA molecule include targeting domains comprising, e.g., consisting of, SEQ ID NO: 336 and SEQ ID NO: 186, respectively. In an aspect, the first gRNA molecule and the second gRNA molecule include targeting domains comprising, e.g., consisting of, SEQ ID NO: 336 and SEQ ID NO: 337, respectively. In an aspect, the first gRNA molecule and the second gRNA molecule include targeting domains comprising, e.g., consisting of, SEQ ID NO: 337 and SEQ ID NO: 244, respectively. In an aspect, the first gRNA molecule and the second gRNA molecule include targeting domains comprising, e.g., consisting of, SEQ ID NO: 337 and SEQ ID NO: 199, respectively. In an aspect, the first gRNA molecule and the second gRNA molecule include targeting domains comprising, e.g., consisting of, SEQ ID NO: 337 and SEQ ID NO: 251, respectively. In an aspect, the

first gRNA molecule and the second gRNA molecule include targeting domains comprising, e.g., consisting of, SEQ ID NO: 337 and SEQ ID NO: 250, respectively. In an aspect, the first gRNA molecule and the second gRNA molecule include targeting domains comprising, e.g., consisting of, SEQ ID NO: 337 and SEQ ID NO: 334, respectively. In an aspect, the first gRNA molecule and the second gRNA molecule include targeting domains comprising, e.g., consisting of, SEQ ID NO: 337 and SEQ ID NO: 185, respectively. In an aspect, the first gRNA molecule and the second gRNA molecule include targeting domains comprising, e.g., consisting of, SEQ ID NO: 337 and SEQ ID NO: 186, respectively. In an aspect, the first gRNA molecule and the second gRNA molecule include targeting domains comprising, e.g., consisting of, SEQ ID NO: 337 and SEQ ID NO: 336, respectively. In an aspect, the first gRNA molecule and the second gRNA molecule include targeting domains comprising, e.g., consisting of, SEQ ID NO: 337 and SEQ ID NO: 246, respectively. In an aspect, the first gRNA molecule and the second gRNA molecule include targeting domains comprising, e.g., consisting of, SEQ ID NO: 337 and SEQ ID NO: 248, respectively. In an aspect, the first gRNA molecule and the second gRNA molecule include targeting domains comprising, e.g., consisting of, SEQ ID NO: 337 and SEQ ID NO: 247, respectively. In an aspect, the first gRNA molecule and the second gRNA molecule include targeting domains comprising, e.g., consisting of, SEQ ID NO: 337 and SEQ ID NO: 245, respectively. In an aspect, the first gRNA molecule and the second gRNA molecule include targeting domains comprising, e.g., consisting of, SEQ ID NO: 337 and SEQ ID NO: 249, respectively. In an aspect, the first gRNA molecule and the second gRNA molecule include targeting domains comprising, e.g., consisting of, SEQ ID NO: 337 and SEQ ID NO: 244, respectively. In an aspect, the first gRNA molecule and the second gRNA molecule include targeting domains comprising, e.g., consisting of, SEQ ID NO: 337 and SEQ ID NO: 199, respectively. In an aspect, the first gRNA molecule and the second gRNA molecule include targeting domains comprising, e.g., consisting of, SEQ ID NO: 337 and SEQ ID NO: 251, respectively. In an aspect, the first gRNA molecule and the second gRNA molecule include targeting domains comprising, e.g., consisting of, SEQ ID NO: 337 and SEQ ID NO: 250, respectively. In an aspect, the first gRNA molecule and the second gRNA molecule include targeting domains comprising, e.g., consisting of, SEQ ID NO: 337 and SEQ ID NO: 334, respectively. In an aspect, the first gRNA molecule and the second gRNA molecule include targeting domains comprising, e.g., consisting of, SEQ ID NO: 337 and SEQ ID NO: 185, respectively. In an aspect, the first gRNA molecule and the second gRNA molecule include targeting domains comprising, e.g., consisting of, SEQ ID NO: 337 and SEQ ID NO: 186, respectively. In an aspect, the first gRNA molecule and the second gRNA molecule include targeting domains comprising, e.g., consisting of, SEQ ID NO: 337 and SEQ ID NO: 336, respectively.

In embodiments, the aspects of the invention relate to or incorporate a gRNA molecule that is complementary to a target sequence within the +58 enhancer region of the BCL11a gene which is

disposed 3' to the GATA-1 binding site, e.g., 3' to the GATA1 binding site and TAL-1 binding site. In embodiments, the CRISPR system comprising a gRNA molecule described herein induces one or more indels at or near the target site. In embodiments, the indel does not comprise a nucleotide of a GATA-1 binding site and/or does not comprise a nucleotide of a TAL-1 binding site. In embodiments, the CRISPR system induces one or more frameshift indels at or near the target site, e.g., at an overall frameshift indel rate of at least about 10%, at least about 20%, at least about 30%, at least about 40%, or at least about 50%, e.g., as measured by NGS. In embodiments, the overall indel rate is at least about 70%, at least about 80%, at least about 90%, or at least about 95%, e.g., as measured by NGS.

Table 8: Preferred Guide RNA Targeting Domains directed to the +62 Enhancer Region of the BCL11a Gene (i.e., to a BCL11a Enhancer)

Id.	Exon/ Feature	Strand	Targeting domain	Locations	SEQ ID NO:
CR00171	62	-	AGCUCUGGAAUGAUGGCUUA	Chr2:60490354-60490376	278
CR00172	62	-	AUUGUGGAGCUCUGGAAUGA	Chr2:60490361-60490383	279
CR00173	62	-	CUGGAAUAGAAAAUUGGAGU	Chr2:60490384-60490406	280
CR00174	62	-	UGGGUACGGGGAACUAAGAC	Chr2:60490403-60490425	281
CR00175	62	+	UUAGUUCCCCGUACCCAUCA	Chr2:60490409-60490431	282
CR00176	62	-	UAUUUUCCUUGAUGGGUACG	Chr2:60490415-60490437	283
CR00177	62	-	AUAUUUUCCUUGAUGGGUAC	Chr2:60490416-60490438	284
CR00178	62	-	AAUAUUUUCCUUGAUGGGUA	Chr2:60490417-60490439	285
CR00179	62	-	GGAAGGAAAUGAGAACGGAA	Chr2:60490456-60490478	286
CR00180	62	-	AGGAAGGAAAUGAGAACGGA	Chr2:60490457-60490479	287
CR00181	62	+	AUACUUCAAGGCCUCAAUGA	Chr2:60490520-60490542	288
CR00182	62	-	GACUAGGUAGACCUUCAUUG	Chr2:60490531-60490553	289
CR00183	62	-	UUCUUCUUGCUAAGGUGACU	Chr2:60490547-60490569	290
CR00184	62	-	GAGAUUGAUUCUUCUUGCUA	Chr2:60490555-60490577	291
CR00185	62	-	GUGUUCUAUGAGGUUGGAGA	Chr2:60490580-60490602	292
CR00186	62	-	GGAUGAGUGUUCUAUGAGGU	Chr2:60490586-60490608	293
CR00187	62	-	CAUGGGAUGAGUGUUCUAUG	Chr2:60490590-60490612	294
CR00188	62	-	UGAGUCAGGGAGUGGUGCAU	Chr2:60490607-60490629	295
CR00189	62	-	AUGAGUCAGGGAGUGGUGCA	Chr2:60490608-60490630	296
CR00190	62	+	CCACUCCCUGACUCAUAUCU	Chr2:60490615-60490637	297
CR00191	62	-	UAAGGCCUAGAUAUGAGUCA	Chr2:60490620-60490642	298
CR00192	62	-	GUAAGGCCUAGAUAUGAGUC	Chr2:60490621-60490643	299

CR00193	62	+	AUAUCUAGGCCUUACAUUGC	Chr2:60490629-60490651	300
CR00194	62	-	AAAUUAAUUAGAGGCAUAGA	Chr2:60490656-60490678	301
CR00195	62	-	GAAAUUAAUUAGAGGCAUAG	Chr2:60490657-60490679	302
CR00196	62	-	GAACACAUGAAAUUAAUUAG	Chr2:60490665-60490687	303
CR00197	62	+	CCAAUGAGUUUCUUCAAUAC	Chr2:60490688-60490710	304
CR00198	62	-	CAAAUAUAAUAGAAGCAAGU	Chr2:60490721-60490743	305
CR00199	62	-	AAAUAACUUCCCUUUUAGGA	Chr2:60490821-60490843	306
CR00200	62	-	GGAAAAAUAACUUCCCUUUU	Chr2:60490825-60490847	307
CR00201	62	-	UUUUGAACAGAAAUGAUAUU	Chr2:60490846-60490868	308
CR00202	62	-	AGUUCAAGUAGAUAUCAGAA	Chr2:60490905-60490927	309
CR00203	62	-	AAGUUCAAGUAGAUAUCAGA	Chr2:60490906-60490928	310
CR00204	62	-	GGGUGGCUGUUUAAAGAGGG	Chr2:60490994-60491016	311
CR00205	62	-	GUGGGGUGGCUGUUUAAAGA	Chr2:60490997-60491019	312
CR00206	62	-	UGUGGGGUGGCUGUUUAAAG	Chr2:60490998-60491020	313
CR00207	62	+	UGCCAACCAGACUGUGCGCC	Chr2:60491051-60491073	314
CR00208	62	-	AACCUGGCGCACAGUCUGGU	Chr2:60491053-60491075	315
CR00209	62	+	AACCAGACUGUGCGCCAGGU	Chr2:60491055-60491077	316
CR00210	62	-	UACCAACCUGGCGCACAGUC	Chr2:60491057-60491079	317
CR00211	62	-	UCUGUCAGACUUUACCAACC	Chr2:60491069-60491091	318
CR00212	62	+	AUAUGUGAAGCCCAACUACG	Chr2:60491118-60491140	319
CR00213	62	-	AGUUGCACAACCACGUAGUU	Chr2:60491128-60491150	320
CR00214	62	-	GAGUUGCACAACCACGUAGU	Chr2:60491129-60491151	321
CR00215	62	+	CUAUAGCUGACUUUCAACCA	Chr2:60491151-60491173	322
CR00216	62	-	AACUUCUUUGCAGAUGACCA	Chr2:60491168-60491190	323
CR00217	62	-	UUGCAUUGAGGAUGCGCAGG	Chr2:60491199-60491221	324
CR00218	62	-	UUUUUGCAUUGAGGAUGCGC	Chr2:60491202-60491224	325
CR00221	62	+	GACCUCAUUUUGAUGCCAGA	Chr2:60491281-60491303	326
CR00222	62	-	UGCCCUCUGGCAUCAAAAUG	Chr2:60491283-60491305	327
CR00223	62	+	AUGCCAGAGGGCAGCAAACA	Chr2:60491293-60491315	328
CR00224	62	-	CUGUACUUAAUAGCUGAAGG	Chr2:60491326-60491348	329
CR00225	62	-	ACUGUACUUAAUAGCUGAAG	Chr2:60491327-60491349	330
CR00227	62	+	CAGCUAUUAAGUACAGUAAA	Chr2:60491333-60491355	331
CR00228	62	-	GAGCAUUUCAAAUGAUAGUU	Chr2:60491360-60491382	332
CR00229	62	+	CAUUUGAAAUGCUCCCGGCC	Chr2:60491369-60491391	333

In some aspects of the invention, it is preferred that the gRNA molecule to the +62 Enhancer region of BCL11a comprise a targeting domain of a gRNA listed in Figure 12. In an aspect, the gRNA molecule includes a targeting domain comprising, e.g., consisting of, SEQ ID NO: 318. In an aspect, the gRNA molecule includes a targeting domain comprising, e.g., consisting of, SEQ ID NO: 312. In an aspect, the gRNA molecule includes a targeting domain comprising, e.g., consisting of, SEQ ID NO: 313. In an aspect, the gRNA molecule includes a targeting domain comprising, e.g., consisting of, SEQ ID NO: 294. In an aspect, the gRNA molecule includes a targeting domain comprising, e.g., consisting of, SEQ ID NO: 310. In an aspect, the gRNA molecule includes a targeting domain comprising, e.g., consisting of, SEQ ID NO: 319. In an aspect, the gRNA molecule includes a targeting domain comprising, e.g., consisting of, SEQ ID NO: 298. In an aspect, the gRNA molecule includes a targeting domain comprising, e.g., consisting of, SEQ ID NO: 322. In an aspect, the gRNA molecule includes a targeting domain comprising, e.g., consisting of, SEQ ID NO: 311. In an aspect, the gRNA molecule includes a targeting domain comprising, e.g., consisting of, SEQ ID NO: 315. In an aspect, the gRNA molecule includes a targeting domain comprising, e.g., consisting of, SEQ ID NO: 290. In an aspect, the gRNA molecule includes a targeting domain comprising, e.g., consisting of, SEQ ID NO: 317. In an aspect, the gRNA molecule includes a targeting domain comprising, e.g., consisting of, SEQ ID NO: 309. In an aspect, the gRNA molecule includes a targeting domain comprising, e.g., consisting of, SEQ ID NO: 289. In an aspect, the gRNA molecule includes a targeting domain comprising, e.g., consisting of, SEQ ID NO: 281.

In some aspects of the invention, e.g., as indicated herein, it may be beneficial to include gRNA moleucles targeting more than one, e.g., two, target sites (e.g., a first gRNA molecule and a second gRNA molecule). In some embodiments, the two target sites are both located in the +62 BCL11a enhancer region. In such aspects, any combination of more than one, e.g., two, gRNA molecules (e.g., a first gRNA molecule and a second gRNA molecule) comprising targeting domains listed in Table 8 may be used. In an aspect, the first gRNA molecule and the second gRNA molecule include targeting domains comprising, e.g., consisting of, SEQ ID NO: 318 and SEQ ID NO: 312, respectively. In an aspect, the first gRNA molecule and the second gRNA molecule include targeting domains comprising, e.g., consisting of, SEQ ID NO: 318 and SEQ ID NO: 313, respectively. In an aspect, the first gRNA molecule and the second gRNA molecule include targeting domains comprising, e.g., consisting of, SEQ ID NO: 318 and SEQ ID NO: 294, respectively. In an aspect, the first gRNA molecule and the second gRNA molecule include targeting domains comprising, e.g., consisting of, SEQ ID NO: 318 and SEQ ID NO: 310, respectively. In an aspect, the first gRNA molecule and the second gRNA molecule include targeting domains comprising, e.g., consisting of, SEQ ID NO: 318 and SEQ ID NO: 319, respectively. In an aspect, the first gRNA molecule and the second gRNA molecule include targeting domains comprising, e.g., consisting of, SEQ ID NO: 318 and SEQ ID NO: 298, respectively. In an aspect, the first gRNA molecule and the second gRNA

molecule include targeting domains comprising, e.g., consisting of, SEQ ID NO: 318 and SEQ ID NO: 322, respectively. In an aspect, the first gRNA molecule and the second gRNA molecule include targeting domains comprising, e.g., consisting of, SEQ ID NO: 318 and SEQ ID NO: 311, respectively. In an aspect, the first gRNA molecule and the second gRNA molecule include targeting domains comprising, e.g., consisting of, SEQ ID NO: 318 and SEQ ID NO: 315, respectively. In an aspect, the first gRNA molecule and the second gRNA molecule include targeting domains comprising, e.g., consisting of, SEQ ID NO: 318 and SEQ ID NO: 290, respectively. In an aspect, the first gRNA molecule and the second gRNA molecule include targeting domains comprising, e.g., consisting of, SEQ ID NO: 318 and SEQ ID NO: 317, respectively. In an aspect, the first gRNA molecule and the second gRNA molecule include targeting domains comprising, e.g., consisting of, SEQ ID NO: 318 and SEQ ID NO: 309, respectively. In an aspect, the first gRNA molecule and the second gRNA molecule include targeting domains comprising, e.g., consisting of, SEQ ID NO: 318 and SEQ ID NO: 289, respectively. In an aspect, the first gRNA molecule and the second gRNA molecule include targeting domains comprising, e.g., consisting of, SEQ ID NO: 318 and SEQ ID NO: 281, respectively. In an aspect, the first gRNA molecule and the second gRNA molecule include targeting domains comprising, e.g., consisting of, SEQ ID NO: 312 and SEQ ID NO: 313, respectively. In an aspect, the first gRNA molecule and the second gRNA molecule include targeting domains comprising, e.g., consisting of, SEQ ID NO: 312 and SEQ ID NO: 294, respectively. In an aspect, the first gRNA molecule and the second gRNA molecule include targeting domains comprising, e.g., consisting of, SEQ ID NO: 312 and SEQ ID NO: 310, respectively. In an aspect, the first gRNA molecule and the second gRNA molecule include targeting domains comprising, e.g., consisting of, SEQ ID NO: 312 and SEQ ID NO: 319, respectively. In an aspect, the first gRNA molecule and the second gRNA molecule include targeting domains comprising, e.g., consisting of, SEQ ID NO: 312 and SEQ ID NO: 298, respectively. In an aspect, the first gRNA molecule and the second gRNA molecule include targeting domains comprising, e.g., consisting of, SEQ ID NO: 312 and SEQ ID NO: 322, respectively. In an aspect, the first gRNA molecule and the second gRNA molecule include targeting domains comprising, e.g., consisting of, SEQ ID NO: 312 and SEQ ID NO: 311, respectively. In an aspect, the first gRNA molecule and the second gRNA molecule include targeting domains comprising, e.g., consisting of, SEQ ID NO: 312 and SEQ ID NO: 315, respectively. In an aspect, the first gRNA molecule and the second gRNA molecule include targeting domains comprising, e.g., consisting of, SEQ ID NO: 312 and SEQ ID NO: 290, respectively. In an aspect, the first gRNA molecule and the second gRNA molecule include targeting domains comprising, e.g., consisting of, SEQ ID NO: 312 and SEQ ID NO: 317, respectively. In an aspect, the first gRNA molecule and the second gRNA molecule include targeting domains comprising, e.g., consisting of, SEQ ID NO: 312 and SEQ ID NO: 309, respectively. In an aspect, the first gRNA molecule and the second gRNA molecule include targeting domains comprising, e.g., consisting of, SEQ ID NO: 312 and SEQ ID NO: 289, respectively. In an aspect, the first gRNA molecule and the

second gRNA molecule include targeting domains comprising, e.g., consisting of, SEQ ID NO: 312 and SEQ ID NO: 281, respectively. In an aspect, the first gRNA molecule and the second gRNA molecule include targeting domains comprising, e.g., consisting of, SEQ ID NO: 313 and SEQ ID NO: 312, respectively. In an aspect, the first gRNA molecule and the second gRNA molecule include targeting domains comprising, e.g., consisting of, SEQ ID NO: 313 and SEQ ID NO: 294, respectively. In an aspect, the first gRNA molecule and the second gRNA molecule include targeting domains comprising, e.g., consisting of, SEQ ID NO: 313 and SEQ ID NO: 310, respectively. In an aspect, the first gRNA molecule and the second gRNA molecule include targeting domains comprising, e.g., consisting of, SEQ ID NO: 313 and SEQ ID NO: 319, respectively. In an aspect, the first gRNA molecule and the second gRNA molecule include targeting domains comprising, e.g., consisting of, SEQ ID NO: 313 and SEQ ID NO: 298, respectively. In an aspect, the first gRNA molecule and the second gRNA molecule include targeting domains comprising, e.g., consisting of, SEQ ID NO: 313 and SEQ ID NO: 322, respectively. In an aspect, the first gRNA molecule and the second gRNA molecule include targeting domains comprising, e.g., consisting of, SEQ ID NO: 313 and SEQ ID NO: 311, respectively. In an aspect, the first gRNA molecule and the second gRNA molecule include targeting domains comprising, e.g., consisting of, SEQ ID NO: 313 and SEQ ID NO: 315, respectively. In an aspect, the first gRNA molecule and the second gRNA molecule include targeting domains comprising, e.g., consisting of, SEQ ID NO: 313 and SEQ ID NO: 290, respectively. In an aspect, the first gRNA molecule and the second gRNA molecule include targeting domains comprising, e.g., consisting of, SEQ ID NO: 313 and SEQ ID NO: 317, respectively. In an aspect, the first gRNA molecule and the second gRNA molecule include targeting domains comprising, e.g., consisting of, SEQ ID NO: 313 and SEQ ID NO: 309, respectively. In an aspect, the first gRNA molecule and the second gRNA molecule include targeting domains comprising, e.g., consisting of, SEQ ID NO: 313 and SEQ ID NO: 289, respectively. In an aspect, the first gRNA molecule and the second gRNA molecule include targeting domains comprising, e.g., consisting of, SEQ ID NO: 313 and SEQ ID NO: 281, respectively. In an aspect, the first gRNA molecule and the second gRNA molecule include targeting domains comprising, e.g., consisting of, SEQ ID NO: 294 and SEQ ID NO: 312, respectively. In an aspect, the first gRNA molecule and the second gRNA molecule include targeting domains comprising, e.g., consisting of, SEQ ID NO: 294 and SEQ ID NO: 313, respectively. In an aspect, the first gRNA molecule and the second gRNA molecule include targeting domains comprising, e.g., consisting of, SEQ ID NO: 294 and SEQ ID NO: 310, respectively. In an aspect, the first gRNA molecule and the second gRNA molecule include targeting domains comprising, e.g., consisting of, SEQ ID NO: 294 and SEQ ID NO: 319, respectively. In an aspect, the first gRNA molecule and the second gRNA molecule include targeting domains comprising, e.g., consisting of, SEQ ID NO: 294 and SEQ ID NO: 298, respectively. In an aspect, the first gRNA molecule and the second gRNA molecule include targeting domains comprising, e.g., consisting of, SEQ ID NO: 294 and SEQ ID NO: 322, respectively. In an aspect, the first gRNA

molecule and the second gRNA molecule include targeting domains comprising, e.g., consisting of, SEQ ID NO: 294 and SEQ ID NO: 311, respectively. In an aspect, the first gRNA molecule and the second gRNA molecule include targeting domains comprising, e.g., consisting of, SEQ ID NO: 294 and SEQ ID NO: 315, respectively. In an aspect, the first gRNA molecule and the second gRNA molecule include targeting domains comprising, e.g., consisting of, SEQ ID NO: 294 and SEQ ID NO: 290, respectively. In an aspect, the first gRNA molecule and the second gRNA molecule include targeting domains comprising, e.g., consisting of, SEQ ID NO: 294 and SEQ ID NO: 317, respectively. In an aspect, the first gRNA molecule and the second gRNA molecule include targeting domains comprising, e.g., consisting of, SEQ ID NO: 294 and SEQ ID NO: 309, respectively. In an aspect, the first gRNA molecule and the second gRNA molecule include targeting domains comprising, e.g., consisting of, SEQ ID NO: 294 and SEQ ID NO: 289, respectively. In an aspect, the first gRNA molecule and the second gRNA molecule include targeting domains comprising, e.g., consisting of, SEQ ID NO: 294 and SEQ ID NO: 281, respectively. In an aspect, the first gRNA molecule and the second gRNA molecule include targeting domains comprising, e.g., consisting of, SEQ ID NO: 310 and SEQ ID NO: 312, respectively. In an aspect, the first gRNA molecule and the second gRNA molecule include targeting domains comprising, e.g., consisting of, SEQ ID NO: 310 and SEQ ID NO: 313, respectively. In an aspect, the first gRNA molecule and the second gRNA molecule include targeting domains comprising, e.g., consisting of, SEQ ID NO: 310 and SEQ ID NO: 294, respectively. In an aspect, the first gRNA molecule and the second gRNA molecule include targeting domains comprising, e.g., consisting of, SEQ ID NO: 310 and SEQ ID NO: 319, respectively. In an aspect, the first gRNA molecule and the second gRNA molecule include targeting domains comprising, e.g., consisting of, SEQ ID NO: 310 and SEQ ID NO: 298, respectively. In an aspect, the first gRNA molecule and the second gRNA molecule include targeting domains comprising, e.g., consisting of, SEQ ID NO: 310 and SEQ ID NO: 322, respectively. In an aspect, the first gRNA molecule and the second gRNA molecule include targeting domains comprising, e.g., consisting of, SEQ ID NO: 310 and SEQ ID NO: 311, respectively. In an aspect, the first gRNA molecule and the second gRNA molecule include targeting domains comprising, e.g., consisting of, SEQ ID NO: 310 and SEQ ID NO: 315, respectively. In an aspect, the first gRNA molecule and the second gRNA molecule include targeting domains comprising, e.g., consisting of, SEQ ID NO: 310 and SEQ ID NO: 290, respectively. In an aspect, the first gRNA molecule and the second gRNA molecule include targeting domains comprising, e.g., consisting of, SEQ ID NO: 310 and SEQ ID NO: 317, respectively. In an aspect, the first gRNA molecule and the second gRNA molecule include targeting domains comprising, e.g., consisting of, SEQ ID NO: 310 and SEQ ID NO: 309, respectively. In an aspect, the first gRNA molecule and the second gRNA molecule include targeting domains comprising, e.g., consisting of, SEQ ID NO: 310 and SEQ ID NO: 289, respectively. In an aspect, the first gRNA molecule and the second gRNA molecule include targeting domains comprising, e.g., consisting of, SEQ ID NO: 310 and SEQ ID NO: 281, respectively. In an aspect, the

first gRNA molecule and the second gRNA molecule include targeting domains comprising, e.g., consisting of, SEQ ID NO: 319 and SEQ ID NO: 312, respectively. In an aspect, the first gRNA molecule and the second gRNA molecule include targeting domains comprising, e.g., consisting of, SEQ ID NO: 319 and SEQ ID NO: 313, respectively. In an aspect, the first gRNA molecule and the second gRNA molecule include targeting domains comprising, e.g., consisting of, SEQ ID NO: 319 and SEQ ID NO: 294, respectively. In an aspect, the first gRNA molecule and the second gRNA molecule include targeting domains comprising, e.g., consisting of, SEQ ID NO: 319 and SEQ ID NO: 310, respectively. In an aspect, the first gRNA molecule and the second gRNA molecule include targeting domains comprising, e.g., consisting of, SEQ ID NO: 319 and SEQ ID NO: 298, respectively. In an aspect, the first gRNA molecule and the second gRNA molecule include targeting domains comprising, e.g., consisting of, SEQ ID NO: 319 and SEQ ID NO: 322, respectively. In an aspect, the first gRNA molecule and the second gRNA molecule include targeting domains comprising, e.g., consisting of, SEQ ID NO: 319 and SEQ ID NO: 311, respectively. In an aspect, the first gRNA molecule and the second gRNA molecule include targeting domains comprising, e.g., consisting of, SEQ ID NO: 319 and SEQ ID NO: 315, respectively. In an aspect, the first gRNA molecule and the second gRNA molecule include targeting domains comprising, e.g., consisting of, SEQ ID NO: 319 and SEQ ID NO: 290, respectively. In an aspect, the first gRNA molecule and the second gRNA molecule include targeting domains comprising, e.g., consisting of, SEQ ID NO: 319 and SEQ ID NO: 317, respectively. In an aspect, the first gRNA molecule and the second gRNA molecule include targeting domains comprising, e.g., consisting of, SEQ ID NO: 319 and SEQ ID NO: 309, respectively. In an aspect, the first gRNA molecule and the second gRNA molecule include targeting domains comprising, e.g., consisting of, SEQ ID NO: 319 and SEQ ID NO: 289, respectively. In an aspect, the first gRNA molecule and the second gRNA molecule include targeting domains comprising, e.g., consisting of, SEQ ID NO: 319 and SEQ ID NO: 281, respectively. In an aspect, the first gRNA molecule and the second gRNA molecule include targeting domains comprising, e.g., consisting of, SEQ ID NO: 298 and SEQ ID NO: 312, respectively. In an aspect, the first gRNA molecule and the second gRNA molecule include targeting domains comprising, e.g., consisting of, SEQ ID NO: 298 and SEQ ID NO: 313, respectively. In an aspect, the first gRNA molecule and the second gRNA molecule include targeting domains comprising, e.g., consisting of, SEQ ID NO: 298 and SEQ ID NO: 294, respectively. In an aspect, the first gRNA molecule and the second gRNA molecule include targeting domains comprising, e.g., consisting of, SEQ ID NO: 298 and SEQ ID NO: 310, respectively. In an aspect, the first gRNA molecule and the second gRNA molecule include targeting domains comprising, e.g., consisting of, SEQ ID NO: 298 and SEQ ID NO: 319, respectively. In an aspect, the first gRNA molecule and the second gRNA molecule include targeting domains comprising, e.g., consisting of, SEQ ID NO: 298 and SEQ ID NO: 322, respectively. In an aspect, the first gRNA molecule and the second gRNA molecule include targeting domains comprising, e.g., consisting of, SEQ ID NO: 298 and SEQ ID NO: 311, respectively. In an

aspect, the first gRNA molecule and the second gRNA molecule include targeting domains comprising, e.g., consisting of, SEQ ID NO: 298 and SEQ ID NO: 315, respectively. In an aspect, the first gRNA molecule and the second gRNA molecule include targeting domains comprising, e.g., consisting of, SEQ ID NO: 298 and SEQ ID NO: 290, respectively. In an aspect, the first gRNA molecule and the second gRNA molecule include targeting domains comprising, e.g., consisting of, SEQ ID NO: 298 and SEQ ID NO: 317, respectively. In an aspect, the first gRNA molecule and the second gRNA molecule include targeting domains comprising, e.g., consisting of, SEQ ID NO: 298 and SEQ ID NO: 309, respectively. In an aspect, the first gRNA molecule and the second gRNA molecule include targeting domains comprising, e.g., consisting of, SEQ ID NO: 298 and SEQ ID NO: 289, respectively. In an aspect, the first gRNA molecule and the second gRNA molecule include targeting domains comprising, e.g., consisting of, SEQ ID NO: 298 and SEQ ID NO: 281, respectively. In an aspect, the first gRNA molecule and the second gRNA molecule include targeting domains comprising, e.g., consisting of, SEQ ID NO: 322 and SEQ ID NO: 312, respectively. In an aspect, the first gRNA molecule and the second gRNA molecule include targeting domains comprising, e.g., consisting of, SEQ ID NO: 322 and SEQ ID NO: 313, respectively. In an aspect, the first gRNA molecule and the second gRNA molecule include targeting domains comprising, e.g., consisting of, SEQ ID NO: 322 and SEQ ID NO: 294, respectively. In an aspect, the first gRNA molecule and the second gRNA molecule include targeting domains comprising, e.g., consisting of, SEQ ID NO: 322 and SEQ ID NO: 310, respectively. In an aspect, the first gRNA molecule and the second gRNA molecule include targeting domains comprising, e.g., consisting of, SEQ ID NO: 322 and SEQ ID NO: 319, respectively. In an aspect, the first gRNA molecule and the second gRNA molecule include targeting domains comprising, e.g., consisting of, SEQ ID NO: 322 and SEQ ID NO: 298, respectively. In an aspect, the first gRNA molecule and the second gRNA molecule include targeting domains comprising, e.g., consisting of, SEQ ID NO: 322 and SEQ ID NO: 311, respectively. In an aspect, the first gRNA molecule and the second gRNA molecule include targeting domains comprising, e.g., consisting of, SEQ ID NO: 322 and SEQ ID NO: 315, respectively. In an aspect, the first gRNA molecule and the second gRNA molecule include targeting domains comprising, e.g., consisting of, SEQ ID NO: 322 and SEQ ID NO: 290, respectively. In an aspect, the first gRNA molecule and the second gRNA molecule include targeting domains comprising, e.g., consisting of, SEQ ID NO: 322 and SEQ ID NO: 317, respectively. In an aspect, the first gRNA molecule and the second gRNA molecule include targeting domains comprising, e.g., consisting of, SEQ ID NO: 322 and SEQ ID NO: 309, respectively. In an aspect, the first gRNA molecule and the second gRNA molecule include targeting domains comprising, e.g., consisting of, SEQ ID NO: 322 and SEQ ID NO: 289, respectively. In an aspect, the first gRNA molecule and the second gRNA molecule include targeting domains comprising, e.g., consisting of, SEQ ID NO: 322 and SEQ ID NO: 281, respectively. In an aspect, the first gRNA molecule and the second gRNA molecule include targeting domains comprising, e.g., consisting of, SEQ ID NO: 311 and SEQ ID NO: 312,

respectively. In an aspect, the first gRNA molecule and the second gRNA molecule include targeting domains comprising, e.g., consisting of, SEQ ID NO: 311 and SEQ ID NO: 313, respectively. In an aspect, the first gRNA molecule and the second gRNA molecule include targeting domains comprising, e.g., consisting of, SEQ ID NO: 311 and SEQ ID NO: 294, respectively. In an aspect, the first gRNA molecule and the second gRNA molecule include targeting domains comprising, e.g., consisting of, SEQ ID NO: 311 and SEQ ID NO: 310, respectively. In an aspect, the first gRNA molecule and the second gRNA molecule include targeting domains comprising, e.g., consisting of, SEQ ID NO: 311 and SEQ ID NO: 319, respectively. In an aspect, the first gRNA molecule and the second gRNA molecule include targeting domains comprising, e.g., consisting of, SEQ ID NO: 311 and SEQ ID NO: 298, respectively. In an aspect, the first gRNA molecule and the second gRNA molecule include targeting domains comprising, e.g., consisting of, SEQ ID NO: 311 and SEQ ID NO: 322, respectively. In an aspect, the first gRNA molecule and the second gRNA molecule include targeting domains comprising, e.g., consisting of, SEQ ID NO: 311 and SEQ ID NO: 315, respectively. In an aspect, the first gRNA molecule and the second gRNA molecule include targeting domains comprising, e.g., consisting of, SEQ ID NO: 311 and SEQ ID NO: 290, respectively. In an aspect, the first gRNA molecule and the second gRNA molecule include targeting domains comprising, e.g., consisting of, SEQ ID NO: 311 and SEQ ID NO: 317, respectively. In an aspect, the first gRNA molecule and the second gRNA molecule include targeting domains comprising, e.g., consisting of, SEQ ID NO: 311 and SEQ ID NO: 309, respectively. In an aspect, the first gRNA molecule and the second gRNA molecule include targeting domains comprising, e.g., consisting of, SEQ ID NO: 311 and SEQ ID NO: 289, respectively. In an aspect, the first gRNA molecule and the second gRNA molecule include targeting domains comprising, e.g., consisting of, SEQ ID NO: 311 and SEQ ID NO: 281, respectively. In an aspect, the first gRNA molecule and the second gRNA molecule include targeting domains comprising, e.g., consisting of, SEQ ID NO: 315 and SEQ ID NO: 312, respectively. In an aspect, the first gRNA molecule and the second gRNA molecule include targeting domains comprising, e.g., consisting of, SEQ ID NO: 315 and SEQ ID NO: 313, respectively. In an aspect, the first gRNA molecule and the second gRNA molecule include targeting domains comprising, e.g., consisting of, SEQ ID NO: 315 and SEQ ID NO: 294, respectively. In an aspect, the first gRNA molecule and the second gRNA molecule include targeting domains comprising, e.g., consisting of, SEQ ID NO: 315 and SEQ ID NO: 310, respectively. In an aspect, the first gRNA molecule and the second gRNA molecule include targeting domains comprising, e.g., consisting of, SEQ ID NO: 315 and SEQ ID NO: 319, respectively. In an aspect, the first gRNA molecule and the second gRNA molecule include targeting domains comprising, e.g., consisting of, SEQ ID NO: 315 and SEQ ID NO: 298, respectively. In an aspect, the first gRNA molecule and the second gRNA molecule include targeting domains comprising, e.g., consisting of, SEQ ID NO: 315 and SEQ ID NO: 322, respectively. In an aspect, the first gRNA molecule and the second gRNA molecule include targeting domains comprising, e.g., consisting of, SEQ ID NO: 315 and SEQ ID

NO: 311, respectively. In an aspect, the first gRNA molecule and the second gRNA molecule include targeting domains comprising, e.g., consisting of, SEQ ID NO: 315 and SEQ ID NO: 290, respectively. In an aspect, the first gRNA molecule and the second gRNA molecule include targeting domains comprising, e.g., consisting of, SEQ ID NO: 315 and SEQ ID NO: 317, respectively. In an aspect, the first gRNA molecule and the second gRNA molecule include targeting domains comprising, e.g., consisting of, SEQ ID NO: 315 and SEQ ID NO: 309, respectively. In an aspect, the first gRNA molecule and the second gRNA molecule include targeting domains comprising, e.g., consisting of, SEQ ID NO: 315 and SEQ ID NO: 289, respectively. In an aspect, the first gRNA molecule and the second gRNA molecule include targeting domains comprising, e.g., consisting of, SEQ ID NO: 315 and SEQ ID NO: 281, respectively. In an aspect, the first gRNA molecule and the second gRNA molecule include targeting domains comprising, e.g., consisting of, SEQ ID NO: 290 and SEQ ID NO: 312, respectively. In an aspect, the first gRNA molecule and the second gRNA molecule include targeting domains comprising, e.g., consisting of, SEQ ID NO: 290 and SEQ ID NO: 313, respectively. In an aspect, the first gRNA molecule and the second gRNA molecule include targeting domains comprising, e.g., consisting of, SEQ ID NO: 290 and SEQ ID NO: 294, respectively. In an aspect, the first gRNA molecule and the second gRNA molecule include targeting domains comprising, e.g., consisting of, SEQ ID NO: 290 and SEQ ID NO: 310, respectively. In an aspect, the first gRNA molecule and the second gRNA molecule include targeting domains comprising, e.g., consisting of, SEQ ID NO: 290 and SEQ ID NO: 319, respectively. In an aspect, the first gRNA molecule and the second gRNA molecule include targeting domains comprising, e.g., consisting of, SEQ ID NO: 290 and SEQ ID NO: 298, respectively. In an aspect, the first gRNA molecule and the second gRNA molecule include targeting domains comprising, e.g., consisting of, SEQ ID NO: 290 and SEQ ID NO: 322, respectively. In an aspect, the first gRNA molecule and the second gRNA molecule include targeting domains comprising, e.g., consisting of, SEQ ID NO: 290 and SEQ ID NO: 311, respectively. In an aspect, the first gRNA molecule and the second gRNA molecule include targeting domains comprising, e.g., consisting of, SEQ ID NO: 290 and SEQ ID NO: 315, respectively. In an aspect, the first gRNA molecule and the second gRNA molecule include targeting domains comprising, e.g., consisting of, SEQ ID NO: 290 and SEQ ID NO: 317, respectively. In an aspect, the first gRNA molecule and the second gRNA molecule include targeting domains comprising, e.g., consisting of, SEQ ID NO: 290 and SEQ ID NO: 309, respectively. In an aspect, the first gRNA molecule and the second gRNA molecule include targeting domains comprising, e.g., consisting of, SEQ ID NO: 290 and SEQ ID NO: 289, respectively. In an aspect, the first gRNA molecule and the second gRNA molecule include targeting domains comprising, e.g., consisting of, SEQ ID NO: 290 and SEQ ID NO: 281, respectively. In an aspect, the first gRNA molecule and the second gRNA molecule include targeting domains comprising, e.g., consisting of, SEQ ID NO: 317 and SEQ ID NO: 312, respectively. In an aspect, the first gRNA molecule and the second gRNA molecule include targeting domains comprising, e.g., consisting of, SEQ ID NO: 317

and SEQ ID NO: 313, respectively. In an aspect, the first gRNA molecule and the second gRNA molecule include targeting domains comprising, e.g., consisting of, SEQ ID NO: 317 and SEQ ID NO: 294, respectively. In an aspect, the first gRNA molecule and the second gRNA molecule include targeting domains comprising, e.g., consisting of, SEQ ID NO: 317 and SEQ ID NO: 310, respectively. In an aspect, the first gRNA molecule and the second gRNA molecule include targeting domains comprising, e.g., consisting of, SEQ ID NO: 317 and SEQ ID NO: 319, respectively. In an aspect, the first gRNA molecule and the second gRNA molecule include targeting domains comprising, e.g., consisting of, SEQ ID NO: 317 and SEQ ID NO: 298, respectively. In an aspect, the first gRNA molecule and the second gRNA molecule include targeting domains comprising, e.g., consisting of, SEQ ID NO: 317 and SEQ ID NO: 322, respectively. In an aspect, the first gRNA molecule and the second gRNA molecule include targeting domains comprising, e.g., consisting of, SEQ ID NO: 317 and SEQ ID NO: 311, respectively. In an aspect, the first gRNA molecule and the second gRNA molecule include targeting domains comprising, e.g., consisting of, SEQ ID NO: 317 and SEQ ID NO: 315, respectively. In an aspect, the first gRNA molecule and the second gRNA molecule include targeting domains comprising, e.g., consisting of, SEQ ID NO: 317 and SEQ ID NO: 290, respectively. In an aspect, the first gRNA molecule and the second gRNA molecule include targeting domains comprising, e.g., consisting of, SEQ ID NO: 317 and SEQ ID NO: 309, respectively. In an aspect, the first gRNA molecule and the second gRNA molecule include targeting domains comprising, e.g., consisting of, SEQ ID NO: 317 and SEQ ID NO: 289, respectively. In an aspect, the first gRNA molecule and the second gRNA molecule include targeting domains comprising, e.g., consisting of, SEQ ID NO: 317 and SEQ ID NO: 281, respectively. In an aspect, the first gRNA molecule and the second gRNA molecule include targeting domains comprising, e.g., consisting of, SEQ ID NO: 309 and SEQ ID NO: 312, respectively. In an aspect, the first gRNA molecule and the second gRNA molecule include targeting domains comprising, e.g., consisting of, SEQ ID NO: 309 and SEQ ID NO: 313, respectively. In an aspect, the first gRNA molecule and the second gRNA molecule include targeting domains comprising, e.g., consisting of, SEQ ID NO: 309 and SEQ ID NO: 294, respectively. In an aspect, the first gRNA molecule and the second gRNA molecule include targeting domains comprising, e.g., consisting of, SEQ ID NO: 309 and SEQ ID NO: 310, respectively. In an aspect, the first gRNA molecule and the second gRNA molecule include targeting domains comprising, e.g., consisting of, SEQ ID NO: 309 and SEQ ID NO: 319, respectively. In an aspect, the first gRNA molecule and the second gRNA molecule include targeting domains comprising, e.g., consisting of, SEQ ID NO: 309 and SEQ ID NO: 298, respectively. In an aspect, the first gRNA molecule and the second gRNA molecule include targeting domains comprising, e.g., consisting of, SEQ ID NO: 309 and SEQ ID NO: 322, respectively. In an aspect, the first gRNA molecule and the second gRNA molecule include targeting domains comprising, e.g., consisting of, SEQ ID NO: 309 and SEQ ID NO: 311, respectively. In an aspect, the first gRNA molecule and the second gRNA molecule include targeting domains comprising, e.g., consisting of,

SEQ ID NO: 309 and SEQ ID NO: 315, respectively. In an aspect, the first gRNA molecule and the second gRNA molecule include targeting domains comprising, e.g., consisting of, SEQ ID NO: 309 and SEQ ID NO: 290, respectively. In an aspect, the first gRNA molecule and the second gRNA molecule include targeting domains comprising, e.g., consisting of, SEQ ID NO: 309 and SEQ ID NO: 317, respectively. In an aspect, the first gRNA molecule and the second gRNA molecule include targeting domains comprising, e.g., consisting of, SEQ ID NO: 309 and SEQ ID NO: 289, respectively. In an aspect, the first gRNA molecule and the second gRNA molecule include targeting domains comprising, e.g., consisting of, SEQ ID NO: 309 and SEQ ID NO: 281, respectively. In an aspect, the first gRNA molecule and the second gRNA molecule include targeting domains comprising, e.g., consisting of, SEQ ID NO: 289 and SEQ ID NO: 312, respectively. In an aspect, the first gRNA molecule and the second gRNA molecule include targeting domains comprising, e.g., consisting of, SEQ ID NO: 289 and SEQ ID NO: 313, respectively. In an aspect, the first gRNA molecule and the second gRNA molecule include targeting domains comprising, e.g., consisting of, SEQ ID NO: 289 and SEQ ID NO: 294, respectively. In an aspect, the first gRNA molecule and the second gRNA molecule include targeting domains comprising, e.g., consisting of, SEQ ID NO: 289 and SEQ ID NO: 310, respectively. In an aspect, the first gRNA molecule and the second gRNA molecule include targeting domains comprising, e.g., consisting of, SEQ ID NO: 289 and SEQ ID NO: 319, respectively. In an aspect, the first gRNA molecule and the second gRNA molecule include targeting domains comprising, e.g., consisting of, SEQ ID NO: 289 and SEQ ID NO: 298, respectively. In an aspect, the first gRNA molecule and the second gRNA molecule include targeting domains comprising, e.g., consisting of, SEQ ID NO: 289 and SEQ ID NO: 322, respectively. In an aspect, the first gRNA molecule and the second gRNA molecule include targeting domains comprising, e.g., consisting of, SEQ ID NO: 289 and SEQ ID NO: 311, respectively. In an aspect, the first gRNA molecule and the second gRNA molecule include targeting domains comprising, e.g., consisting of, SEQ ID NO: 289 and SEQ ID NO: 315, respectively. In an aspect, the first gRNA molecule and the second gRNA molecule include targeting domains comprising, e.g., consisting of, SEQ ID NO: 289 and SEQ ID NO: 290, respectively. In an aspect, the first gRNA molecule and the second gRNA molecule include targeting domains comprising, e.g., consisting of, SEQ ID NO: 289 and SEQ ID NO: 317, respectively. In an aspect, the first gRNA molecule and the second gRNA molecule include targeting domains comprising, e.g., consisting of, SEQ ID NO: 289 and SEQ ID NO: 309, respectively. In an aspect, the first gRNA molecule and the second gRNA molecule include targeting domains comprising, e.g., consisting of, SEQ ID NO: 289 and SEQ ID NO: 281, respectively. In an aspect, the first gRNA molecule and the second gRNA molecule include targeting domains comprising, e.g., consisting of, SEQ ID NO: 281 and SEQ ID NO: 312, respectively. In an aspect, the first gRNA molecule and the second gRNA molecule include targeting domains comprising, e.g., consisting of, SEQ ID NO: 281 and SEQ ID NO: 313, respectively. In an aspect, the first gRNA molecule and the second gRNA molecule include targeting domains

comprising, e.g., consisting of, SEQ ID NO: 281 and SEQ ID NO: 294, respectively. In an aspect, the first gRNA molecule and the second gRNA molecule include targeting domains comprising, e.g., consisting of, SEQ ID NO: 281 and SEQ ID NO: 310, respectively. In an aspect, the first gRNA molecule and the second gRNA molecule include targeting domains comprising, e.g., consisting of, SEQ ID NO: 281 and SEQ ID NO: 319, respectively. In an aspect, the first gRNA molecule and the second gRNA molecule include targeting domains comprising, e.g., consisting of, SEQ ID NO: 281 and SEQ ID NO: 298, respectively. In an aspect, the first gRNA molecule and the second gRNA molecule include targeting domains comprising, e.g., consisting of, SEQ ID NO: 281 and SEQ ID NO: 322, respectively. In an aspect, the first gRNA molecule and the second gRNA molecule include targeting domains comprising, e.g., consisting of, SEQ ID NO: 281 and SEQ ID NO: 311, respectively. In an aspect, the first gRNA molecule and the second gRNA molecule include targeting domains comprising, e.g., consisting of, SEQ ID NO: 281 and SEQ ID NO: 315, respectively. In an aspect, the first gRNA molecule and the second gRNA molecule include targeting domains comprising, e.g., consisting of, SEQ ID NO: 281 and SEQ ID NO: 290, respectively. In an aspect, the first gRNA molecule and the second gRNA molecule include targeting domains comprising, e.g., consisting of, SEQ ID NO: 281 and SEQ ID NO: 317, respectively. In an aspect, the first gRNA molecule and the second gRNA molecule include targeting domains comprising, e.g., consisting of, SEQ ID NO: 281 and SEQ ID NO: 309, respectively. In an aspect, the first gRNA molecule and the second gRNA molecule include targeting domains comprising, e.g., consisting of, SEQ ID NO: 281 and SEQ ID NO: 289, respectively.

Table 9. Preferred Guide RNA Targeting Domains directed to the +55 Enhancer Region of the BCL11a Gene (i.e., to a BCL11a Enhancer)

ID	**Species**	**Strand**	**Location**	**Targeting Domain Sequence**	**SEQ ID NO:**
CR002142	h	+	Chr2:60498031 -60498053	CCUGGCAGACCCUCAAGAGC	1596
CR002143	h	-	Chr2:60498031 -60498053	CCUGGCAGACCCUCAAGAGC	1597
CR002144	h	+	Chr2:60498032 -60498054	CUGGCAGACCCUCAAGAGCA	1598
CR002145	h	+	Chr2:60498033 -60498055	UGGCAGACCCUCAAGAGCAG	1599
CR002146	h	-	Chr2:60498040 -60498062	CCCUCAAGAGCAGGGGUCUU	1600
CR002147	h	-	Chr2:60498041 -60498063	CCUCAAGAGCAGGGGUCUUC	1601
CR001262	h	+	Chr1:55039155 -55039177	UAAGGCCAGUGGAAAGAAUU	1602
CR002148	h	+	Chr2:60498045 -60498067	AAGAGCAGGGGUCUUCUCUU	1603
CR002149	h	+	Chr2:60498046 -60498068	AGAGCAGGGGUCUUCUCUUU	1604

CR002150	h	+	Chr2:60498047 -60498069	GAGCAGGGGUCUUCUCUUUG	1605
CR002151	h	+	Chr2:60498048 -60498070	AGCAGGGGUCUUCUCUUUGG	1606
CR002152	h	+	Chr2:60498051 -60498073	AGGGGUCUUCUCUUUGGGGG	1607
CR002153	h	+	Chr2:60498068 -60498090	GGGAGGACAUCACUCUUAGC	1608
CR002154	h	+	Chr2:60498069 -60498091	GGAGGACAUCACUCUUAGCA	1609
CR001261	h	-	Chr1:55039269 -55039291	GCCAGACUCCAAGUUCUGCC	1610
CR002155	h	+	Chr2:60498073 -60498095	GACAUCACUCUUAGCAGGGC	1611
CR002156	h	+	Chr2:60498074 -60498096	ACAUCACUCUUAGCAGGGCU	1612
CR002157	h	+	Chr2:60498075 -60498097	CAUCACUCUUAGCAGGGCUG	1613
CR002158	h	+	Chr2:60498091 -60498113	GCUGGGGUGAGUCAAAAGUC	1614
CR002159	h	+	Chr2:60498092 -60498114	CUGGGGUGAGUCAAAAGUCU	1615
CR002160	h	+	Chr2:60498099 -60498121	GAGUCAAAAGUCUGGGAGAA	1616
CR002161	h	+	Chr2:60498102 -60498124	UCAAAAGUCUGGGAGAAUGG	1617
CR002162	h	+	Chr2:60498107 -60498129	AGUCUGGGAGAAUGGAGGUG	1618
CR002163	h	+	Chr2:60498110 -60498132	CUGGGAGAAUGGAGGUGUGG	1619
CR002164	h	+	Chr2:60498111 -60498133	UGGGAGAAUGGAGGUGUGGA	1620
CR002165	h	+	Chr2:60498112 -60498134	GGGAGAAUGGAGGUGUGGAG	1621
CR002166	h	+	Chr2:60498120 -60498142	GGAGGUGUGGAGGGGAUAAC	1622
CR001263	h	+	Chr1:55039180 -55039202	GGCAGCGAGGAGUCCACAGU	1623
CR002167	h	+	Chr2:60498121 -60498143	GAGGUGUGGAGGGGAUAACU	1624
CR002168	h	+	Chr2:60498137 -60498159	AACUGGGUCAGACCCCAAGC	1625
CR002169	h	+	Chr2:60498141 -60498163	GGGUCAGACCCCAAGCAGGA	1626
CR002170	h	+	Chr2:60498142 -60498164	GGUCAGACCCCAAGCAGGAA	1627
CR002171	h	-	Chr2:60498149 -60498171	CCCCAAGCAGGAAGGGCCUC	1628
CR002172	h	-	Chr2:60498150 -60498172	CCCAAGCAGGAAGGGCCUCU	1629
CR002173	h	-	Chr2:60498151 -60498173	CCAAGCAGGAAGGGCCUCUA	1630
CR002174	h	+	Chr2:60498157 -60498179	AGGAAGGGCCUCUAUGUAGA	1631

CR002175	h	+	Chr2:60498158 -60498180	GGAAGGGCCUCUAUGUAGAC	1632
CR002176	h	+	Chr2:60498165 -60498187	CCUCUAUGUAGACGGGUGUG	1633
CR002177	h	-	Chr2:60498165 -60498187	CCUCUAUGUAGACGGGUGUG	1634
CR002178	h	+	Chr2:60498175 -60498197	GACGGGUGUGUGGCUCCUUA	1635
CR002179	h	-	Chr2:60498190 -60498212	CCUUAAGGUGACCCAGCAGC	1636
CR002180	h	+	Chr2:60498192 -60498214	UUAAGGUGACCCAGCAGCCC	1637
CR002181	h	+	Chr2:60498193 -60498215	UAAGGUGACCCAGCAGCCCU	1638
CR002182	h	-	Chr2:60498201 -60498223	CCCAGCAGCCCUGGGCACAG	1639
CR002183	h	-	Chr2:60498202 -60498224	CCAGCAGCCCUGGGCACAGA	1640
CR001261	h	-	Chr1:55039269 -55039291	GCCAGACUCCAAGUUCUGCC	1641
CR002184	h	+	Chr2:60498204 -60498226	AGCAGCCCUGGGCACAGAAG	1642
CR002185	h	-	Chr2:60498209 -60498231	CCCUGGGCACAGAAGUGGUG	1643
CR002186	h	-	Chr2:60498210 -60498232	CCUGGGCACAGAAGUGGUGC	1644
CR002187	h	+	Chr2:60498211 -60498233	CUGGGCACAGAAGUGGUGCG	1645
CR002188	h	+	Chr2:60498240 -60498262	UGCCAACAGUGAUAACCAGC	1646
CR002189	h	+	Chr2:60498241 -60498263	GCCAACAGUGAUAACCAGCA	1647
CR001262	h	+	Chr1:55039155 -55039177	UAAGGCCAGUGGAAAGAAUU	1648
CR002190	h	-	Chr2:60498242 -60498264	CCAACAGUGAUAACCAGCAG	1649
CR002191	h	+	Chr2:60498255 -60498277	CCAGCAGGGCCUGUCAGAAG	1650
CR002192	h	-	Chr2:60498255 -60498277	CCAGCAGGGCCUGUCAGAAG	1651
CR002193	h	+	Chr2:60498261 -60498283	GGGCCUGUCAGAAGAGGCCC	1652
CR002194	h	-	Chr2:60498264 -60498286	CCUGUCAGAAGAGGCCCUGG	1653
CR002195	h	+	Chr2:60498271 -60498293	GAAGAGGCCCUGGACACUGA	1654
CR002196	h	+	Chr2:60498275 -60498297	AGGCCCUGGACACUGAAGGC	1655
CR002197	h	+	Chr2:60498276 -60498298	GGCCCUGGACACUGAAGGCU	1656
CR001264	h	-	Chr1:55039149 -55039171	UCUUUCCACUGGCCUUAACC	1657
CR002198	h	-	Chr2:60498278 -60498300	CCCUGGACACUGAAGGCUGG	1658

CR002199	h	-	Chr2:60498279 -60498301	CCUGGACACUGAAGGCUGGG	1659
CR002200	h	+	Chr2:60498287 -60498309	CUGAAGGCUGGGCACAGCCU	1660
CR002201	h	+	Chr2:60498288 -60498310	UGAAGGCUGGGCACAGCCUU	1661
CR002202	h	+	Chr2:60498289 -60498311	GAAGGCUGGGCACAGCCUUG	1662
CR002203	h	+	Chr2:60498301 -60498323	CAGCCUUGGGGACCGCUCAC	1663
CR002204	h	-	Chr2:60498304 -60498326	CCUUGGGGACCGCUCACAGG	1664
CR002205	h	-	Chr2:60498313 -60498335	CCGCUCACAGGACAUGCAGC	1665
CR002206	h	-	Chr2:60498341 -60498363	CCGACAACUCCCUACCGCGA	1666
CR002207	h	-	Chr2:60498350 -60498372	CCCUACCGCGACCCCUAUCA	1667
CR002208	h	-	Chr2:60498351 -60498373	CCUACCGCGACCCCUAUCAG	1668
CR002209	h	-	Chr2:60498355 -60498377	CCGCGACCCCUAUCAGUGCC	1669
CR002210	h	-	Chr2:60498361 -60498383	CCCCUAUCAGUGCCGACCAA	1670
CR002211	h	-	Chr2:60498362 -60498384	CCCUAUCAGUGCCGACCAAG	1671
CR002212	h	-	Chr2:60498363 -60498385	CCUAUCAGUGCCGACCAAGC	1672
CR002213	h	-	Chr2:60498373 -60498395	CCGACCAAGCACACAAGAUG	1673
CR002214	h	-	Chr2:60498377 -60498399	CCAAGCACACAAGAUGCACA	1674
CR002215	h	+	Chr2:60498380 -60498402	AGCACACAAGAUGCACACCC	1675
CR002216	h	+	Chr2:60498384 -60498406	CACAAGAUGCACACCCAGGC	1676
CR002217	h	+	Chr2:60498385 -60498407	ACAAGAUGCACACCCAGGCU	1677
CR001264	h	-	Chr1:55039149 -55039171	UCUUUCCACUGGCCUUAACC	1678
CR002218	h	+	Chr2:60498389 -60498411	GAUGCACACCCAGGCUGGGC	1679
CR002219	h	+	Chr2:60498396 -60498418	ACCCAGGCUGGGCUGGACAG	1680
CR002220	h	+	Chr2:60498397 -60498419	CCCAGGCUGGGCUGGACAGA	1681
CR002221	h	-	Chr2:60498397 -60498419	CCCAGGCUGGGCUGGACAGA	1682
CR002222	h	+	Chr2:60498398 -60498420	CCAGGCUGGGCUGGACAGAG	1683
CR002223	h	-	Chr2:60498398 -60498420	CCAGGCUGGGCUGGACAGAG	1684
CR002224	h	+	Chr2:60498415 -60498437	GAGGGGUCCCACAAGAUCAC	1685

CR002225	h	+	Chr2:60498416 -60498438	AGGGGUCCCACAAGAUCACA	1686
CR002226	h	-	Chr2:60498422 -60498444	CCCACAAGAUCACAGGGUGU	1687
CR001263	h	+	Chr1:55039180 -55039202	GGCAGCGAGGAGUCCACAGU	1688
CR002227	h	-	Chr2:60498423 -60498445	CCACAAGAUCACAGGGUGUG	1689
CR002228	h	+	Chr2:60498431 -60498453	UCACAGGGUGUGCCCUGAGA	1690
CR002229	h	+	Chr2:60498434 -60498456	CAGGGUGUGCCCUGAGAAGG	1691

In some aspects of the invention, it is preferred that the gRNA molecule to the +55 Enhancer region of BCL11a comprise a targeting domain comprising, e.g., consisting of a targeting domain sequence selected from SEQ ID NO: 1683, SEQ ID NO: 1638, SEQ ID NO: 1647, SEQ ID NO: 1609, SEQ ID NO: 1621, SEQ ID NO: 1617, SEQ ID NO: 1654, SEQ ID NO: 1631, SEQ ID NO: 1620, SEQ ID NO: 1637, SEQ ID NO: 1612, SEQ ID NO: 1656, SEQ ID NO: 1619, SEQ ID NO: 1675, SEQ ID NO: 1645, SEQ ID NO: 1598, SEQ ID NO: 1599, SEQ ID NO: 1663, SEQ ID NO: 1677, and SEQ ID NO: 1626.

In some aspects of the invention, e.g., as indicated herein, it may be beneficial to include gRNA moleucles targeting more than one, e.g., two, target sites (e.g., a first gRNA molecule and a second gRNA molecule). In some embodiments, the two target sites are both located in the +55 BCL11a enhancer region. In such aspects, any combination of more than one, e.g., two, gRNA molecules (e.g., a first gRNA molecule and a second gRNA molecule) comprising, e.g., consisting of, targeting domains listed in Table 9 may be used, that target different target sites of the +55 BCL11a enhancer region. In an aspect, the first gRNA molecule and the second gRNA molecule include targeting domains comprising, e.g., consisting of, SEQ ID NO: 1683 and SEQ ID NO: 1638, respectively. In an aspect, the first gRNA molecule and the second gRNA molecule include targeting domains comprising, e.g., consisting of, SEQ ID NO: 1683 and SEQ ID NO: 1647, respectively. In an aspect, the first gRNA molecule and the second gRNA molecule include targeting domains comprising, e.g., consisting of, SEQ ID NO: 1683 and SEQ ID NO: 1609, respectively. In an aspect, the first gRNA molecule and the second gRNA molecule include targeting domains comprising, e.g., consisting of, SEQ ID NO: 1683 and SEQ ID NO: 1621, respectively. In an aspect, the first gRNA molecule and the second gRNA molecule include targeting domains comprising, e.g., consisting of, SEQ ID NO: 1683 and SEQ ID NO: 1617, respectively. In an aspect, the first gRNA molecule and the second gRNA molecule include targeting domains comprising, e.g., consisting of, SEQ ID NO: 1683 and SEQ ID NO: 1654, respectively. In an aspect, the first gRNA molecule and the second gRNA molecule include targeting domains comprising, e.g., consisting of, SEQ ID NO: 1683 and SEQ ID

NO: 1631, respectively. In an aspect, the first gRNA molecule and the second gRNA molecule include targeting domains comprising, e.g., consisting of, SEQ ID NO: 1683 and SEQ ID NO: 1620, respectively. In an aspect, the first gRNA molecule and the second gRNA molecule include targeting domains comprising, e.g., consisting of, SEQ ID NO: 1683 and SEQ ID NO: 1637, respectively. In an aspect, the first gRNA molecule and the second gRNA molecule include targeting domains comprising, e.g., consisting of, SEQ ID NO: 1683 and SEQ ID NO: 1612, respectively. In an aspect, the first gRNA molecule and the second gRNA molecule include targeting domains comprising, e.g., consisting of, SEQ ID NO: 1683 and SEQ ID NO: 1656, respectively. In an aspect, the first gRNA molecule and the second gRNA molecule include targeting domains comprising, e.g., consisting of, SEQ ID NO: 1683 and SEQ ID NO: 1619, respectively. In an aspect, the first gRNA molecule and the second gRNA molecule include targeting domains comprising, e.g., consisting of, SEQ ID NO: 1683 and SEQ ID NO: 1675, respectively. In an aspect, the first gRNA molecule and the second gRNA molecule include targeting domains comprising, e.g., consisting of, SEQ ID NO: 1683 and SEQ ID NO: 1645, respectively. In an aspect, the first gRNA molecule and the second gRNA molecule include targeting domains comprising, e.g., consisting of, SEQ ID NO: 1683 and SEQ ID NO: 1598, respectively. In an aspect, the first gRNA molecule and the second gRNA molecule include targeting domains comprising, e.g., consisting of, SEQ ID NO: 1683 and SEQ ID NO: 1599, respectively. In an aspect, the first gRNA molecule and the second gRNA molecule include targeting domains comprising, e.g., consisting of, SEQ ID NO: 1683 and SEQ ID NO: 1663, respectively. In an aspect, the first gRNA molecule and the second gRNA molecule include targeting domains comprising, e.g., consisting of, SEQ ID NO: 1683 and SEQ ID NO: 1677, respectively. In an aspect, the first gRNA molecule and the second gRNA molecule include targeting domains comprising, e.g., consisting of, SEQ ID NO: 1683 and SEQ ID NO: 1626, respectively. In an aspect, the first gRNA molecule and the second gRNA molecule include targeting domains comprising, e.g., consisting of, SEQ ID NO: 1638 and SEQ ID NO: 1647, respectively. In an aspect, the first gRNA molecule and the second gRNA molecule include targeting domains comprising, e.g., consisting of, SEQ ID NO: 1638 and SEQ ID NO: 1609, respectively. In an aspect, the first gRNA molecule and the second gRNA molecule include targeting domains comprising, e.g., consisting of, SEQ ID NO: 1638 and SEQ ID NO: 1621, respectively. In an aspect, the first gRNA molecule and the second gRNA molecule include targeting domains comprising, e.g., consisting of, SEQ ID NO: 1638 and SEQ ID NO: 1617, respectively. In an aspect, the first gRNA molecule and the second gRNA molecule include targeting domains comprising, e.g., consisting of, SEQ ID NO: 1638 and SEQ ID NO: 1654, respectively. In an aspect, the first gRNA molecule and the second gRNA molecule include targeting domains comprising, e.g., consisting of, SEQ ID NO: 1638 and SEQ ID NO: 1631, respectively. In an aspect, the first gRNA molecule and the second gRNA molecule include targeting domains comprising, e.g., consisting of, SEQ ID NO: 1638 and SEQ ID NO: 1620, respectively. In an aspect, the first gRNA molecule and the second gRNA molecule include targeting domains comprising, e.g.,

consisting of, SEQ ID NO: 1638 and SEQ ID NO: 1637, respectively. In an aspect, the first gRNA molecule and the second gRNA molecule include targeting domains comprising, e.g., consisting of, SEQ ID NO: 1638 and SEQ ID NO: 1612, respectively. In an aspect, the first gRNA molecule and the second gRNA molecule include targeting domains comprising, e.g., consisting of, SEQ ID NO: 1638 and SEQ ID NO: 1656, respectively. In an aspect, the first gRNA molecule and the second gRNA molecule include targeting domains comprising, e.g., consisting of, SEQ ID NO: 1638 and SEQ ID NO: 1619, respectively. In an aspect, the first gRNA molecule and the second gRNA molecule include targeting domains comprising, e.g., consisting of, SEQ ID NO: 1638 and SEQ ID NO: 1675, respectively. In an aspect, the first gRNA molecule and the second gRNA molecule include targeting domains comprising, e.g., consisting of, SEQ ID NO: 1638 and SEQ ID NO: 1645, respectively. In an aspect, the first gRNA molecule and the second gRNA molecule include targeting domains comprising, e.g., consisting of, SEQ ID NO: 1638 and SEQ ID NO: 1598, respectively. In an aspect, the first gRNA molecule and the second gRNA molecule include targeting domains comprising, e.g., consisting of, SEQ ID NO: 1638 and SEQ ID NO: 1599, respectively. In an aspect, the first gRNA molecule and the second gRNA molecule include targeting domains comprising, e.g., consisting of, SEQ ID NO: 1638 and SEQ ID NO: 1663, respectively. In an aspect, the first gRNA molecule and the second gRNA molecule include targeting domains comprising, e.g., consisting of, SEQ ID NO: 1638 and SEQ ID NO: 1677, respectively. In an aspect, the first gRNA molecule and the second gRNA molecule include targeting domains comprising, e.g., consisting of, SEQ ID NO: 1638 and SEQ ID NO: 1626, respectively. In an aspect, the first gRNA molecule and the second gRNA molecule include targeting domains comprising, e.g., consisting of, SEQ ID NO: 1647 and SEQ ID NO: 1638, respectively. In an aspect, the first gRNA molecule and the second gRNA molecule include targeting domains comprising, e.g., consisting of, SEQ ID NO: 1647 and SEQ ID NO: 1609, respectively. In an aspect, the first gRNA molecule and the second gRNA molecule include targeting domains comprising, e.g., consisting of, SEQ ID NO: 1647 and SEQ ID NO: 1621, respectively. In an aspect, the first gRNA molecule and the second gRNA molecule include targeting domains comprising, e.g., consisting of, SEQ ID NO: 1647 and SEQ ID NO: 1617, respectively. In an aspect, the first gRNA molecule and the second gRNA molecule include targeting domains comprising, e.g., consisting of, SEQ ID NO: 1647 and SEQ ID NO: 1654, respectively. In an aspect, the first gRNA molecule and the second gRNA molecule include targeting domains comprising, e.g., consisting of, SEQ ID NO: 1647 and SEQ ID NO: 1631, respectively. In an aspect, the first gRNA molecule and the second gRNA molecule include targeting domains comprising, e.g., consisting of, SEQ ID NO: 1647 and SEQ ID NO: 1620, respectively. In an aspect, the first gRNA molecule and the second gRNA molecule include targeting domains comprising, e.g., consisting of, SEQ ID NO: 1647 and SEQ ID NO: 1637, respectively. In an aspect, the first gRNA molecule and the second gRNA molecule include targeting domains comprising, e.g., consisting of, SEQ ID NO: 1647 and SEQ ID NO: 1612, respectively. In an aspect, the first gRNA molecule and the second gRNA

molecule include targeting domains comprising, e.g., consisting of, SEQ ID NO: 1647 and SEQ ID NO: 1656, respectively. In an aspect, the first gRNA molecule and the second gRNA molecule include targeting domains comprising, e.g., consisting of, SEQ ID NO: 1647 and SEQ ID NO: 1619, respectively. In an aspect, the first gRNA molecule and the second gRNA molecule include targeting domains comprising, e.g., consisting of, SEQ ID NO: 1647 and SEQ ID NO: 1675, respectively. In an aspect, the first gRNA molecule and the second gRNA molecule include targeting domains comprising, e.g., consisting of, SEQ ID NO: 1647 and SEQ ID NO: 1645, respectively. In an aspect, the first gRNA molecule and the second gRNA molecule include targeting domains comprising, e.g., consisting of, SEQ ID NO: 1647 and SEQ ID NO: 1598, respectively. In an aspect, the first gRNA molecule and the second gRNA molecule include targeting domains comprising, e.g., consisting of, SEQ ID NO: 1647 and SEQ ID NO: 1599, respectively. In an aspect, the first gRNA molecule and the second gRNA molecule include targeting domains comprising, e.g., consisting of, SEQ ID NO: 1647 and SEQ ID NO: 1663, respectively. In an aspect, the first gRNA molecule and the second gRNA molecule include targeting domains comprising, e.g., consisting of, SEQ ID NO: 1647 and SEQ ID NO: 1677, respectively. In an aspect, the first gRNA molecule and the second gRNA molecule include targeting domains comprising, e.g., consisting of, SEQ ID NO: 1647 and SEQ ID NO: 1626, respectively. In an aspect, the first gRNA molecule and the second gRNA molecule include targeting domains comprising, e.g., consisting of, SEQ ID NO: 1609 and SEQ ID NO: 1638, respectively. In an aspect, the first gRNA molecule and the second gRNA molecule include targeting domains comprising, e.g., consisting of, SEQ ID NO: 1609 and SEQ ID NO: 1647, respectively. In an aspect, the first gRNA molecule and the second gRNA molecule include targeting domains comprising, e.g., consisting of, SEQ ID NO: 1609 and SEQ ID NO: 1621, respectively. In an aspect, the first gRNA molecule and the second gRNA molecule include targeting domains comprising, e.g., consisting of, SEQ ID NO: 1609 and SEQ ID NO: 1617, respectively. In an aspect, the first gRNA molecule and the second gRNA molecule include targeting domains comprising, e.g., consisting of, SEQ ID NO: 1609 and SEQ ID NO: 1654, respectively. In an aspect, the first gRNA molecule and the second gRNA molecule include targeting domains comprising, e.g., consisting of, SEQ ID NO: 1609 and SEQ ID NO: 1631, respectively. In an aspect, the first gRNA molecule and the second gRNA molecule include targeting domains comprising, e.g., consisting of, SEQ ID NO: 1609 and SEQ ID NO: 1620, respectively. In an aspect, the first gRNA molecule and the second gRNA molecule include targeting domains comprising, e.g., consisting of, SEQ ID NO: 1609 and SEQ ID NO: 1637, respectively. In an aspect, the first gRNA molecule and the second gRNA molecule include targeting domains comprising, e.g., consisting of, SEQ ID NO: 1609 and SEQ ID NO: 1612, respectively. In an aspect, the first gRNA molecule and the second gRNA molecule include targeting domains comprising, e.g., consisting of, SEQ ID NO: 1609 and SEQ ID NO: 1656, respectively. In an aspect, the first gRNA molecule and the second gRNA molecule include targeting domains comprising, e.g., consisting of, SEQ ID NO: 1609 and SEQ ID NO: 1619, respectively. In

an aspect, the first gRNA molecule and the second gRNA molecule include targeting domains comprising, e.g., consisting of, SEQ ID NO: 1609 and SEQ ID NO: 1675, respectively. In an aspect, the first gRNA molecule and the second gRNA molecule include targeting domains comprising, e.g., consisting of, SEQ ID NO: 1609 and SEQ ID NO: 1645, respectively. In an aspect, the first gRNA molecule and the second gRNA molecule include targeting domains comprising, e.g., consisting of, SEQ ID NO: 1609 and SEQ ID NO: 1598, respectively. In an aspect, the first gRNA molecule and the second gRNA molecule include targeting domains comprising, e.g., consisting of, SEQ ID NO: 1609 and SEQ ID NO: 1599, respectively. In an aspect, the first gRNA molecule and the second gRNA molecule include targeting domains comprising, e.g., consisting of, SEQ ID NO: 1609 and SEQ ID NO: 1663, respectively. In an aspect, the first gRNA molecule and the second gRNA molecule include targeting domains comprising, e.g., consisting of, SEQ ID NO: 1609 and SEQ ID NO: 1677, respectively. In an aspect, the first gRNA molecule and the second gRNA molecule include targeting domains comprising, e.g., consisting of, SEQ ID NO: 1609 and SEQ ID NO: 1626, respectively. In an aspect, the first gRNA molecule and the second gRNA molecule include targeting domains comprising, e.g., consisting of, SEQ ID NO: 1621 and SEQ ID NO: 1638, respectively. In an aspect, the first gRNA molecule and the second gRNA molecule include targeting domains comprising, e.g., consisting of, SEQ ID NO: 1621 and SEQ ID NO: 1647, respectively. In an aspect, the first gRNA molecule and the second gRNA molecule include targeting domains comprising, e.g., consisting of, SEQ ID NO: 1621 and SEQ ID NO: 1609, respectively. In an aspect, the first gRNA molecule and the second gRNA molecule include targeting domains comprising, e.g., consisting of, SEQ ID NO: 1621 and SEQ ID NO: 1617, respectively. In an aspect, the first gRNA molecule and the second gRNA molecule include targeting domains comprising, e.g., consisting of, SEQ ID NO: 1621 and SEQ ID NO: 1654, respectively. In an aspect, the first gRNA molecule and the second gRNA molecule include targeting domains comprising, e.g., consisting of, SEQ ID NO: 1621 and SEQ ID NO: 1631, respectively. In an aspect, the first gRNA molecule and the second gRNA molecule include targeting domains comprising, e.g., consisting of, SEQ ID NO: 1621 and SEQ ID NO: 1620, respectively. In an aspect, the first gRNA molecule and the second gRNA molecule include targeting domains comprising, e.g., consisting of, SEQ ID NO: 1621 and SEQ ID NO: 1637, respectively. In an aspect, the first gRNA molecule and the second gRNA molecule include targeting domains comprising, e.g., consisting of, SEQ ID NO: 1621 and SEQ ID NO: 1612, respectively. In an aspect, the first gRNA molecule and the second gRNA molecule include targeting domains comprising, e.g., consisting of, SEQ ID NO: 1621 and SEQ ID NO: 1656, respectively. In an aspect, the first gRNA molecule and the second gRNA molecule include targeting domains comprising, e.g., consisting of, SEQ ID NO: 1621 and SEQ ID NO: 1619, respectively. In an aspect, the first gRNA molecule and the second gRNA molecule include targeting domains comprising, e.g., consisting of, SEQ ID NO: 1621 and SEQ ID NO: 1675, respectively. In an aspect, the first gRNA molecule and the second gRNA molecule include targeting domains comprising, e.g., consisting of,

SEQ ID NO: 1621 and SEQ ID NO: 1645, respectively. In an aspect, the first gRNA molecule and the second gRNA molecule include targeting domains comprising, e.g., consisting of, SEQ ID NO: 1621 and SEQ ID NO: 1598, respectively. In an aspect, the first gRNA molecule and the second gRNA molecule include targeting domains comprising, e.g., consisting of, SEQ ID NO: 1621 and SEQ ID NO: 1599, respectively. In an aspect, the first gRNA molecule and the second gRNA molecule include targeting domains comprising, e.g., consisting of, SEQ ID NO: 1621 and SEQ ID NO: 1663, respectively. In an aspect, the first gRNA molecule and the second gRNA molecule include targeting domains comprising, e.g., consisting of, SEQ ID NO: 1621 and SEQ ID NO: 1677, respectively. In an aspect, the first gRNA molecule and the second gRNA molecule include targeting domains comprising, e.g., consisting of, SEQ ID NO: 1621 and SEQ ID NO: 1626, respectively. In an aspect, the first gRNA molecule and the second gRNA molecule include targeting domains comprising, e.g., consisting of, SEQ ID NO: 1617 and SEQ ID NO: 1638, respectively. In an aspect, the first gRNA molecule and the second gRNA molecule include targeting domains comprising, e.g., consisting of, SEQ ID NO: 1617 and SEQ ID NO: 1647, respectively. In an aspect, the first gRNA molecule and the second gRNA molecule include targeting domains comprising, e.g., consisting of, SEQ ID NO: 1617 and SEQ ID NO: 1609, respectively. In an aspect, the first gRNA molecule and the second gRNA molecule include targeting domains comprising, e.g., consisting of, SEQ ID NO: 1617 and SEQ ID NO: 1621, respectively. In an aspect, the first gRNA molecule and the second gRNA molecule include targeting domains comprising, e.g., consisting of, SEQ ID NO: 1617 and SEQ ID NO: 1654, respectively. In an aspect, the first gRNA molecule and the second gRNA molecule include targeting domains comprising, e.g., consisting of, SEQ ID NO: 1617 and SEQ ID NO: 1631, respectively. In an aspect, the first gRNA molecule and the second gRNA molecule include targeting domains comprising, e.g., consisting of, SEQ ID NO: 1617 and SEQ ID NO: 1620, respectively. In an aspect, the first gRNA molecule and the second gRNA molecule include targeting domains comprising, e.g., consisting of, SEQ ID NO: 1617 and SEQ ID NO: 1637, respectively. In an aspect, the first gRNA molecule and the second gRNA molecule include targeting domains comprising, e.g., consisting of, SEQ ID NO: 1617 and SEQ ID NO: 1612, respectively. In an aspect, the first gRNA molecule and the second gRNA molecule include targeting domains comprising, e.g., consisting of, SEQ ID NO: 1617 and SEQ ID NO: 1656, respectively. In an aspect, the first gRNA molecule and the second gRNA molecule include targeting domains comprising, e.g., consisting of, SEQ ID NO: 1617 and SEQ ID NO: 1619, respectively. In an aspect, the first gRNA molecule and the second gRNA molecule include targeting domains comprising, e.g., consisting of, SEQ ID NO: 1617 and SEQ ID NO: 1675, respectively. In an aspect, the first gRNA molecule and the second gRNA molecule include targeting domains comprising, e.g., consisting of, SEQ ID NO: 1617 and SEQ ID NO: 1645, respectively. In an aspect, the first gRNA molecule and the second gRNA molecule include targeting domains comprising, e.g., consisting of, SEQ ID NO: 1617 and SEQ ID NO: 1598, respectively. In an aspect, the first gRNA molecule and the second gRNA molecule

include targeting domains comprising, e.g., consisting of, SEQ ID NO: 1617 and SEQ ID NO: 1599, respectively. In an aspect, the first gRNA molecule and the second gRNA molecule include targeting domains comprising, e.g., consisting of, SEQ ID NO: 1617 and SEQ ID NO: 1663, respectively. In an aspect, the first gRNA molecule and the second gRNA molecule include targeting domains comprising, e.g., consisting of, SEQ ID NO: 1617 and SEQ ID NO: 1677, respectively. In an aspect, the first gRNA molecule and the second gRNA molecule include targeting domains comprising, e.g., consisting of, SEQ ID NO: 1617 and SEQ ID NO: 1626, respectively. In an aspect, the first gRNA molecule and the second gRNA molecule include targeting domains comprising, e.g., consisting of, SEQ ID NO: 1654 and SEQ ID NO: 1638, respectively. In an aspect, the first gRNA molecule and the second gRNA molecule include targeting domains comprising, e.g., consisting of, SEQ ID NO: 1654 and SEQ ID NO: 1647, respectively. In an aspect, the first gRNA molecule and the second gRNA molecule include targeting domains comprising, e.g., consisting of, SEQ ID NO: 1654 and SEQ ID NO: 1609, respectively. In an aspect, the first gRNA molecule and the second gRNA molecule include targeting domains comprising, e.g., consisting of, SEQ ID NO: 1654 and SEQ ID NO: 1621, respectively. In an aspect, the first gRNA molecule and the second gRNA molecule include targeting domains comprising, e.g., consisting of, SEQ ID NO: 1654 and SEQ ID NO: 1617, respectively. In an aspect, the first gRNA molecule and the second gRNA molecule include targeting domains comprising, e.g., consisting of, SEQ ID NO: 1654 and SEQ ID NO: 1631, respectively. In an aspect, the first gRNA molecule and the second gRNA molecule include targeting domains comprising, e.g., consisting of, SEQ ID NO: 1654 and SEQ ID NO: 1620, respectively. In an aspect, the first gRNA molecule and the second gRNA molecule include targeting domains comprising, e.g., consisting of, SEQ ID NO: 1654 and SEQ ID NO: 1637, respectively. In an aspect, the first gRNA molecule and the second gRNA molecule include targeting domains comprising, e.g., consisting of, SEQ ID NO: 1654 and SEQ ID NO: 1612, respectively. In an aspect, the first gRNA molecule and the second gRNA molecule include targeting domains comprising, e.g., consisting of, SEQ ID NO: 1654 and SEQ ID NO: 1656, respectively. In an aspect, the first gRNA molecule and the second gRNA molecule include targeting domains comprising, e.g., consisting of, SEQ ID NO: 1654 and SEQ ID NO: 1619, respectively. In an aspect, the first gRNA molecule and the second gRNA molecule include targeting domains comprising, e.g., consisting of, SEQ ID NO: 1654 and SEQ ID NO: 1675, respectively. In an aspect, the first gRNA molecule and the second gRNA molecule include targeting domains comprising, e.g., consisting of, SEQ ID NO: 1654 and SEQ ID NO: 1645, respectively. In an aspect, the first gRNA molecule and the second gRNA molecule include targeting domains comprising, e.g., consisting of, SEQ ID NO: 1654 and SEQ ID NO: 1598, respectively. In an aspect, the first gRNA molecule and the second gRNA molecule include targeting domains comprising, e.g., consisting of, SEQ ID NO: 1654 and SEQ ID NO: 1599, respectively. In an aspect, the first gRNA molecule and the second gRNA molecule include targeting domains comprising, e.g., consisting of, SEQ ID NO: 1654 and SEQ ID NO: 1663, respectively. In an aspect, the first gRNA

molecule and the second gRNA molecule include targeting domains comprising, e.g., consisting of, SEQ ID NO: 1654 and SEQ ID NO: 1677, respectively. In an aspect, the first gRNA molecule and the second gRNA molecule include targeting domains comprising, e.g., consisting of, SEQ ID NO: 1654 and SEQ ID NO: 1626, respectively. In an aspect, the first gRNA molecule and the second gRNA molecule include targeting domains comprising, e.g., consisting of, SEQ ID NO: 1631 and SEQ ID NO: 1638, respectively. In an aspect, the first gRNA molecule and the second gRNA molecule include targeting domains comprising, e.g., consisting of, SEQ ID NO: 1631 and SEQ ID NO: 1647, respectively. In an aspect, the first gRNA molecule and the second gRNA molecule include targeting domains comprising, e.g., consisting of, SEQ ID NO: 1631 and SEQ ID NO: 1609, respectively. In an aspect, the first gRNA molecule and the second gRNA molecule include targeting domains comprising, e.g., consisting of, SEQ ID NO: 1631 and SEQ ID NO: 1621, respectively. In an aspect, the first gRNA molecule and the second gRNA molecule include targeting domains comprising, e.g., consisting of, SEQ ID NO: 1631 and SEQ ID NO: 1617, respectively. In an aspect, the first gRNA molecule and the second gRNA molecule include targeting domains comprising, e.g., consisting of, SEQ ID NO: 1631 and SEQ ID NO: 1654, respectively. In an aspect, the first gRNA molecule and the second gRNA molecule include targeting domains comprising, e.g., consisting of, SEQ ID NO: 1631 and SEQ ID NO: 1620, respectively. In an aspect, the first gRNA molecule and the second gRNA molecule include targeting domains comprising, e.g., consisting of, SEQ ID NO: 1631 and SEQ ID NO: 1637, respectively. In an aspect, the first gRNA molecule and the second gRNA molecule include targeting domains comprising, e.g., consisting of, SEQ ID NO: 1631 and SEQ ID NO: 1612, respectively. In an aspect, the first gRNA molecule and the second gRNA molecule include targeting domains comprising, e.g., consisting of, SEQ ID NO: 1631 and SEQ ID NO: 1656, respectively. In an aspect, the first gRNA molecule and the second gRNA molecule include targeting domains comprising, e.g., consisting of, SEQ ID NO: 1631 and SEQ ID NO: 1619, respectively. In an aspect, the first gRNA molecule and the second gRNA molecule include targeting domains comprising, e.g., consisting of, SEQ ID NO: 1631 and SEQ ID NO: 1675, respectively. In an aspect, the first gRNA molecule and the second gRNA molecule include targeting domains comprising, e.g., consisting of, SEQ ID NO: 1631 and SEQ ID NO: 1645, respectively. In an aspect, the first gRNA molecule and the second gRNA molecule include targeting domains comprising, e.g., consisting of, SEQ ID NO: 1631 and SEQ ID NO: 1598, respectively. In an aspect, the first gRNA molecule and the second gRNA molecule include targeting domains comprising, e.g., consisting of, SEQ ID NO: 1631 and SEQ ID NO: 1599, respectively. In an aspect, the first gRNA molecule and the second gRNA molecule include targeting domains comprising, e.g., consisting of, SEQ ID NO: 1631 and SEQ ID NO: 1663, respectively. In an aspect, the first gRNA molecule and the second gRNA molecule include targeting domains comprising, e.g., consisting of, SEQ ID NO: 1631 and SEQ ID NO: 1677, respectively. In an aspect, the first gRNA molecule and the second gRNA molecule include targeting domains comprising, e.g., consisting of, SEQ ID NO: 1631 and SEQ ID

NO: 1626, respectively. In an aspect, the first gRNA molecule and the second gRNA molecule include targeting domains comprising, e.g., consisting of, SEQ ID NO: 1620 and SEQ ID NO: 1638, respectively. In an aspect, the first gRNA molecule and the second gRNA molecule include targeting domains comprising, e.g., consisting of, SEQ ID NO: 1620 and SEQ ID NO: 1647, respectively. In an aspect, the first gRNA molecule and the second gRNA molecule include targeting domains comprising, e.g., consisting of, SEQ ID NO: 1620 and SEQ ID NO: 1609, respectively. In an aspect, the first gRNA molecule and the second gRNA molecule include targeting domains comprising, e.g., consisting of, SEQ ID NO: 1620 and SEQ ID NO: 1621, respectively. In an aspect, the first gRNA molecule and the second gRNA molecule include targeting domains comprising, e.g., consisting of, SEQ ID NO: 1620 and SEQ ID NO: 1617, respectively. In an aspect, the first gRNA molecule and the second gRNA molecule include targeting domains comprising, e.g., consisting of, SEQ ID NO: 1620 and SEQ ID NO: 1654, respectively. In an aspect, the first gRNA molecule and the second gRNA molecule include targeting domains comprising, e.g., consisting of, SEQ ID NO: 1620 and SEQ ID NO: 1631, respectively. In an aspect, the first gRNA molecule and the second gRNA molecule include targeting domains comprising, e.g., consisting of, SEQ ID NO: 1620 and SEQ ID NO: 1637, respectively. In an aspect, the first gRNA molecule and the second gRNA molecule include targeting domains comprising, e.g., consisting of, SEQ ID NO: 1620 and SEQ ID NO: 1612, respectively. In an aspect, the first gRNA molecule and the second gRNA molecule include targeting domains comprising, e.g., consisting of, SEQ ID NO: 1620 and SEQ ID NO: 1656, respectively. In an aspect, the first gRNA molecule and the second gRNA molecule include targeting domains comprising, e.g., consisting of, SEQ ID NO: 1620 and SEQ ID NO: 1619, respectively. In an aspect, the first gRNA molecule and the second gRNA molecule include targeting domains comprising, e.g., consisting of, SEQ ID NO: 1620 and SEQ ID NO: 1675, respectively. In an aspect, the first gRNA molecule and the second gRNA molecule include targeting domains comprising, e.g., consisting of, SEQ ID NO: 1620 and SEQ ID NO: 1645, respectively. In an aspect, the first gRNA molecule and the second gRNA molecule include targeting domains comprising, e.g., consisting of, SEQ ID NO: 1620 and SEQ ID NO: 1598, respectively. In an aspect, the first gRNA molecule and the second gRNA molecule include targeting domains comprising, e.g., consisting of, SEQ ID NO: 1620 and SEQ ID NO: 1599, respectively. In an aspect, the first gRNA molecule and the second gRNA molecule include targeting domains comprising, e.g., consisting of, SEQ ID NO: 1620 and SEQ ID NO: 1663, respectively. In an aspect, the first gRNA molecule and the second gRNA molecule include targeting domains comprising, e.g., consisting of, SEQ ID NO: 1620 and SEQ ID NO: 1677, respectively. In an aspect, the first gRNA molecule and the second gRNA molecule include targeting domains comprising, e.g., consisting of, SEQ ID NO: 1620 and SEQ ID NO: 1626, respectively. In an aspect, the first gRNA molecule and the second gRNA molecule include targeting domains comprising, e.g., consisting of, SEQ ID NO: 1637 and SEQ ID NO: 1638, respectively. In an aspect, the first gRNA molecule and the second gRNA molecule include targeting

domains comprising, e.g., consisting of, SEQ ID NO: 1637 and SEQ ID NO: 1647, respectively. In an aspect, the first gRNA molecule and the second gRNA molecule include targeting domains comprising, e.g., consisting of, SEQ ID NO: 1637 and SEQ ID NO: 1609, respectively. In an aspect, the first gRNA molecule and the second gRNA molecule include targeting domains comprising, e.g., consisting of, SEQ ID NO: 1637 and SEQ ID NO: 1621, respectively. In an aspect, the first gRNA molecule and the second gRNA molecule include targeting domains comprising, e.g., consisting of, SEQ ID NO: 1637 and SEQ ID NO: 1617, respectively. In an aspect, the first gRNA molecule and the second gRNA molecule include targeting domains comprising, e.g., consisting of, SEQ ID NO: 1637 and SEQ ID NO: 1654, respectively. In an aspect, the first gRNA molecule and the second gRNA molecule include targeting domains comprising, e.g., consisting of, SEQ ID NO: 1637 and SEQ ID NO: 1631, respectively. In an aspect, the first gRNA molecule and the second gRNA molecule include targeting domains comprising, e.g., consisting of, SEQ ID NO: 1637 and SEQ ID NO: 1620, respectively. In an aspect, the first gRNA molecule and the second gRNA molecule include targeting domains comprising, e.g., consisting of, SEQ ID NO: 1637 and SEQ ID NO: 1612, respectively. In an aspect, the first gRNA molecule and the second gRNA molecule include targeting domains comprising, e.g., consisting of, SEQ ID NO: 1637 and SEQ ID NO: 1656, respectively. In an aspect, the first gRNA molecule and the second gRNA molecule include targeting domains comprising, e.g., consisting of, SEQ ID NO: 1637 and SEQ ID NO: 1619, respectively. In an aspect, the first gRNA molecule and the second gRNA molecule include targeting domains comprising, e.g., consisting of, SEQ ID NO: 1637 and SEQ ID NO: 1675, respectively. In an aspect, the first gRNA molecule and the second gRNA molecule include targeting domains comprising, e.g., consisting of, SEQ ID NO: 1637 and SEQ ID NO: 1645, respectively. In an aspect, the first gRNA molecule and the second gRNA molecule include targeting domains comprising, e.g., consisting of, SEQ ID NO: 1637 and SEQ ID NO: 1598, respectively. In an aspect, the first gRNA molecule and the second gRNA molecule include targeting domains comprising, e.g., consisting of, SEQ ID NO: 1637 and SEQ ID NO: 1599, respectively. In an aspect, the first gRNA molecule and the second gRNA molecule include targeting domains comprising, e.g., consisting of, SEQ ID NO: 1637 and SEQ ID NO: 1663, respectively. In an aspect, the first gRNA molecule and the second gRNA molecule include targeting domains comprising, e.g., consisting of, SEQ ID NO: 1637 and SEQ ID NO: 1677, respectively. In an aspect, the first gRNA molecule and the second gRNA molecule include targeting domains comprising, e.g., consisting of, SEQ ID NO: 1637 and SEQ ID NO: 1626, respectively. In an aspect, the first gRNA molecule and the second gRNA molecule include targeting domains comprising, e.g., consisting of, SEQ ID NO: 1612 and SEQ ID NO: 1638, respectively. In an aspect, the first gRNA molecule and the second gRNA molecule include targeting domains comprising, e.g., consisting of, SEQ ID NO: 1612 and SEQ ID NO: 1647, respectively. In an aspect, the first gRNA molecule and the second gRNA molecule include targeting domains comprising, e.g., consisting of, SEQ ID NO: 1612 and SEQ ID NO: 1609, respectively. In an aspect, the first gRNA molecule and

the second gRNA molecule include targeting domains comprising, e.g., consisting of, SEQ ID NO: 1612 and SEQ ID NO: 1621, respectively. In an aspect, the first gRNA molecule and the second gRNA molecule include targeting domains comprising, e.g., consisting of, SEQ ID NO: 1612 and SEQ ID NO: 1617, respectively. In an aspect, the first gRNA molecule and the second gRNA molecule include targeting domains comprising, e.g., consisting of, SEQ ID NO: 1612 and SEQ ID NO: 1654, respectively. In an aspect, the first gRNA molecule and the second gRNA molecule include targeting domains comprising, e.g., consisting of, SEQ ID NO: 1612 and SEQ ID NO: 1631, respectively. In an aspect, the first gRNA molecule and the second gRNA molecule include targeting domains comprising, e.g., consisting of, SEQ ID NO: 1612 and SEQ ID NO: 1620, respectively. In an aspect, the first gRNA molecule and the second gRNA molecule include targeting domains comprising, e.g., consisting of, SEQ ID NO: 1612 and SEQ ID NO: 1637, respectively. In an aspect, the first gRNA molecule and the second gRNA molecule include targeting domains comprising, e.g., consisting of, SEQ ID NO: 1612 and SEQ ID NO: 1656, respectively. In an aspect, the first gRNA molecule and the second gRNA molecule include targeting domains comprising, e.g., consisting of, SEQ ID NO: 1612 and SEQ ID NO: 1619, respectively. In an aspect, the first gRNA molecule and the second gRNA molecule include targeting domains comprising, e.g., consisting of, SEQ ID NO: 1612 and SEQ ID NO: 1675, respectively. In an aspect, the first gRNA molecule and the second gRNA molecule include targeting domains comprising, e.g., consisting of, SEQ ID NO: 1612 and SEQ ID NO: 1645, respectively. In an aspect, the first gRNA molecule and the second gRNA molecule include targeting domains comprising, e.g., consisting of, SEQ ID NO: 1612 and SEQ ID NO: 1598, respectively. In an aspect, the first gRNA molecule and the second gRNA molecule include targeting domains comprising, e.g., consisting of, SEQ ID NO: 1612 and SEQ ID NO: 1599, respectively. In an aspect, the first gRNA molecule and the second gRNA molecule include targeting domains comprising, e.g., consisting of, SEQ ID NO: 1612 and SEQ ID NO: 1663, respectively. In an aspect, the first gRNA molecule and the second gRNA molecule include targeting domains comprising, e.g., consisting of, SEQ ID NO: 1612 and SEQ ID NO: 1677, respectively. In an aspect, the first gRNA molecule and the second gRNA molecule include targeting domains comprising, e.g., consisting of, SEQ ID NO: 1612 and SEQ ID NO: 1626, respectively. In an aspect, the first gRNA molecule and the second gRNA molecule include targeting domains comprising, e.g., consisting of, SEQ ID NO: 1656 and SEQ ID NO: 1638, respectively. In an aspect, the first gRNA molecule and the second gRNA molecule include targeting domains comprising, e.g., consisting of, SEQ ID NO: 1656 and SEQ ID NO: 1647, respectively. In an aspect, the first gRNA molecule and the second gRNA molecule include targeting domains comprising, e.g., consisting of, SEQ ID NO: 1656 and SEQ ID NO: 1609, respectively. In an aspect, the first gRNA molecule and the second gRNA molecule include targeting domains comprising, e.g., consisting of, SEQ ID NO: 1656 and SEQ ID NO: 1621, respectively. In an aspect, the first gRNA molecule and the second gRNA molecule include targeting domains comprising, e.g., consisting of, SEQ ID NO: 1656 and SEQ ID NO: 1617,

respectively. In an aspect, the first gRNA molecule and the second gRNA molecule include targeting domains comprising, e.g., consisting of, SEQ ID NO: 1656 and SEQ ID NO: 1654, respectively. In an aspect, the first gRNA molecule and the second gRNA molecule include targeting domains comprising, e.g., consisting of, SEQ ID NO: 1656 and SEQ ID NO: 1631, respectively. In an aspect, the first gRNA molecule and the second gRNA molecule include targeting domains comprising, e.g., consisting of, SEQ ID NO: 1656 and SEQ ID NO: 1620, respectively. In an aspect, the first gRNA molecule and the second gRNA molecule include targeting domains comprising, e.g., consisting of, SEQ ID NO: 1656 and SEQ ID NO: 1637, respectively. In an aspect, the first gRNA molecule and the second gRNA molecule include targeting domains comprising, e.g., consisting of, SEQ ID NO: 1656 and SEQ ID NO: 1612, respectively. In an aspect, the first gRNA molecule and the second gRNA molecule include targeting domains comprising, e.g., consisting of, SEQ ID NO: 1656 and SEQ ID NO: 1619, respectively. In an aspect, the first gRNA molecule and the second gRNA molecule include targeting domains comprising, e.g., consisting of, SEQ ID NO: 1656 and SEQ ID NO: 1675, respectively. In an aspect, the first gRNA molecule and the second gRNA molecule include targeting domains comprising, e.g., consisting of, SEQ ID NO: 1656 and SEQ ID NO: 1645, respectively. In an aspect, the first gRNA molecule and the second gRNA molecule include targeting domains comprising, e.g., consisting of, SEQ ID NO: 1656 and SEQ ID NO: 1598, respectively. In an aspect, the first gRNA molecule and the second gRNA molecule include targeting domains comprising, e.g., consisting of, SEQ ID NO: 1656 and SEQ ID NO: 1599, respectively. In an aspect, the first gRNA molecule and the second gRNA molecule include targeting domains comprising, e.g., consisting of, SEQ ID NO: 1656 and SEQ ID NO: 1663, respectively. In an aspect, the first gRNA molecule and the second gRNA molecule include targeting domains comprising, e.g., consisting of, SEQ ID NO: 1656 and SEQ ID NO: 1677, respectively. In an aspect, the first gRNA molecule and the second gRNA molecule include targeting domains comprising, e.g., consisting of, SEQ ID NO: 1656 and SEQ ID NO: 1626, respectively. In an aspect, the first gRNA molecule and the second gRNA molecule include targeting domains comprising, e.g., consisting of, SEQ ID NO: 1619 and SEQ ID NO: 1638, respectively. In an aspect, the first gRNA molecule and the second gRNA molecule include targeting domains comprising, e.g., consisting of, SEQ ID NO: 1619 and SEQ ID NO: 1647, respectively. In an aspect, the first gRNA molecule and the second gRNA molecule include targeting domains comprising, e.g., consisting of, SEQ ID NO: 1619 and SEQ ID NO: 1609, respectively. In an aspect, the first gRNA molecule and the second gRNA molecule include targeting domains comprising, e.g., consisting of, SEQ ID NO: 1619 and SEQ ID NO: 1621, respectively. In an aspect, the first gRNA molecule and the second gRNA molecule include targeting domains comprising, e.g., consisting of, SEQ ID NO: 1619 and SEQ ID NO: 1617, respectively. In an aspect, the first gRNA molecule and the second gRNA molecule include targeting domains comprising, e.g., consisting of, SEQ ID NO: 1619 and SEQ ID NO: 1654, respectively. In an aspect, the first gRNA molecule and the second gRNA molecule include targeting domains comprising, e.g., consisting of,

SEQ ID NO: 1619 and SEQ ID NO: 1631, respectively. In an aspect, the first gRNA molecule and the second gRNA molecule include targeting domains comprising, e.g., consisting of, SEQ ID NO: 1619 and SEQ ID NO: 1620, respectively. In an aspect, the first gRNA molecule and the second gRNA molecule include targeting domains comprising, e.g., consisting of, SEQ ID NO: 1619 and SEQ ID NO: 1637, respectively. In an aspect, the first gRNA molecule and the second gRNA molecule include targeting domains comprising, e.g., consisting of, SEQ ID NO: 1619 and SEQ ID NO: 1612, respectively. In an aspect, the first gRNA molecule and the second gRNA molecule include targeting domains comprising, e.g., consisting of, SEQ ID NO: 1619 and SEQ ID NO: 1656, respectively. In an aspect, the first gRNA molecule and the second gRNA molecule include targeting domains comprising, e.g., consisting of, SEQ ID NO: 1619 and SEQ ID NO: 1675, respectively. In an aspect, the first gRNA molecule and the second gRNA molecule include targeting domains comprising, e.g., consisting of, SEQ ID NO: 1619 and SEQ ID NO: 1645, respectively. In an aspect, the first gRNA molecule and the second gRNA molecule include targeting domains comprising, e.g., consisting of, SEQ ID NO: 1619 and SEQ ID NO: 1598, respectively. In an aspect, the first gRNA molecule and the second gRNA molecule include targeting domains comprising, e.g., consisting of, SEQ ID NO: 1619 and SEQ ID NO: 1599, respectively. In an aspect, the first gRNA molecule and the second gRNA molecule include targeting domains comprising, e.g., consisting of, SEQ ID NO: 1619 and SEQ ID NO: 1663, respectively. In an aspect, the first gRNA molecule and the second gRNA molecule include targeting domains comprising, e.g., consisting of, SEQ ID NO: 1619 and SEQ ID NO: 1677, respectively. In an aspect, the first gRNA molecule and the second gRNA molecule include targeting domains comprising, e.g., consisting of, SEQ ID NO: 1619 and SEQ ID NO: 1626, respectively. In an aspect, the first gRNA molecule and the second gRNA molecule include targeting domains comprising, e.g., consisting of, SEQ ID NO: 1675 and SEQ ID NO: 1638, respectively. In an aspect, the first gRNA molecule and the second gRNA molecule include targeting domains comprising, e.g., consisting of, SEQ ID NO: 1675 and SEQ ID NO: 1647, respectively. In an aspect, the first gRNA molecule and the second gRNA molecule include targeting domains comprising, e.g., consisting of, SEQ ID NO: 1675 and SEQ ID NO: 1609, respectively. In an aspect, the first gRNA molecule and the second gRNA molecule include targeting domains comprising, e.g., consisting of, SEQ ID NO: 1675 and SEQ ID NO: 1621, respectively. In an aspect, the first gRNA molecule and the second gRNA molecule include targeting domains comprising, e.g., consisting of, SEQ ID NO: 1675 and SEQ ID NO: 1617, respectively. In an aspect, the first gRNA molecule and the second gRNA molecule include targeting domains comprising, e.g., consisting of, SEQ ID NO: 1675 and SEQ ID NO: 1654, respectively. In an aspect, the first gRNA molecule and the second gRNA molecule include targeting domains comprising, e.g., consisting of, SEQ ID NO: 1675 and SEQ ID NO: 1631, respectively. In an aspect, the first gRNA molecule and the second gRNA molecule include targeting domains comprising, e.g., consisting of, SEQ ID NO: 1675 and SEQ ID NO: 1620, respectively. In an aspect, the first gRNA molecule and the second gRNA

molecule include targeting domains comprising, e.g., consisting of, SEQ ID NO: 1675 and SEQ ID NO: 1637, respectively. In an aspect, the first gRNA molecule and the second gRNA molecule include targeting domains comprising, e.g., consisting of, SEQ ID NO: 1675 and SEQ ID NO: 1612, respectively. In an aspect, the first gRNA molecule and the second gRNA molecule include targeting domains comprising, e.g., consisting of, SEQ ID NO: 1675 and SEQ ID NO: 1656, respectively. In an aspect, the first gRNA molecule and the second gRNA molecule include targeting domains comprising, e.g., consisting of, SEQ ID NO: 1675 and SEQ ID NO: 1619, respectively. In an aspect, the first gRNA molecule and the second gRNA molecule include targeting domains comprising, e.g., consisting of, SEQ ID NO: 1675 and SEQ ID NO: 1645, respectively. In an aspect, the first gRNA molecule and the second gRNA molecule include targeting domains comprising, e.g., consisting of, SEQ ID NO: 1675 and SEQ ID NO: 1598, respectively. In an aspect, the first gRNA molecule and the second gRNA molecule include targeting domains comprising, e.g., consisting of, SEQ ID NO: 1675 and SEQ ID NO: 1599, respectively. In an aspect, the first gRNA molecule and the second gRNA molecule include targeting domains comprising, e.g., consisting of, SEQ ID NO: 1675 and SEQ ID NO: 1663, respectively. In an aspect, the first gRNA molecule and the second gRNA molecule include targeting domains comprising, e.g., consisting of, SEQ ID NO: 1675 and SEQ ID NO: 1677, respectively. In an aspect, the first gRNA molecule and the second gRNA molecule include targeting domains comprising, e.g., consisting of, SEQ ID NO: 1675 and SEQ ID NO: 1626, respectively. In an aspect, the first gRNA molecule and the second gRNA molecule include targeting domains comprising, e.g., consisting of, SEQ ID NO: 1645 and SEQ ID NO: 1638, respectively. In an aspect, the first gRNA molecule and the second gRNA molecule include targeting domains comprising, e.g., consisting of, SEQ ID NO: 1645 and SEQ ID NO: 1647, respectively. In an aspect, the first gRNA molecule and the second gRNA molecule include targeting domains comprising, e.g., consisting of, SEQ ID NO: 1645 and SEQ ID NO: 1609, respectively. In an aspect, the first gRNA molecule and the second gRNA molecule include targeting domains comprising, e.g., consisting of, SEQ ID NO: 1645 and SEQ ID NO: 1621, respectively. In an aspect, the first gRNA molecule and the second gRNA molecule include targeting domains comprising, e.g., consisting of, SEQ ID NO: 1645 and SEQ ID NO: 1617, respectively. In an aspect, the first gRNA molecule and the second gRNA molecule include targeting domains comprising, e.g., consisting of, SEQ ID NO: 1645 and SEQ ID NO: 1654, respectively. In an aspect, the first gRNA molecule and the second gRNA molecule include targeting domains comprising, e.g., consisting of, SEQ ID NO: 1645 and SEQ ID NO: 1631, respectively. In an aspect, the first gRNA molecule and the second gRNA molecule include targeting domains comprising, e.g., consisting of, SEQ ID NO: 1645 and SEQ ID NO: 1620, respectively. In an aspect, the first gRNA molecule and the second gRNA molecule include targeting domains comprising, e.g., consisting of, SEQ ID NO: 1645 and SEQ ID NO: 1637, respectively. In an aspect, the first gRNA molecule and the second gRNA molecule include targeting domains comprising, e.g., consisting of, SEQ ID NO: 1645 and SEQ ID NO: 1612, respectively. In

an aspect, the first gRNA molecule and the second gRNA molecule include targeting domains comprising, e.g., consisting of, SEQ ID NO: 1645 and SEQ ID NO: 1656, respectively. In an aspect, the first gRNA molecule and the second gRNA molecule include targeting domains comprising, e.g., consisting of, SEQ ID NO: 1645 and SEQ ID NO: 1619, respectively. In an aspect, the first gRNA molecule and the second gRNA molecule include targeting domains comprising, e.g., consisting of, SEQ ID NO: 1645 and SEQ ID NO: 1675, respectively. In an aspect, the first gRNA molecule and the second gRNA molecule include targeting domains comprising, e.g., consisting of, SEQ ID NO: 1598 and SEQ ID NO: 1638, respectively. In an aspect, the first gRNA molecule and the second gRNA molecule include targeting domains comprising, e.g., consisting of, SEQ ID NO: 1598 and SEQ ID NO: 1647, respectively. In an aspect, the first gRNA molecule and the second gRNA molecule include targeting domains comprising, e.g., consisting of, SEQ ID NO: 1598 and SEQ ID NO: 1609, respectively. In an aspect, the first gRNA molecule and the second gRNA molecule include targeting domains comprising, e.g., consisting of, SEQ ID NO: 1598 and SEQ ID NO: 1621, respectively. In an aspect, the first gRNA molecule and the second gRNA molecule include targeting domains comprising, e.g., consisting of, SEQ ID NO: 1598 and SEQ ID NO: 1617, respectively. In an aspect, the first gRNA molecule and the second gRNA molecule include targeting domains comprising, e.g., consisting of, SEQ ID NO: 1598 and SEQ ID NO: 1654, respectively. In an aspect, the first gRNA molecule and the second gRNA molecule include targeting domains comprising, e.g., consisting of, SEQ ID NO: 1598 and SEQ ID NO: 1631, respectively. In an aspect, the first gRNA molecule and the second gRNA molecule include targeting domains comprising, e.g., consisting of, SEQ ID NO: 1598 and SEQ ID NO: 1620, respectively. In an aspect, the first gRNA molecule and the second gRNA molecule include targeting domains comprising, e.g., consisting of, SEQ ID NO: 1598 and SEQ ID NO: 1637, respectively. In an aspect, the first gRNA molecule and the second gRNA molecule include targeting domains comprising, e.g., consisting of, SEQ ID NO: 1598 and SEQ ID NO: 1612, respectively. In an aspect, the first gRNA molecule and the second gRNA molecule include targeting domains comprising, e.g., consisting of, SEQ ID NO: 1598 and SEQ ID NO: 1656, respectively. In an aspect, the first gRNA molecule and the second gRNA molecule include targeting domains comprising, e.g., consisting of, SEQ ID NO: 1598 and SEQ ID NO: 1619, respectively. In an aspect, the first gRNA molecule and the second gRNA molecule include targeting domains comprising, e.g., consisting of, SEQ ID NO: 1598 and SEQ ID NO: 1675, respectively. In an aspect, the first gRNA molecule and the second gRNA molecule include targeting domains comprising, e.g., consisting of, SEQ ID NO: 1598 and SEQ ID NO: 1645, respectively. In an aspect, the first gRNA molecule and the second gRNA molecule include targeting domains comprising, e.g., consisting of, SEQ ID NO: 1598 and SEQ ID NO: 1599, respectively. In an aspect, the first gRNA molecule and the second gRNA molecule include targeting domains comprising, e.g., consisting of, SEQ ID NO: 1598 and SEQ ID NO: 1663, respectively. In an aspect, the first gRNA molecule and the second gRNA molecule include targeting domains comprising, e.g., consisting of, SEQ ID NO:

1598 and SEQ ID NO: 1677, respectively. In an aspect, the first gRNA molecule and the second gRNA molecule include targeting domains comprising, e.g., consisting of, SEQ ID NO: 1598 and SEQ ID NO: 1626, respectively. In an aspect, the first gRNA molecule and the second gRNA molecule include targeting domains comprising, e.g., consisting of, SEQ ID NO: 1599 and SEQ ID NO: 1638, respectively. In an aspect, the first gRNA molecule and the second gRNA molecule include targeting domains comprising, e.g., consisting of, SEQ ID NO: 1599 and SEQ ID NO: 1647, respectively. In an aspect, the first gRNA molecule and the second gRNA molecule include targeting domains comprising, e.g., consisting of, SEQ ID NO: 1599 and SEQ ID NO: 1609, respectively. In an aspect, the first gRNA molecule and the second gRNA molecule include targeting domains comprising, e.g., consisting of, SEQ ID NO: 1599 and SEQ ID NO: 1621, respectively. In an aspect, the first gRNA molecule and the second gRNA molecule include targeting domains comprising, e.g., consisting of, SEQ ID NO: 1599 and SEQ ID NO: 1617, respectively. In an aspect, the first gRNA molecule and the second gRNA molecule include targeting domains comprising, e.g., consisting of, SEQ ID NO: 1599 and SEQ ID NO: 1654, respectively. In an aspect, the first gRNA molecule and the second gRNA molecule include targeting domains comprising, e.g., consisting of, SEQ ID NO: 1599 and SEQ ID NO: 1631, respectively. In an aspect, the first gRNA molecule and the second gRNA molecule include targeting domains comprising, e.g., consisting of, SEQ ID NO: 1599 and SEQ ID NO: 1620, respectively. In an aspect, the first gRNA molecule and the second gRNA molecule include targeting domains comprising, e.g., consisting of, SEQ ID NO: 1599 and SEQ ID NO: 1637, respectively. In an aspect, the first gRNA molecule and the second gRNA molecule include targeting domains comprising, e.g., consisting of, SEQ ID NO: 1599 and SEQ ID NO: 1612, respectively. In an aspect, the first gRNA molecule and the second gRNA molecule include targeting domains comprising, e.g., consisting of, SEQ ID NO: 1599 and SEQ ID NO: 1656, respectively. In an aspect, the first gRNA molecule and the second gRNA molecule include targeting domains comprising, e.g., consisting of, SEQ ID NO: 1599 and SEQ ID NO: 1619, respectively. In an aspect, the first gRNA molecule and the second gRNA molecule include targeting domains comprising, e.g., consisting of, SEQ ID NO: 1599 and SEQ ID NO: 1675, respectively. In an aspect, the first gRNA molecule and the second gRNA molecule include targeting domains comprising, e.g., consisting of, SEQ ID NO: 1599 and SEQ ID NO: 1645, respectively. In an aspect, the first gRNA molecule and the second gRNA molecule include targeting domains comprising, e.g., consisting of, SEQ ID NO: 1599 and SEQ ID NO: 1598, respectively. In an aspect, the first gRNA molecule and the second gRNA molecule include targeting domains comprising, e.g., consisting of, SEQ ID NO: 1599 and SEQ ID NO: 1663, respectively. In an aspect, the first gRNA molecule and the second gRNA molecule include targeting domains comprising, e.g., consisting of, SEQ ID NO: 1599 and SEQ ID NO: 1677, respectively. In an aspect, the first gRNA molecule and the second gRNA molecule include targeting domains comprising, e.g., consisting of, SEQ ID NO: 1599 and SEQ ID NO: 1626, respectively. In an aspect, the first gRNA molecule and the second gRNA molecule include

targeting domains comprising, e.g., consisting of, SEQ ID NO: 1663 and SEQ ID NO: 1638, respectively. In an aspect, the first gRNA molecule and the second gRNA molecule include targeting domains comprising, e.g., consisting of, SEQ ID NO: 1663 and SEQ ID NO: 1647, respectively. In an aspect, the first gRNA molecule and the second gRNA molecule include targeting domains comprising, e.g., consisting of, SEQ ID NO: 1663 and SEQ ID NO: 1609, respectively. In an aspect, the first gRNA molecule and the second gRNA molecule include targeting domains comprising, e.g., consisting of, SEQ ID NO: 1663 and SEQ ID NO: 1621, respectively. In an aspect, the first gRNA molecule and the second gRNA molecule include targeting domains comprising, e.g., consisting of, SEQ ID NO: 1663 and SEQ ID NO: 1617, respectively. In an aspect, the first gRNA molecule and the second gRNA molecule include targeting domains comprising, e.g., consisting of, SEQ ID NO: 1663 and SEQ ID NO: 1654, respectively. In an aspect, the first gRNA molecule and the second gRNA molecule include targeting domains comprising, e.g., consisting of, SEQ ID NO: 1663 and SEQ ID NO: 1631, respectively. In an aspect, the first gRNA molecule and the second gRNA molecule include targeting domains comprising, e.g., consisting of, SEQ ID NO: 1663 and SEQ ID NO: 1620, respectively. In an aspect, the first gRNA molecule and the second gRNA molecule include targeting domains comprising, e.g., consisting of, SEQ ID NO: 1663 and SEQ ID NO: 1637, respectively. In an aspect, the first gRNA molecule and the second gRNA molecule include targeting domains comprising, e.g., consisting of, SEQ ID NO: 1663 and SEQ ID NO: 1612, respectively. In an aspect, the first gRNA molecule and the second gRNA molecule include targeting domains comprising, e.g., consisting of, SEQ ID NO: 1663 and SEQ ID NO: 1656, respectively. In an aspect, the first gRNA molecule and the second gRNA molecule include targeting domains comprising, e.g., consisting of, SEQ ID NO: 1663 and SEQ ID NO: 1619, respectively. In an aspect, the first gRNA molecule and the second gRNA molecule include targeting domains comprising, e.g., consisting of, SEQ ID NO: 1663 and SEQ ID NO: 1675, respectively. In an aspect, the first gRNA molecule and the second gRNA molecule include targeting domains comprising, e.g., consisting of, SEQ ID NO: 1663 and SEQ ID NO: 1645, respectively. In an aspect, the first gRNA molecule and the second gRNA molecule include targeting domains comprising, e.g., consisting of, SEQ ID NO: 1663 and SEQ ID NO: 1598, respectively. In an aspect, the first gRNA molecule and the second gRNA molecule include targeting domains comprising, e.g., consisting of, SEQ ID NO: 1663 and SEQ ID NO: 1599, respectively. In an aspect, the first gRNA molecule and the second gRNA molecule include targeting domains comprising, e.g., consisting of, SEQ ID NO: 1663 and SEQ ID NO: 1677, respectively. In an aspect, the first gRNA molecule and the second gRNA molecule include targeting domains comprising, e.g., consisting of, SEQ ID NO: 1663 and SEQ ID NO: 1626, respectively. In an aspect, the first gRNA molecule and the second gRNA molecule include targeting domains comprising, e.g., consisting of, SEQ ID NO: 1677 and SEQ ID NO: 1638, respectively. In an aspect, the first gRNA molecule and the second gRNA molecule include targeting domains comprising, e.g., consisting of, SEQ ID NO: 1677 and SEQ ID NO: 1647, respectively. In an aspect, the first gRNA

molecule and the second gRNA molecule include targeting domains comprising, e.g., consisting of, SEQ ID NO: 1677 and SEQ ID NO: 1609, respectively. In an aspect, the first gRNA molecule and the second gRNA molecule include targeting domains comprising, e.g., consisting of, SEQ ID NO: 1677 and SEQ ID NO: 1621, respectively. In an aspect, the first gRNA molecule and the second gRNA molecule include targeting domains comprising, e.g., consisting of, SEQ ID NO: 1677 and SEQ ID NO: 1617, respectively. In an aspect, the first gRNA molecule and the second gRNA molecule include targeting domains comprising, e.g., consisting of, SEQ ID NO: 1677 and SEQ ID NO: 1654, respectively. In an aspect, the first gRNA molecule and the second gRNA molecule include targeting domains comprising, e.g., consisting of, SEQ ID NO: 1677 and SEQ ID NO: 1631, respectively. In an aspect, the first gRNA molecule and the second gRNA molecule include targeting domains comprising, e.g., consisting of, SEQ ID NO: 1677 and SEQ ID NO: 1620, respectively. In an aspect, the first gRNA molecule and the second gRNA molecule include targeting domains comprising, e.g., consisting of, SEQ ID NO: 1677 and SEQ ID NO: 1637, respectively. In an aspect, the first gRNA molecule and the second gRNA molecule include targeting domains comprising, e.g., consisting of, SEQ ID NO: 1677 and SEQ ID NO: 1612, respectively. In an aspect, the first gRNA molecule and the second gRNA molecule include targeting domains comprising, e.g., consisting of, SEQ ID NO: 1677 and SEQ ID NO: 1656, respectively. In an aspect, the first gRNA molecule and the second gRNA molecule include targeting domains comprising, e.g., consisting of, SEQ ID NO: 1677 and SEQ ID NO: 1619, respectively. In an aspect, the first gRNA molecule and the second gRNA molecule include targeting domains comprising, e.g., consisting of, SEQ ID NO: 1677 and SEQ ID NO: 1675, respectively. In an aspect, the first gRNA molecule and the second gRNA molecule include targeting domains comprising, e.g., consisting of, SEQ ID NO: 1677 and SEQ ID NO: 1645, respectively. In an aspect, the first gRNA molecule and the second gRNA molecule include targeting domains comprising, e.g., consisting of, SEQ ID NO: 1677 and SEQ ID NO: 1598, respectively. In an aspect, the first gRNA molecule and the second gRNA molecule include targeting domains comprising, e.g., consisting of, SEQ ID NO: 1677 and SEQ ID NO: 1599, respectively. In an aspect, the first gRNA molecule and the second gRNA molecule include targeting domains comprising, e.g., consisting of, SEQ ID NO: 1677 and SEQ ID NO: 1663, respectively. In an aspect, the first gRNA molecule and the second gRNA molecule include targeting domains comprising, e.g., consisting of, SEQ ID NO: 1677 and SEQ ID NO: 1626, respectively. In an aspect, the first gRNA molecule and the second gRNA molecule include targeting domains comprising, e.g., consisting of, SEQ ID NO: 1626 and SEQ ID NO: 1638, respectively. In an aspect, the first gRNA molecule and the second gRNA molecule include targeting domains comprising, e.g., consisting of, SEQ ID NO: 1626 and SEQ ID NO: 1647, respectively. In an aspect, the first gRNA molecule and the second gRNA molecule include targeting domains comprising, e.g., consisting of, SEQ ID NO: 1626 and SEQ ID NO: 1609, respectively. In an aspect, the first gRNA molecule and the second gRNA molecule include targeting domains comprising, e.g., consisting of, SEQ ID NO: 1626 and SEQ ID

NO: 1621, respectively. In an aspect, the first gRNA molecule and the second gRNA molecule include targeting domains comprising, e.g., consisting of, SEQ ID NO: 1626 and SEQ ID NO: 1617, respectively. In an aspect, the first gRNA molecule and the second gRNA molecule include targeting domains comprising, e.g., consisting of, SEQ ID NO: 1626 and SEQ ID NO: 1654, respectively. In an aspect, the first gRNA molecule and the second gRNA molecule include targeting domains comprising, e.g., consisting of, SEQ ID NO: 1626 and SEQ ID NO: 1631, respectively. In an aspect, the first gRNA molecule and the second gRNA molecule include targeting domains comprising, e.g., consisting of, SEQ ID NO: 1626 and SEQ ID NO: 1620, respectively. In an aspect, the first gRNA molecule and the second gRNA molecule include targeting domains comprising, e.g., consisting of, SEQ ID NO: 1626 and SEQ ID NO: 1637, respectively. In an aspect, the first gRNA molecule and the second gRNA molecule include targeting domains comprising, e.g., consisting of, SEQ ID NO: 1626 and SEQ ID NO: 1612, respectively. In an aspect, the first gRNA molecule and the second gRNA molecule include targeting domains comprising, e.g., consisting of, SEQ ID NO: 1626 and SEQ ID NO: 1656, respectively. In an aspect, the first gRNA molecule and the second gRNA molecule include targeting domains comprising, e.g., consisting of, SEQ ID NO: 1626 and SEQ ID NO: 1619, respectively. In an aspect, the first gRNA molecule and the second gRNA molecule include targeting domains comprising, e.g., consisting of, SEQ ID NO: 1626 and SEQ ID NO: 1675, respectively. In an aspect, the first gRNA molecule and the second gRNA molecule include targeting domains comprising, e.g., consisting of, SEQ ID NO: 1626 and SEQ ID NO: 1645, respectively. In an aspect, the first gRNA molecule and the second gRNA molecule include targeting domains comprising, e.g., consisting of, SEQ ID NO: 1626 and SEQ ID NO: 1598, respectively. In an aspect, the first gRNA molecule and the second gRNA molecule include targeting domains comprising, e.g., consisting of, SEQ ID NO: 1626 and SEQ ID NO: 1599, respectively. In an aspect, the first gRNA molecule and the second gRNA molecule include targeting domains comprising, e.g., consisting of, SEQ ID NO: 1626 and SEQ ID NO: 1663, respectively. In an aspect, the first gRNA molecule and the second gRNA molecule include targeting domains comprising, e.g., consisting of, SEQ ID NO: 1626 and SEQ ID NO: 1677, respectively.

III. Methods for Designing gRNAs

Methods for designing gRNAs are described herein, including methods for selecting, designing and validating target sequences. Exemplary targeting domains are also provided herein. Targeting Domains discussed herein can be incorporated into the gRNAs described herein.

Methods for selection and validation of target sequences as well as off-target analyses are described, e.g., in. Mali el al. , 2013 SCIENCE 339(6121): 823-826; Hsu et al , 2013 NAT BIOTECHNOL, 31 (9): 827-32; Fu et al , 2014 NAT BIOTECHNOL, doi: 10.1038/nbt.2808. PubMed PM ID: 24463574; Heigwer et al, 2014 NAT METHODS ll (2): 122-3. doi: 10.1038/nmeth.2812. PubMed PMID:

24481216; Bae el al , 2014 BIOINFORMATICS PubMed PMID: 24463181 ; Xiao A el al , 2014 BIOINFORMATICS PubMed PMID: 24389662.

For example, a software tool can be used to optimize the choice of gRNA within a user's target sequence, e.g., to minimize total off-target activity across the genome. Off target activity may be other than cleavage. For each possible gRNA choice e.g., using S. pyogenes Cas9, the tool can identify all off-target sequences (e.g., preceding either NAG or NGG PAMs) across the genome that contain up to certain number (e.g., 1 , 2, 3, 4, 5, 6, 7, 8, 9, or 10) of mismatched base-pairs. The cleavage efficiency at each off-target sequence can be predicted, e.g., using an experimentally-derived weighting scheme. Each possible gRNA is then ranked according to its total predicted off-target cleavage; the top-ranked gRNAs represent those that are likely to have the greatest on-target and the least off-target cleavage. Other functions, e.g., automated reagent design for CRISPR construction, primer design for the on-target Surveyor assay, and primer design for high-throughput detection and quantification of off-target cleavage via next-gen sequencing, can also be included in the tool. Candidate gRNA molecules can be evaluated by art-known methods or as described herein.

Although software algorithms may be used to generate an initial list of potential gRNA molecules, cutting efficiency and specificity will not necessarily reflect the predicted values, and gRNA molecules typically require screening in specific cell lines, e.g., primary human cell lines, e.g., human HSPCs, e.g., human CD34+ cells, to determine, for example, cutting efficiency, indel formation, cutting specificity and change in desired phenotype. These properties may be assayed by the methods described herein.

In aspects of the invention, a gRNA comprising the targeting domain of CR00312 (SEQ ID NO: 248, underlined below), e.g., one of the gRNA molecules described below, is useful in the CRISPR systems, methods, cells and other aspects and embodiments of the invention, including in aspects involving more than one gRNA molecule, e.g., described herein:

sgRNA CR00312 #1:

GUUUGGCCUCUGAUUAGGGUGUUUUAGAGCUAGAAAUAGCAAGUUAAAAUAAGGCUAGUCCGUUAUCAACUUGAAAAAGUGGCACCGAGUCGGUGCUUUU (SEQ ID NO: 342)

sgRNA CR00312 #2:

mG*mU*mU*UGGCCUCUGAUUAGGGUGUUUUAGAGCUAGAAAUAGCAAGUUAAAAUAAGGCUAGUCCGUUAUCAACUUGAAAAAGUGGCACCGAGUCGGUGCU*mU*mU*mU (SEQ ID NO: 343)

sgRNA CR00312 #3:

mG*mU*mU*UGGCCUCUGAUUAGGGUGUUUUAGAGCUAGAAAUAGCAAGUUAAAAUA AGGCUAGUCCGUUAUCAACUUGAAAAAGUGGCACCGAGUCGGUGCmU*mU*mU*U (SEQ ID NO: 1762))

dgRNA CR00312 #1:

crRNA: GUUUGGCCUCUGAUUAGGGUGUUUUAGAGCUAUGCUGUUUUG (SEQ ID NO: 344)

tracr: AACAGCAUAGCAAGUUAAAAUAAGGCUAGUCCGUUAUCAACUUGAAAAAGUGGCACC GAGUCGGUGCUUUUUUU (SEQ ID NO: 6660)

dgRNA CR00312 #2:

crRNA: mG*mU*mU*UGGCCUCUGAUUAGGGUGUUUUAGAGCUAUGCUGUU*mU*mU*mG (SEQ ID NO: 345)

tracr: mA*mA*mC*AGCAUAGCAAGUUAAAAUAAGGCUAGUCCGUUAUCAACUUGAAAAAGUG GCACCGAGUCGGUGCUUUU*mU*mU*mU (SEQ ID NO: 346)

dgRNA CR00312 #3:

crRNA: mG*mU*mU*UGGCCUCUGAUUAGGGUGUUUUAGAGCUAUGCUGUU*mU*mU*mG (SEQ ID NO: 345)

tracr: AACAGCAUAGCAAGUUAAAAUAAGGCUAGUCCGUUAUCAACUUGAAAAAGUGGCACC GAGUCGGUGCUUUUUUU (SEQ ID NO: 6660).

In aspects of the invention, a gRNA comprising the targeting domain of CR001128 (SEQ ID NO: 338, underlined below), e.g., one of the gRNA molecules described below, is useful in the CRISPR systems, methods, cells and other aspects and embodiments of the invention, including in aspects involving more than one gRNA molecule, e.g., described herein:

sgRNA CR001128 #1:

AUCAGAGGCCAAACCCUUCCGUUUUAGAGCUAGAAAUAGCAAGUUAAAAUAAGGCUA GUCCGUUAUCAACUUGAAAAAGUGGCACCGAGUCGGUGCUUUU (SEQ ID NO: 347)

sgRNA CR001128 #2:

mA*mU*mC*AGAGGCCAAACCCUUCCGUUUUAGAGCUAGAAAUAGCAAGUUAAAAUAA GGCUAGUCCGUUAUCAACUUGAAAAAGUGGCACCGAGUCGGUGCU*mU*mU*mU (SEQ ID NO: 348)

sgRNA CR001128 #3:

mA*mU*mC*AGAGGCCAAACCCUUCCGUUUUAGAGCUAGAAAUAGCAAGUUAAAAUAA GGCUAGUCCGUUAUCAACUUGAAAAAGUGGCACCGAGUCGGUGCmU*mU*mU*U (SEQ ID NO: 1763)

dgRNA CR001128 #1:

crRNA: AUCAGAGGCCAAACCCUUCCGUUUUAGAGCUAUGCUGUUUUG (SEQ ID NO: 349)

tracr: AACAGCAUAGCAAGUUAAAAUAAGGCUAGUCCGUUAUCAACUUGAAAAAGUGGCACC GAGUCGGUGCUUUUUUU (SEQ ID NO: 6660)

dgRNA CR001128 #2:

crRNA: mA*mU*mC*AGAGGCCAAACCCUUCCGUUUUAGAGCUAUGCUGUU*mU*mU*mG (SEQ ID NO: 350)

tracr: mA*mA*mC*AGCAUAGCAAGUUAAAAUAAGGCUAGUCCGUUAUCAACUUGAAAAAGUG GCACCGAGUCGGUGCUUUU*mU*mU*mU (SEQ ID NO: 346)

dgRNA CR001128 #3:

crRNA: mA*mU*mC*AGAGGCCAAACCCUUCCGUUUUAGAGCUAUGCUGUU*mU*mU*mG (SEQ ID NO: 350)

tracr: AACAGCAUAGCAAGUUAAAAUAAGGCUAGUCCGUUAUCAACUUGAAAAAGUGGCACC GAGUCGGUGCUUUUUUU (SEQ ID NO: 6660).

In aspects of the invention, a gRNA comprising the targeting domain of CR001126 (SEQ ID NO: 336, underlined below), e.g., one of the gRNA molecules described below, is useful in the CRISPR systems, methods, cells and other aspects and embodiments of the invention, including in aspects involving more than one gRNA molecule, e.g., described herein:

sgRNA CR001126 #1:

UUUAUCACAGGCUCCAGGAAGUUUUAGAGCUAGAAAUAGCAAGUUAAAAUAAGGCUA GUCCGUUAUCAACUUGAAAAAGUGGCACCGAGUCGGUGCUUUU (SEQ ID NO: 351)

sgRNA CR001126 #2:

mU*mU*mU*AUCACAGGCUCCAGGAAGUUUUAGAGCUAGAAAUAGCAAGUUAAAAUAA GGCUAGUCCGUUAUCAACUUGAAAAAGUGGCACCGAGUCGGUGCU*mU*mU*mU (SEQ ID NO: 352)

sgRNA CR001126 #3:

mU*mU*mU*AUCACAGGCUCCAGGAAGUUUUAGAGCUAGAAAUAGCAAGUUAAAAUAA GGCUAGUCCGUUAUCAACUUGAAAAAGUGGCACCGAGUCGGUGCmU*mU*mU*U (SEQ ID NO: 1764)

dgRNA CR001126 #1:

crRNA: UUUAUCACAGGCUCCAGGAAGUUUUAGAGCUAUGCUGUUUUG (SEQ ID NO: 353)

tracr:
AACAGCAUAGCAAGUUAAAAUAAGGCUAGUCCGUUAUCAACUUGAAAAAGUGGCACC GAGUCGGUGCUUUUUUU (SEQ ID NO: 6660)

dgRNA CR001126 #2:

crRNA: mU*mU*mU*AUCACAGGCUCCAGGAAGUUUUAGAGCUAUGCUGUU*mU*mU*mG (SEQ ID NO: 354)

tracr:
mA*mA*mC*AGCAUAGCAAGUUAAAAUAAGGCUAGUCCGUUAUCAACUUGAAAAAGUG GCACCGAGUCGGUGCUUUU*mU*mU*mU (SEQ ID NO: 346)

dgRNA CR001126 #3:

crRNA: mU*mU*mU*AUCACAGGCUCCAGGAAGUUUUAGAGCUAUGCUGUU*mU*mU*mG (SEQ ID NO: 354)

tracr:
AACAGCAUAGCAAGUUAAAAUAAGGCUAGUCCGUUAUCAACUUGAAAAAGUGGCACC GAGUCGGUGCUUUUUUU (SEQ ID NO: 6660).

In aspects of the invention, a gRNA comprising the targeting domain of CR00311 (SEQ ID NO: 247, underlined below), e.g., one of the gRNA molecules described below, is useful in the CRISPR systems, methods, cells and other aspects and embodiments of the invention, including in aspects involving more than one gRNA molecule, e.g., described herein:

sgRNA CR00311 #1:

UUUGGCCUCUGAUUAGGGUGGUUUUAGAGCUAGAAAUAGCAAGUUAAAAUAAGGCUA GUCCGUUAUCAACUUGAAAAAGUGGCACCGAGUCGGUGCUUUU (SEQ ID NO: 355)

sgRNA CR00311 #2:

mU*mU*mU*GGCCUCUGAUUAGGGUGGUUUUAGAGCUAGAAAUAGCAAGUUAAAAUA AGGCUAGUCCGUUAUCAACUUGAAAAAGUGGCACCGAGUCGGUGCU*mU*mU*mU (SEQ ID NO: 356)

sgRNA CR00311 #3:

mU*mU*mU*GGCCUCUGAUUAGGGUGGUUUUAGAGCUAGAAAUAGCAAGUUAAAAUA AGGCUAGUCCGUUAUCAACUUGAAAAAGUGGCACCGAGUCGGUGCmU*mU*mU*U (SEQ ID NO: 1765)

dgRNA CR00311 #1:

crRNA: UUUGGCCUCUGAUUAGGGUGGUUUUAGAGCUAUGCUGUUUUG (SEQ ID NO: 357)

tracr:
AACAGCAUAGCAAGUUAAAAUAAGGCUAGUCCGUUAUCAACUUGAAAAAGUGGCACC GAGUCGGUGCUUUUUUU (SEQ ID NO: 6660)

dgRNA CR00311 #2:

crRNA:
mU*mU*mU*GGCCUCUGAUUAGGGUGGUUUUAGAGCUAUGCUGUU*mU*mU*mG (SEQ ID NO: 358)

tracr:
mA*mA*mC*AGCAUAGCAAGUUAAAAUAAGGCUAGUCCGUUAUCAACUUGAAAAAGUG GCACCGAGUCGGUGCUUUU*mU*mU*mU (SEQ ID NO: 346)

dgRNA CR00311 #3:

crRNA:
mU*mU*mU*GGCCUCUGAUUAGGGUGGUUUUAGAGCUAUGCUGUU*mU*mU*mG (SEQ ID NO: 358)

tracr:
AACAGCAUAGCAAGUUAAAAUAAGGCUAGUCCGUUAUCAACUUGAAAAAGUGGCACC GAGUCGGUGCUUUUUUU (SEQ ID NO: 6660).

In aspects of the invention, a gRNA comprising the targeting domain of CR00309 (SEQ ID NO: 245, underlined below), e.g., one of the gRNA molecules described below, is useful in the CRISPR systems, methods, cells and other aspects and embodiments of the invention, including in aspects involving more than one gRNA molecule, e.g., described herein:

sgRNA CR00309 #1:

CACGCCCCCACCCUAAUCAGGUUUUAGAGCUAGAAAUAGCAAGUUAAAAUAAGGCUA GUCCGUUAUCAACUUGAAAAAGUGGCACCGAGUCGGUGCUUUU (SEQ ID NO: 359)

sgRNA CR00309 #2:

mC*mA*mC*GCCCCCACCCUAAUCAGGUUUUAGAGCUAGAAAUAGCAAGUUAAAAUAA GGCUAGUCCGUUAUCAACUUGAAAAAGUGGCACCGAGUCGGUGCU*mU*mU*mU (SEQ ID NO: 360)

sgRNA CR00309 #3:

mC*mA*mC*GCCCCCACCCUAAUCAGGUUUUAGAGCUAGAAAUAGCAAGUUAAAAUAA GGCUAGUCCGUUAUCAACUUGAAAAAGUGGCACCGAGUCGGUGCmU*mU*mU*U (SEQ ID NO: 1766)

dgRNA CR00309 #1:

crRNA: CACGCCCCCACCCUAAUCAGGUUUUAGAGCUAUGCUGUUUUG (SEQ ID NO: 361)

tracr:
AACAGCAUAGCAAGUUAAAAUAAGGCUAGUCCGUUAUCAACUUGAAAAAGUGGCACC GAGUCGGUGCUUUUUUU (SEQ ID NO: 6660)

dgRNA CR00309 #2:

crRNA: mC*mA*mC*GCCCCCACCCUAAUCAGGUUUUAGAGCUAUGCUGUU*mU*mU*mG (SEQ ID NO: 362)

tracr:
mA*mA*mC*AGCAUAGCAAGUUAAAAUAAGGCUAGUCCGUUAUCAACUUGAAAAAGUG GCACCGAGUCGGUGCUUUU*mU*mU*mU (SEQ ID NO: 346)

dgRNA CR00309 #3:

crRNA: mC*mA*mC*GCCCCCACCCUAAUCAGGUUUUAGAGCUAUGCUGUU*mU*mU*mG (SEQ ID NO: 362)

tracr:
AACAGCAUAGCAAGUUAAAAUAAGGCUAGUCCGUUAUCAACUUGAAAAAGUGGCACC
GAGUCGGUGCUUUUUUU (SEQ ID NO: 6660).

In aspects of the invention, a gRNA comprising the targeting domain of CR001127 (SEQ ID NO: 337, underlined below), e.g., one of the gRNA molecules described below, is useful in the CRISPR systems, methods, cells and other aspects and embodiments of the invention, including in aspects involving more than one gRNA molecule, e.g., described herein:

sgRNA CR001127 #1:

CACAGGCUCCAGGAAGGGUUGUUUUAGAGCUAGAAAUAGCAAGUUAAAAUAAGGCUA
GUCCGUUAUCAACUUGAAAAAGUGGCACCGAGUCGGUGCUUUU (SEQ ID NO: 363)

sgRNA CR001127 #2:

mC*mA*mC*AGGCUCCAGGAAGGGUUGUUUUAGAGCUAGAAAUAGCAAGUUAAAAUAA
GGCUAGUCCGUUAUCAACUUGAAAAAGUGGCACCGAGUCGGUGCU*mU*mU*mU (SEQ ID NO: 364)

sgRNA CR001127 #3:

mC*mA*mC*AGGCUCCAGGAAGGGUUGUUUUAGAGCUAGAAAUAGCAAGUUAAAAUAA
GGCUAGUCCGUUAUCAACUUGAAAAAGUGGCACCGAGUCGGUGCmU*mU*mU*U (SEQ ID NO: 1767)

dgRNA CR001127 #1:

crRNA: CACAGGCUCCAGGAAGGGUUGUUUUAGAGCUAUGCUGUUUUG (SEQ ID NO: 365)

tracr:
AACAGCAUAGCAAGUUAAAAUAAGGCUAGUCCGUUAUCAACUUGAAAAAGUGGCACC
GAGUCGGUGCUUUUUUU (SEQ ID NO: 6660)

dgRNA CR001127 #2:

crRNA: mC*mA*mC*AGGCUCCAGGAAGGGUUGUUUUAGAGCUAUGCUGUU*mU*mU*mG (SEQ ID NO: 366)

tracr:
mA*mA*mC*AGCAUAGCAAGUUAAAAUAAGGCUAGUCCGUUAUCAACUUGAAAAAGUG
GCACCGAGUCGGUGCUUUU*mU*mU*mU (SEQ ID NO: 346)

dgRNA CR001127 #3:

crRNA: mC*mA*mC*AGGCUCCAGGAAGGGUUGUUUUAGAGCUAUGCUGUU*mU*mU*mG (SEQ ID NO: 366)

tracr: AACAGCAUAGCAAGUUAAAAUAAGGCUAGUCCGUUAUCAACUUGAAAAAGUGGCACC GAGUCGGUGCUUUUUUU (SEQ ID NO: 6660).

In aspects of the invention, a gRNA comprising the targeting domain of CR00316 (SEQ ID NO: 252, underlined below), e.g., one of the gRNA molecules described below, is useful in the CRISPR systems, methods, cells and other aspects and embodiments of the invention, including in aspects involving more than one gRNA molecule, e.g., described herein:

sgRNA CR00316 #1:

UUGCUUUUAUCACAGGCUCCGUUUUAGAGCUAGAAAUAGCAAGUUAAAAUAAGGCUA GUCCGUUAUCAACUUGAAAAAGUGGCACCGAGUCGGUGCUUUU (SEQ ID NO: 367)

sgRNA CR00316 #2:

mU*mU*mG*CUUUUAUCACAGGCUCCGUUUUAGAGCUAGAAAUAGCAAGUUAAAAUAA GGCUAGUCCGUUAUCAACUUGAAAAAGUGGCACCGAGUCGGUGCU*mU*mU*mU (SEQ ID NO: 368)

sgRNA CR00316 #3:

mU*mU*mG*CUUUUAUCACAGGCUCCGUUUUAGAGCUAGAAAUAGCAAGUUAAAAUAA GGCUAGUCCGUUAUCAACUUGAAAAAGUGGCACCGAGUCGGUGCmU*mU*mU*U (SEQ ID NO: 1768)

dgRNA CR00316 #1:

crRNA: UUGCUUUUAUCACAGGCUCCGUUUUAGAGCUAUGCUGUUUUG (SEQ ID NO: 369)

tracr: AACAGCAUAGCAAGUUAAAAUAAGGCUAGUCCGUUAUCAACUUGAAAAAGUGGCACC GAGUCGGUGCUUUUUUU (SEQ ID NO: 6660)

dgRNA CR00316 #2:

crRNA: mU*mU*mG*CUUUUAUCACAGGCUCCGUUUUAGAGCUAUGCUGUU*mU*mU*mG (SEQ ID NO: 370)

tracr:
mA*mA*mC*AGCAUAGCAAGUUAAAAUAAGGCUAGUCCGUUAUCAACUUGAAAAAGUG
GCACCGAGUCGGUGCUUUU*mU*mU*mU (SEQ ID NO: 346)

dgRNA CR00316 #3:

crRNA: mU*mU*mG*CUUUUAUCACAGGCUCCGUUUUAGAGCUAUGCUGUU*mU*mU*mG (SEQ ID NO: 370)

tracr:
AACAGCAUAGCAAGUUAAAAUAAGGCUAGUCCGUUAUCAACUUGAAAAAGUGGCACC
GAGUCGGUGCUUUUUUU (SEQ ID NO: 6660).

In aspects of the invention, a gRNA comprising the targeting domain of CR001125 (SEQ ID NO: 335, underlined below), e.g., one of the gRNA molecules described below, is useful in the CRISPR systems, methods, cells and other aspects and embodiments of the invention, including in aspects involving more than one gRNA molecule, e.g., described herein:

sgRNA CR001125 #1:

UUUUAUCACAGGCUCCAGGAGUUUUAGAGCUAGAAAUAGCAAGUUAAAAUAAGGCUA
GUCCGUUAUCAACUUGAAAAAGUGGCACCGAGUCGGUGCUUUU (SEQ ID NO: 371)

sgRNA CR001125 #2:

mU*mU*mU*UAUCACAGGCUCCAGGAGUUUUAGAGCUAGAAAUAGCAAGUUAAAAUAA
GGCUAGUCCGUUAUCAACUUGAAAAAGUGGCACCGAGUCGGUGCU*mU*mU*mU (SEQ ID NO: 372)

sgRNA CR001125 #3:

mU*mU*mU*UAUCACAGGCUCCAGGAGUUUUAGAGCUAGAAAUAGCAAGUUAAAAUAA
GGCUAGUCCGUUAUCAACUUGAAAAAGUGGCACCGAGUCGGUGCmU*mU*mU*U (SEQ ID NO: 1769)

dgRNA CR001125 #1:

crRNA: UUUUAUCACAGGCUCCAGGAGUUUUAGAGCUAUGCUGUUUUG (SEQ ID NO: 373)

tracr:
AACAGCAUAGCAAGUUAAAAUAAGGCUAGUCCGUUAUCAACUUGAAAAAGUGGCACC
GAGUCGGUGCUUUUUUU (SEQ ID NO: 6660)

dgRNA CR001125 #2:

crRNA: mU*mU*mU*UAUCACAGGCUCCAGGAGUUUUAGAGCUAUGCUGUU*mU*mU*mG (SEQ ID NO: 374)

tracr:
mA*mA*mC*AGCAUAGCAAGUUAAAAUAAGGCUAGUCCGUUAUCAACUUGAAAAAGUG
GCACCGAGUCGGUGCUUUU*mU*mU*mU (SEQ ID NO: 346)

dgRNA CR001125 #3:

crRNA: mU*mU*mU*UAUCACAGGCUCCAGGAGUUUUAGAGCUAUGCUGUU*mU*mU*mG (SEQ ID NO: 374)

tracr:
AACAGCAUAGCAAGUUAAAAUAAGGCUAGUCCGUUAUCAACUUGAAAAAGUGGCACC
GAGUCGGUGCUUUUUUU (SEQ ID NO: 6660).

In aspects of the invention, a gRNA comprising the targeting domain of CR001030 (SEQ ID NO: 100, underlined below), e.g., one of the gRNA molecules described below, is useful in the CRISPR systems, methods, cells and other aspects and embodiments of the invention, including in aspects involving more than one gRNA molecule, e.g., described herein:

sgRNA CR001030 #1:

ACUGCUGAAAGAGAUGCGGUGUUUUAGAGCUAGAAAUAGCAAGUUAAAAUAAGGCUA
GUCCGUUAUCAACUUGAAAAAGUGGCACCGAGUCGGUGCUUUU (SEQ ID NO: 375)

sgRNA CR001030 #2:

mA*mC*mU*GCUGAAAGAGAUGCGGUGUUUUAGAGCUAGAAAUAGCAAGUUAAAAUA
AGGCUAGUCCGUUAUCAACUUGAAAAAGUGGCACCGAGUCGGUGCU*mU*mU*mU
(SEQ ID NO: 376)

sgRNA CR001030 #3:

mA*mC*mU*GCUGAAAGAGAUGCGGUGUUUUAGAGCUAGAAAUAGCAAGUUAAAAUA
AGGCUAGUCCGUUAUCAACUUGAAAAAGUGGCACCGAGUCGGUGCmU*mU*mU*U
(SEQ ID NO: 1770)

dgRNA CR001030 #1:

crRNA: ACUGCUGAAAGAGAUGCGGUGUUUUAGAGCUAUGCUGUUUUG (SEQ ID NO: 377)

tracr:
AACAGCAUAGCAAGUUAAAAUAAGGCUAGUCCGUUAUCAACUUGAAAAAGUGGCACC
GAGUCGGUGCUUUUUUU (SEQ ID NO: 6660)

dgRNA CR001030 #2:

crRNA:
mA*mC*mU*GCUGAAAGAGAUGCGGUGUUUUAGAGCUAUGCUGUU*mU*mU*mG (SEQ ID NO: 378)

tracr:
mA*mA*mC*AGCAUAGCAAGUUAAAAUAAGGCUAGUCCGUUAUCAACUUGAAAAAGUG
GCACCGAGUCGGUGCUUUU*mU*mU*mU (SEQ ID NO: 346)

dgRNA CR001030 #3:

crRNA:
mA*mC*mU*GCUGAAAGAGAUGCGGUGUUUUAGAGCUAUGCUGUU*mU*mU*mG (SEQ ID NO: 378)

tracr:
AACAGCAUAGCAAGUUAAAAUAAGGCUAGUCCGUUAUCAACUUGAAAAAGUGGCACC
GAGUCGGUGCUUUUUUU (SEQ ID NO: 6660).

In aspects of the invention, a gRNA comprising the targeting domain of CR001028 (SEQ ID NO: 98, underlined below), e.g., one of the gRNA molecules described below, is useful in the CRISPR systems, methods, cells and other aspects and embodiments of the invention , including in aspects involving more than one gRNA molecule, e.g., described herein:

sgRNA CR001028 #1:

UGCGGUGGGGAGAUAUGUAGGUUUUAGAGCUAGAAAUAGCAAGUUAAAAUAAGGCUA
GUCCGUUAUCAACUUGAAAAAGUGGCACCGAGUCGGUGCUUUU (SEQ ID NO: 379)

sgRNA CR001028 #2:

mU*mG*mC*GGUGGGGAGAUAUGUAGGUUUUAGAGCUAGAAAUAGCAAGUUAAAAUA
AGGCUAGUCCGUUAUCAACUUGAAAAAGUGGCACCGAGUCGGUGCU*mU*mU*mU
(SEQ ID NO: 380)

sgRNA CR001028 #3:

mU*mG*mC*GGUGGGGAGAUAUGUAGGUUUUAGAGCUAGAAAUAGCAAGUUAAAAUA AGGCUAGUCCGUUAUCAACUUGAAAAAGUGGCACCGAGUCGGUGCmU*mU*mU*U (SEQ ID NO: 1771)

dgRNA CR001028 #1:

crRNA: UGCGGUGGGGAGAUAUGUAGGUUUUAGAGCUAUGCUGUUUUG (SEQ ID NO: 381)

tracr: AACAGCAUAGCAAGUUAAAAUAAGGCUAGUCCGUUAUCAACUUGAAAAAGUGGCACC GAGUCGGUGCUUUUUUU (SEQ ID NO: 6660)

dgRNA CR001028 #2:

crRNA: mU*mG*mC*GGUGGGGAGAUAUGUAGGUUUUAGAGCUAUGCUGUU*mU*mU*mG (SEQ ID NO: 382)

tracr: mA*mA*mC*AGCAUAGCAAGUUAAAAUAAGGCUAGUCCGUUAUCAACUUGAAAAAGUG GCACCGAGUCGGUGCUUUU*mU*mU*mU (SEQ ID NO: 346)

dgRNA CR001028 #3:

crRNA: mU*mG*mC*GGUGGGGAGAUAUGUAGGUUUUAGAGCUAUGCUGUU*mU*mU*mG (SEQ ID NO: 382)

tracr: AACAGCAUAGCAAGUUAAAAUAAGGCUAGUCCGUUAUCAACUUGAAAAAGUGGCACC GAGUCGGUGCUUUUUUU (SEQ ID NO: 6660).

In aspects of the invention, a gRNA comprising the targeting domain of CR001221 (SEQ ID NO: 1589, underlined below), e.g., one of the gRNA molecules described below, is useful in the CRISPR systems, methods, cells and other aspects and embodiments of the invention, including in aspects involving more than one gRNA molecule, e.g., described herein:

sgRNA CR001221 #1:

GAAACAAUGAGGACCUGACUGUUUUAGAGCUAGAAAUAGCAAGUUAAAAUAAGGCUA GUCCGUUAUCAACUUGAAAAAGUGGCACCGAGUCGGUGCUUUU (SEQ ID NO: 383)

sgRNA CR001221 #2:

mG*mA*mA*ACAAUGAGGACCUGACUGUUUUAGAGCUAGAAAUAGCAAGUUAAAAUA AGGCUAGUCCGUUAUCAACUUGAAAAAGUGGCACCGAGUCGGUGCU*mU*mU*mU (SEQ ID NO: 384)

sgRNA CR001221 #3:

mG*mA*mA*ACAAUGAGGACCUGACUGUUUUAGAGCUAGAAAUAGCAAGUUAAAAUA AGGCUAGUCCGUUAUCAACUUGAAAAAGUGGCACCGAGUCGGUGCmU*mU*mU*U (SEQ ID NO: 1772)

dgRNA CR001221 #1:

crRNA: GAAACAAUGAGGACCUGACUGUUUUAGAGCUAUGCUGUUUUG (SEQ ID NO: 385)

tracr: AACAGCAUAGCAAGUUAAAAUAAGGCUAGUCCGUUAUCAACUUGAAAAAGUGGCACC GAGUCGGUGCUUUUUUU (SEQ ID NO: 6660)

dgRNA CR001221 #2:

crRNA: mG*mA*mA*ACAAUGAGGACCUGACUGUUUUAGAGCUAUGCUGUU*mU*mU*mG (SEQ ID NO: 386)

tracr: mA*mA*mC*AGCAUAGCAAGUUAAAAUAAGGCUAGUCCGUUAUCAACUUGAAAAAGUG GCACCGAGUCGGUGCUUUU*mU*mU*mU (SEQ ID NO: 346)

dgRNA CR001221 #3:

crRNA: mG*mA*mA*ACAAUGAGGACCUGACUGUUUUAGAGCUAUGCUGUU*mU*mU*mG (SEQ ID NO: 386)

tracr: AACAGCAUAGCAAGUUAAAAUAAGGCUAGUCCGUUAUCAACUUGAAAAAGUGGCACC GAGUCGGUGCUUUUUUU (SEQ ID NO: 6660).

In aspects of the invention, a gRNA comprising the targeting domain of CR001137 (SEQ ID NO: 1505, underlined below), e.g., one of the gRNA molecules described below, is useful in the CRISPR systems, methods, cells and other aspects and embodiments of the invention, including in aspects involving more than one gRNA molecule, e.g., described herein:

sgRNA CR001137 #1:

GUAAGCAUUUAAGUGGCUACGUUUUAGAGCUAGAAAUAGCAAGUUAAAAUAAGGCUA GUCCGUUAUCAACUUGAAAAAGUGGCACCGAGUCGGUGCUUUU (SEQ ID NO: 387)

sgRNA CR001137 #2:

mG*mU*mA*AGCAUUUAAGUGGCUACGUUUUAGAGCUAGAAAUAGCAAGUUAAAAUA AGGCUAGUCCGUUAUCAACUUGAAAAAGUGGCACCGAGUCGGUGCU*mU*mU*mU (SEQ ID NO: 388)

sgRNA CR001137 #3:

mG*mU*mA*AGCAUUUAAGUGGCUACGUUUUAGAGCUAGAAAUAGCAAGUUAAAAUA AGGCUAGUCCGUUAUCAACUUGAAAAAGUGGCACCGAGUCGGUGCmU*mU*mU*U (SEQ ID NO: 1773)

dgRNA CR001137 #1:

crRNA: GUAAGCAUUUAAGUGGCUACGUUUUAGAGCUAUGCUGUUUUG (SEQ ID NO: 389)

tracr:
AACAGCAUAGCAAGUUAAAAUAAGGCUAGUCCGUUAUCAACUUGAAAAAGUGGCACC GAGUCGGUGCUUUUUUU (SEQ ID NO: 6660)

dgRNA CR001137 #2:

crRNA:
mG*mU*mA*AGCAUUUAAGUGGCUACGUUUUAGAGCUAUGCUGUU*mU*mU*mG (SEQ ID NO: 390)

tracr:
mA*mA*mC*AGCAUAGCAAGUUAAAAUAAGGCUAGUCCGUUAUCAACUUGAAAAAGUG GCACCGAGUCGGUGCUUUU*mU*mU*mU (SEQ ID NO: 346)

dgRNA CR001137 #3:

crRNA:
mG*mU*mA*AGCAUUUAAGUGGCUACGUUUUAGAGCUAUGCUGUU*mU*mU*mG (SEQ ID NO: 390)

tracr:
AACAGCAUAGCAAGUUAAAAUAAGGCUAGUCCGUUAUCAACUUGAAAAAGUGGCACC GAGUCGGUGCUUUUUUU (SEQ ID NO: 6660).

In aspects of the invention, a gRNA comprising the targeting domain of CR003035 (SEQ ID NO: 1505, underlined below), e.g., one of the gRNA molecules described below, is useful in the CRISPR systems, methods, cells and other aspects and embodiments of the invention, including in aspects involving more than one gRNA molecule, e.g., described herein:

sgRNA CR003035 #1:

AGGCACCUCAGACUCAGCAUGUUUUAGAGCUAGAAAUAGCAAGUUAAAAUAAGGCUAGUCCGUUAUCAACUUGAAAAAGUGGCACCGAGUCGGUGCUUUU (SEQ ID NO: 391)

sgRNA CR003035 #2:

mA*mG*mG*CACCUCAGACUCAGCAUGUUUUAGAGCUAGAAAUAGCAAGUUAAAAUAAGGCUAGUCCGUUAUCAACUUGAAAAAGUGGCACCGAGUCGGUGCU*mU*mU*mU (SEQ ID NO: 392)

sgRNA CR003035 #3:

mA*mG*mG*CACCUCAGACUCAGCAUGUUUUAGAGCUAGAAAUAGCAAGUUAAAAUAAGGCUAGUCCGUUAUCAACUUGAAAAAGUGGCACCGAGUCGGUGCmU*mU*mU*U (SEQ ID NO: 1774)

dgRNA CR003035 #1:

crRNA: AGGCACCUCAGACUCAGCAUGUUUUAGAGCUAUGCUGUUUUG (SEQ ID NO: 393)

tracr:
AACAGCAUAGCAAGUUAAAAUAAGGCUAGUCCGUUAUCAACUUGAAAAAGUGGCACCGAGUCGGUGCUUUUUUU (SEQ ID NO: 6660)

dgRNA CR003035 #2:

crRNA: mA*mG*mG*CACCUCAGACUCAGCAUGUUUUAGAGCUAUGCUGUU*mU*mU*mG (SEQ ID NO: 394)

tracr:
mA*mA*mC*AGCAUAGCAAGUUAAAAUAAGGCUAGUCCGUUAUCAACUUGAAAAAGUGGCACCGAGUCGGUGCUUUU*mU*mU*mU (SEQ ID NO: 346)

dgRNA CR003035 #3:

crRNA: mA*mG*mG*CACCUCAGACUCAGCAUGUUUUAGAGCUAUGCUGUU*mU*mU*mG (SEQ ID NO: 394)

tracr:
AACAGCAUAGCAAGUUAAAAUAAGGCUAGUCCGUUAUCAACUUGAAAAAGUGGCACC
GAGUCGGUGCUUUUUUU (SEQ ID NO: 6660).

In aspects of the invention, a gRNA comprising the targeting domain of CR003085 (SEQ ID NO: 1750, underlined below), e.g., one of the gRNA molecules described below, is useful in the CRISPR systems, methods, cells and other aspects and embodiments of the invention, including in aspects involving more than one gRNA molecule, e.g., described herein:

sgRNA CR003085 #1:

AUGGUAUGGGAGGUAUACUAGUUUUAGAGCUAGAAAUAGCAAGUUAAAAUAAGGCUA
GUCCGUUAUCAACUUGAAAAAGUGGCACCGAGUCGGUGCUUUU (SEQ ID NO: 395)

sgRNA CR003085 #2:

mA*mU*mG*GUAUGGGAGGUAUACUAGUUUUAGAGCUAGAAAUAGCAAGUUAAAAUA
AGGCUAGUCCGUUAUCAACUUGAAAAAGUGGCACCGAGUCGGUGCU*mU*mU*mU
(SEQ ID NO: 396)

sgRNA CR003085 #3:

mA*mU*mG*GUAUGGGAGGUAUACUAGUUUUAGAGCUAGAAAUAGCAAGUUAAAAUA
AGGCUAGUCCGUUAUCAACUUGAAAAAGUGGCACCGAGUCGGUGCmU*mU*mU*U
(SEQ ID NO: 1775)

dgRNA CR003085 #1:

crRNA: AUGGUAUGGGAGGUAUACUAGUUUUAGAGCUAUGCUGUUUUG (SEQ ID NO: 397)

tracr:
AACAGCAUAGCAAGUUAAAAUAAGGCUAGUCCGUUAUCAACUUGAAAAAGUGGCACC
GAGUCGGUGCUUUUUUU (SEQ ID NO: 6660)

dgRNA CR003085 #2:

crRNA:
mA*mU*mG*GUAUGGGAGGUAUACUAGUUUUAGAGCUAUGCUGUU*mU*mU*mG (SEQ ID NO: 398)

tracr:
mA*mA*mC*AGCAUAGCAAGUUAAAAUAAGGCUAGUCCGUUAUCAACUUGAAAAAGUG
GCACCGAGUCGGUGCUUUU*mU*mU*mU (SEQ ID NO: 346)

dgRNA CR003085 #3:

crRNA:
mA*mU*mG*GUAUGGGAGGUAUACUAGUUUUAGAGCUAUGCUGUU*mU*mU*mG (SEQ ID NO: 398)

tracr:
AACAGCAUAGCAAGUUAAAAUAAGGCUAGUCCGUUAUCAACUUGAAAAAGUGGCACCGAGUCGGUGCUUUUUUU (SEQ ID NO: 6660).

In each of the gRNA molecules described above, a "*" denotes a phosphorothioate bond between the adjacent nucleotides, and "mN" (where N = A, G, C or U) denotes a 2'-OMe modified nucleotide. In embodiments, any of the gRNA molecules described herein, e.g., described above, is complexed with a Cas9 molecule, e.g., as described herein, to form a ribonuclear protein complex (RNP). Such RNPs are particularly useful in the methods, cells, and other aspects and embodiments of the invention, e.g., described herein.

IV. Cas Molecules

Cas9 Molecules

In preferred embodiments, the Cas molecule is a Cas9 molecule. Cas9 molecules of a variety of species can be used in the methods and compositions described herein. While the S. pyogenes Cas9 molecule are the subject of much of the disclosure herein, Cas9 molecules of, derived from, or based on the Cas9 proteins of other species listed herein can be used as well. In other words, other Cas9 molecules, e.g., S. thermophilus, Staphylococcus aureus and/or Neisseria meningitidis Cas9 molecules, may be used in the systems, methods and compositions described herein. Additional Cas9 species include: Acidovorax avenae, Actinobacillus pleuropneumoniae, Actinobacillus succinogenes, Actinobacillus suis, Actinomyces sp., cycliphilus denitrificans, Aminomonas paucivorans, Bacillus cereus, Bacillus smithii, Bacillus thuringiensis, Bacteroides sp., Blastopirellula marina, Bradyrhizobium sp., Brevibacillus latemsporus, Campylobacter coli, Campylobacter jejuni, Campylobacter lad, Candidatus Puniceispirillum, Clostridiu cellulolyticum, Clostridium perfringens, Corynebacterium accolens, Corynebacterium diphtheria, Corynebacterium matruchotii, Dinoroseobacter sliibae, Eubacterium dolichum, gamma proteobacterium, Gluconacetobacler diazotrophicus, Haemophilus parainfluenzae, Haemophilus sputorum, Helicobacter canadensis, Helicobacter cinaedi, Helicobacter mustelae, Ilyobacler polytropus, Kingella kingae, Lactobacillus crispatus, Listeria ivanovii, Listeria monocytogenes, Listeriaceae bacterium, Methylocystis sp., Methylosinus trichosporium, Mobiluncus mulieris, Neisseria bacilliformis, Neisseria cinerea, Neisseria flavescens, Neisseria lactamica. Neisseria sp., Neisseria wadsworthii, Nitrosomonas sp., Parvibaculum lavamentivorans, Pasteurella multocida, Phascolarctobacterium succinatutens, Ralstonia syzygii, Rhodopseudomonas palustris,

Rhodovulum sp., Simonsiella muelleri, Sphingomonas sp., Sporolactobacillus vineae, Staphylococcus lugdunensis, Streptococcus sp., Subdoligranulum sp., Tislrella mobilis, Treponema sp., or Verminephrobacter eiseniae.

A Cas9 molecule, as that term is used herein, refers to a molecule that can interact with a gRNA molecule (e.g., sequence of a domain of a tracr) and, in concert with the gRNA molecule, localize (e.g., target or home) to a site which comprises a target sequence and PAM sequence.

In an embodiment, the Cas9 molecule is capable of cleaving a target nucleic acid molecule, which may be referred to herein as an active Cas9 molecule. In an embodiment, an active Cas9 molecule, comprises one or more of the following activities: a nickase activity, i.e., .the ability to cleave a single strand, e.g., the non-complementary strand or the complementary strand, of a nucleic acid molecule; a double stranded nuclease activity, i.e., the ability to cleave both strands of a double stranded nucleic acid and create a double stranded break, which in an embodiment is the presence of two nickase activities; an endonuclease activity; an exonuclease activity; and a helicase activity, i.e., the ability to unwind the helical structure of a double stranded nucleic acid.

In an embodiment, an enzymatically active Cas9 molecule cleaves both DNA strands and results in a double stranded break. In an embodiment, a Cas9 molecule cleaves only one strand, e.g., the strand to which the gRNA hybridizes to, or the strand complementary to the strand the gRNA hybridizes with. In an embodiment, an active Cas9 molecule comprises cleavage activity associated with an HNH-like domain. In an embodiment, an active Cas9 molecule comprises cleavage activity associated with an N-terminal RuvC-like domain. In an embodiment, an active Cas9 molecule comprises cleavage activity associated with an HNH-like domain and cleavage activity associated with an N-terminal RuvC-like domain. In an embodiment, an active Cas9 molecule comprises an active, or cleavage competent, HNH-like domain and an inactive, or cleavage incompetent, N-terminal RuvC-like domain. In an embodiment, an active Cas9 molecule comprises an inactive, or cleavage incompetent, HNH-like domain and an active, or cleavage competent, N-terminal RuvC-like domain.

In an embodiment, the ability of an active Cas9 molecule to interact with and cleave a target nucleic acid is PAM sequence dependent. A PAM sequence is a sequence in the target nucleic acid. In an embodiment, cleavage of the target nucleic acid occurs upstream from the PAM sequence. Active Cas9 molecules from different bacterial species can recognize different sequence motifs (e.g., PAM sequences). In an embodiment, an active Cas9 molecule of S. pyogenes recognizes the sequence motif NGG and directs cleavage of a target nucleic acid sequence 1 to 10, e.g., 3 to 5, base pairs upstream from that sequence. See, e.g., Mali el ai, SCIENCE 2013; 339(6121): 823- 826. In an embodiment, an active Cas9 molecule of S. thermophilus recognizes the sequence motif NGGNG and NNAG AAW (W = A or T) and directs cleavage of a core target nucleic acid sequence 1 to 10, e.g., 3 to 5, base pairs upstream from these sequences. See, e.g., Horvath et al., SCIENCE 2010; 327(5962): 167- 170,

and Deveau et al , J BACTERIOL 2008; 190(4): 1390- 1400. In an embodiment, an active Cas9 molecule of S. mulans recognizes the sequence motif NGG or NAAR (R - A or G) and directs cleavage of a core target nucleic acid sequence 1 to 10, e.g., 3 to 5 base pairs, upstream from this sequence. See, e.g., Deveau et al. , J BACTERIOL 2008; 190(4): 1 390- 1400.

In an embodiment, an active Cas9 molecule of S. aureus recognizes the sequence motif NNGRR (R = A or G) and directs cleavage of a target nucleic acid sequence 1 to 10, e.g., 3 to 5, base pairs upstream from that sequence. See, e.g., Ran F. et al., NATURE, vol. 520, 2015, pp. 186-191. In an embodiment, an active Cas9 molecule of N. meningitidis recognizes the sequence motif NNNNGATT and directs cleavage of a target nucleic acid sequence 1 to 10, e.g., 3 to 5, base pairs upstream from that sequence. See, e.g., Hou et al., PNAS EARLY EDITION 2013, 1 -6. The ability of a Cas9 molecule to recognize a PAM sequence can be determined, e.g., using a transformation assay described in Jinek et al , SCIENCE 2012, 337:816.

Some Cas9 molecules have the ability to interact with a gRNA molecule, and in conjunction with the gRNA molecule home (e.g., targeted or localized) to a core target domain, but are incapable of cleaving the target nucleic acid, or incapable of cleaving at efficient rates. Cas9 molecules having no, or no substantial, cleavage activity may be referred to herein as an inactive Cas9 (an enzymatically inactive Cas9), a dead Cas9, or a dCas9 molecule. For example, an inactive Cas9 molecule can lack cleavage activity or have substantially less, e.g., less than 20, 10, 5, 1 or 0.1 % of the cleavage activity of a reference Cas9 molecule, as measured by an assay described herein.

Exemplary naturally occurring Cas9 molecules are described in Chylinski et al , RNA Biology 2013; 10:5, 727-737. Such Cas9 molecules include Cas9 molecules of a cluster 1 bacterial family, cluster 2 bacterial family, cluster 3 bacterial family, cluster 4 bacterial family, cluster 5 bacterial family, cluster 6 bacterial family, a cluster 7 bacterial family, a cluster 8 bacterial family, a cluster 9 bacterial family, a cluster 10 bacterial family, a cluster 1 1 bacterial family, a cluster 12 bacterial family, a cluster 13 bacterial family, a cluster 14 bacterial family, a cluster 1 bacterial family, a cluster 16 bacterial family, a cluster 17 bacterial family, a cluster 1 8 bacterial family, a cluster 19 bacterial family, a cluster 20 bacterial family, a cluster 21 bacterial family, a cluster 22 bacterial family, a cluster 23 bacterial family, a cluster 24 bacterial family, a cluster 25 bacterial family, a cluster 26 bacterial family, a cluster 27 bacterial family, a cluster 28 bacterial family, a cluster 29 bacterial family, a cluster 30 bacterial family, a cluster 31 bacterial family, a cluster 32 bacterial family, a cluster 33 bacterial family, a cluster 34 bacterial family, a cluster 35 bacterial family, a cluster 36 bacterial family, a cluster 37 bacterial family, a cluster 38 bacterial family, a cluster 39 bacterial family, a cluster 40 bacterial family, a cluster 41 bacterial family, a cluster 42 bacterial family, a cluster 43 bacterial family, a cluster 44 bacterial family, a cluster 45 bacterial family, a cluster 46 bacterial family, a cluster 47 bacterial family, a cluster 48 bacterial family,. a cluster 49 bacterial family, a

cluster 50 bacterial family, a cluster 5 1 bacterial family, a cluster 52 bacterial family, a cluster 53 bacterial family, a cluster 54 bacterial family, a cluster 55 bacterial family, a cluster 56 bacterial family, a cluster 57 bacterial family, a cluster 58 bacterial family, a cluster 59 bacterial family, a cluster 60 bacterial family, a cluster 61 bacterial family, a cluster 62 bacterial family, a cluster 63 bacterial family, a cluster 64 bacterial family, a cluster 65 bacterial family, a cluster 66 bacterial family, a cluster 67 bacterial family, a cluster 68 bacterial family, a cluster 69 bacterial family, a cluster 70 bacterial family, a cluster 71 bacterial family, a cluster 72 bacterial family, a cluster 73 bacterial family, a cluster 74 bacterial family, a cluster 75 bacterial family, a cluster 76 bacterial family, a cluster 77 bacterial family, or a cluster 78 bacterial family.

Exemplary naturally occurring Cas9 molecules include a Cas9 molecule of a cluster 1 bacterial family. Examples include a Cas9 molecule of: S. pyogenes (e.g., strain SF370, MGAS 10270, MGAS 10750, MGAS2096, MGAS315, MGAS5005, MGAS6180, MGAS9429, NZ131 and SSI- 1), S. thermophilus (e.g., strain LMD-9), S. pseudoporcinus (e.g., strain SPIN 20026), S. mutans (e.g., strain UA 159, NN2025), S. macacae (e.g., strain NCTC1 1558), S. gallolylicus (e.g., strain UCN34, ATCC BAA-2069), S. equines (e.g., strain ATCC 9812, MGCS 124), S. dysdalactiae (e.g., strain GGS 124), S. bovis (e.g., strain ATCC 700338), S. cmginosus (e.g.; strain F021 1), S. agalactia* (e.g., strain NEM316, A909), Listeria monocytogenes (e.g., strain F6854), Listeria innocua (L. innocua, e.g., strain Clip l 1262), EtUerococcus italicus (e.g., strain DSM 15952), or Enterococcus faecium (e.g., strain 1,231 ,408). Additional exemplary Cas9 molecules are a Cas9 molecule of Neisseria meningitidis (Hou et al. PNAS Early Edition 2013, 1 -6) and a S. aureus Cas9 molecule.

In an embodiment, a Cas9 molecule, e.g., an active Cas9 molecule or inactive Cas9 molecule, comprises an amino acid sequence: having 60%, 65%, 70%, 75%, 80%, 85%, 90%, 95%, 96%, 97%, 98%, or 99% homology with; differs at no more than 1%, 2%, 5%, 10%, 15%, 20%, 30%, or 40% of the amino acid residues when compared with; differs by at least 1, 2, 5, 10 or 20 amino acids but by no more than 100, 80, 70, 60, 50, 40 or 30 amino acids from; or is identical to; any Cas9 molecule sequence described herein or a naturally occurring Cas9 molecule sequence, e.g., a Cas9 molecule from a species listed herein or described in Chylinski et al. , RNA Biology 2013, 10:5, 726-737, Hou et al. PNAS Early Edition 2013, 1-6.

In an embodiment, a Cas9 molecule comprises an amino acid sequence having 60%, 65%, 70%, 75%, 80%, 85%, 90%, 95%, 96%, 97%, 98%, or 99% homology with; differs at no more than 1%, 2%, 5%, 10%, 15%, 20%, 30%, or 40% of the amino acid residues when compared with; differs by at least 1, 2, 5, 10 or 20 amino acids but by no more than 100, 80, 70, 60, 50, 40 or 30 amino acids from; or is identical to; *S. pyogenes* Cas9:

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Met Asp Lys Lys Tyr Ser Ile Gly Leu Asp Ile Gly Thr Asn Ser Val
1               5                  10                  15
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Gly Trp Ala Val Ile Thr Asp Glu Tyr Lys Val Pro Ser Lys Lys Phe
            20                  25                  30
Lys Val Leu Gly Asn Thr Asp Arg His Ser Ile Lys Lys Asn Leu Ile
        35                  40                  45
Gly Ala Leu Leu Phe Asp Ser Gly Glu Thr Ala Glu Ala Thr Arg Leu
    50                  55                  60
Lys Arg Thr Ala Arg Arg Arg Tyr Thr Arg Arg Lys Asn Arg Ile Cys
65                  70                  75                  80
Tyr Leu Gln Glu Ile Phe Ser Asn Glu Met Ala Lys Val Asp Asp Ser
                85                  90                  95
Phe Phe His Arg Leu Glu Glu Ser Phe Leu Val Glu Glu Asp Lys Lys
            100                 105                 110
His Glu Arg His Pro Ile Phe Gly Asn Ile Val Asp Glu Val Ala Tyr
        115                 120                 125
His Glu Lys Tyr Pro Thr Ile Tyr His Leu Arg Lys Lys Leu Val Asp
    130                 135                 140
Ser Thr Asp Lys Ala Asp Leu Arg Leu Ile Tyr Leu Ala Leu Ala His
145                 150                 155                 160
Met Ile Lys Phe Arg Gly His Phe Leu Ile Glu Gly Asp Leu Asn Pro
                165                 170                 175
Asp Asn Ser Asp Val Asp Lys Leu Phe Ile Gln Leu Val Gln Thr Tyr
            180                 185                 190
Asn Gln Leu Phe Glu Glu Asn Pro Ile Asn Ala Ser Gly Val Asp Ala
        195                 200                 205
Lys Ala Ile Leu Ser Ala Arg Leu Ser Lys Ser Arg Arg Leu Glu Asn
    210                 215                 220
Leu Ile Ala Gln Leu Pro Gly Glu Lys Lys Asn Gly Leu Phe Gly Asn
225                 230                 235                 240
Leu Ile Ala Leu Ser Leu Gly Leu Thr Pro Asn Phe Lys Ser Asn Phe
                245                 250                 255
Asp Leu Ala Glu Asp Ala Lys Leu Gln Leu Ser Lys Asp Thr Tyr Asp
            260                 265                 270
Asp Asp Leu Asp Asn Leu Leu Ala Gln Ile Gly Asp Gln Tyr Ala Asp
        275                 280                 285
Leu Phe Leu Ala Ala Lys Asn Leu Ser Asp Ala Ile Leu Leu Ser Asp
    290                 295                 300
Ile Leu Arg Val Asn Thr Glu Ile Thr Lys Ala Pro Leu Ser Ala Ser
```

305 310 315 320
Met Ile Lys Arg Tyr Asp Glu His His Gln Asp Leu Thr Leu Leu Lys
325 330 335
Ala Leu Val Arg Gln Gln Leu Pro Glu Lys Tyr Lys Glu Ile Phe Phe
340 345 350
Asp Gln Ser Lys Asn Gly Tyr Ala Gly Tyr Ile Asp Gly Gly Ala Ser
355 360 365
Gln Glu Glu Phe Tyr Lys Phe Ile Lys Pro Ile Leu Glu Lys Met Asp
370 375 380
Gly Thr Glu Glu Leu Leu Val Lys Leu Asn Arg Glu Asp Leu Leu Arg
385 390 395 400
Lys Gln Arg Thr Phe Asp Asn Gly Ser Ile Pro His Gln Ile His Leu
405 410 415
Gly Glu Leu His Ala Ile Leu Arg Arg Gln Glu Asp Phe Tyr Pro Phe
420 425 430
Leu Lys Asp Asn Arg Glu Lys Ile Glu Lys Ile Leu Thr Phe Arg Ile
435 440 445
Pro Tyr Tyr Val Gly Pro Leu Ala Arg Gly Asn Ser Arg Phe Ala Trp
450 455 460
Met Thr Arg Lys Ser Glu Glu Thr Ile Thr Pro Trp Asn Phe Glu Glu
465 470 475 480
Val Val Asp Lys Gly Ala Ser Ala Gln Ser Phe Ile Glu Arg Met Thr
485 490 495
Asn Phe Asp Lys Asn Leu Pro Asn Glu Lys Val Leu Pro Lys His Ser
500 505 510
Leu Leu Tyr Glu Tyr Phe Thr Val Tyr Asn Glu Leu Thr Lys Val Lys
515 520 525
Tyr Val Thr Glu Gly Met Arg Lys Pro Ala Phe Leu Ser Gly Glu Gln
530 535 540
Lys Lys Ala Ile Val Asp Leu Leu Phe Lys Thr Asn Arg Lys Val Thr
545 550 555 560
Val Lys Gln Leu Lys Glu Asp Tyr Phe Lys Lys Ile Glu Cys Phe Asp
565 570 575
Ser Val Glu Ile Ser Gly Val Glu Asp Arg Phe Asn Ala Ser Leu Gly
580 585 590
Thr Tyr His Asp Leu Leu Lys Ile Ile Lys Asp Lys Asp Phe Leu Asp
595 600 605

Asn Glu Glu Asn Glu Asp Ile Leu Glu Asp Ile Val Leu Thr Leu Thr
610 615 620
Leu Phe Glu Asp Arg Glu Met Ile Glu Glu Arg Leu Lys Thr Tyr Ala
625 630 635 640
His Leu Phe Asp Asp Lys Val Met Lys Gln Leu Lys Arg Arg Arg Tyr
645 650 655
Thr Gly Trp Gly Arg Leu Ser Arg Lys Leu Ile Asn Gly Ile Arg Asp
660 665 670
Lys Gln Ser Gly Lys Thr Ile Leu Asp Phe Leu Lys Ser Asp Gly Phe
675 680 685
Ala Asn Arg Asn Phe Met Gln Leu Ile His Asp Asp Ser Leu Thr Phe
690 695 700
Lys Glu Asp Ile Gln Lys Ala Gln Val Ser Gly Gln Gly Asp Ser Leu
705 710 715 720
His Glu His Ile Ala Asn Leu Ala Gly Ser Pro Ala Ile Lys Lys Gly
725 730 735
Ile Leu Gln Thr Val Lys Val Val Asp Glu Leu Val Lys Val Met Gly
740 745 750
Arg His Lys Pro Glu Asn Ile Val Ile Glu Met Ala Arg Glu Asn Gln
755 760 765
Thr Thr Gln Lys Gly Gln Lys Asn Ser Arg Glu Arg Met Lys Arg Ile
770 775 780
Glu Glu Gly Ile Lys Glu Leu Gly Ser Gln Ile Leu Lys Glu His Pro
785 790 795 800
Val Glu Asn Thr Gln Leu Gln Asn Glu Lys Leu Tyr Leu Tyr Tyr Leu
805 810 815
Gln Asn Gly Arg Asp Met Tyr Val Asp Gln Glu Leu Asp Ile Asn Arg
820 825 830
Leu Ser Asp Tyr Asp Val Asp His Ile Val Pro Gln Ser Phe Leu Lys
835 840 845
Asp Asp Ser Ile Asp Asn Lys Val Leu Thr Arg Ser Asp Lys Asn Arg
850 855 860
Gly Lys Ser Asp Asn Val Pro Ser Glu Glu Val Val Lys Lys Met Lys
865 870 875 880
Asn Tyr Trp Arg Gln Leu Leu Asn Ala Lys Leu Ile Thr Gln Arg Lys
885 890 895
Phe Asp Asn Leu Thr Lys Ala Glu Arg Gly Gly Leu Ser Glu Leu Asp

900 905 910

Lys Ala Gly Phe Ile Lys Arg Gln Leu Val Glu Thr Arg Gln Ile Thr

915 920 925

Lys His Val Ala Gln Ile Leu Asp Ser Arg Met Asn Thr Lys Tyr Asp

930 935 940

Glu Asn Asp Lys Leu Ile Arg Glu Val Lys Val Ile Thr Leu Lys Ser

945 950 955 960

Lys Leu Val Ser Asp Phe Arg Lys Asp Phe Gln Phe Tyr Lys Val Arg

965 970 975

Glu Ile Asn Asn Tyr His His Ala His Asp Ala Tyr Leu Asn Ala Val

980 985 990

Val Gly Thr Ala Leu Ile Lys Lys Tyr Pro Lys Leu Glu Ser Glu Phe

995 1000 1005

Val Tyr Gly Asp Tyr Lys Val Tyr Asp Val Arg Lys Met Ile Ala Lys

1010 1015 1020

Ser Glu Gln Glu Ile Gly Lys Ala Thr Ala Lys Tyr Phe Phe Tyr Ser

1025 1030 1035 1040

Asn Ile Met Asn Phe Phe Lys Thr Glu Ile Thr Leu Ala Asn Gly Glu

1045 1050 1055

Ile Arg Lys Arg Pro Leu Ile Glu Thr Asn Gly Glu Thr Gly Glu Ile

1060 1065 1070

Val Trp Asp Lys Gly Arg Asp Phe Ala Thr Val Arg Lys Val Leu Ser

1075 1080 1085

Met Pro Gln Val Asn Ile Val Lys Lys Thr Glu Val Gln Thr Gly Gly

1090 1095 1100

Phe Ser Lys Glu Ser Ile Leu Pro Lys Arg Asn Ser Asp Lys Leu Ile

1105 1110 1115 1120

Ala Arg Lys Lys Asp Trp Asp Pro Lys Lys Tyr Gly Gly Phe Asp Ser

1125 1130 1135

Pro Thr Val Ala Tyr Ser Val Leu Val Val Ala Lys Val Glu Lys Gly

1140 1145 1150

Lys Ser Lys Lys Leu Lys Ser Val Lys Glu Leu Leu Gly Ile Thr Ile

1155 1160 1165

Met Glu Arg Ser Ser Phe Glu Lys Asn Pro Ile Asp Phe Leu Glu Ala

1170 1175 1180

Lys Gly Tyr Lys Glu Val Lys Lys Asp Leu Ile Ile Lys Leu Pro Lys

1185 1190 1195 1200

```
Tyr Ser Leu Phe Glu Leu Glu Asn Gly Arg Lys Arg Met Leu Ala Ser
                1205                1210                1215
Ala Gly Glu Leu Gln Lys Gly Asn Glu Leu Ala Leu Pro Ser Lys Tyr
            1220                1225                1230
Val Asn Phe Leu Tyr Leu Ala Ser His Tyr Glu Lys Leu Lys Gly Ser
        1235                1240                1245
Pro Glu Asp Asn Glu Gln Lys Gln Leu Phe Val Glu Gln His Lys His
    1250                1255                1260
Tyr Leu Asp Glu Ile Ile Glu Gln Ile Ser Glu Phe Ser Lys Arg Val
1265                1270                1275                1280
Ile Leu Ala Asp Ala Asn Leu Asp Lys Val Leu Ser Ala Tyr Asn Lys
                1285                1290                1295
His Arg Asp Lys Pro Ile Arg Glu Gln Ala Glu Asn Ile Ile His Leu
            1300                1305                1310
Phe Thr Leu Thr Asn Leu Gly Ala Pro Ala Ala Phe Lys Tyr Phe Asp
        1315                1320                1325
Thr Thr Ile Asp Arg Lys Arg Tyr Thr Ser Thr Lys Glu Val Leu Asp
    1330                1335                1340
Ala Thr Leu Ile His Gln Ser Ile Thr Gly Leu Tyr Glu Thr Arg Ile
1345                1350                1355                1360
Asp Leu Ser Gln Leu Gly Gly Asp
                1365
```

(SEQ ID NO: 6611)

In embodiments, the Cas9 molecule is a *S. pyogenes* Cas9 variant of SEQ ID NO: 6611 that includes one or more mutations to positively charged amino acids (e.g., lysine, arginine or histidine) that introduce an uncharged or nonpolar amino acid, e.g., alanine, at said position. In embodiments, the mutation is to one or more positively charged amino acids in the nt-groove of Cas9. In embodiments, the Cas9 molecule is a *S. pyogenes* Cas9 variant of SEQ ID NO: 6611 that includes a mutatation at position 855 of SEQ ID NO: 6611, for example a mutation to an uncharged amino acid, e.g., alanine, at position 855 of SEQ ID NO: 6611. In embodiments, the Cas9 molecule has a mutation only at position 855 of SEQ ID NO: 6611, relative to SEQ ID NO: 6611, e.g., to an uncharged amino acid, e.g., alanine. In embodiments, the Cas9 molecule is a *S. pyogenes* Cas9 variant of SEQ ID NO: 6611 that includes a mutatation at position 810, a mutation at position 1003, and/or a mutation at position 1060 of SEQ ID NO: 6611, for example a mutation to alanine at position 810, position 1003, and/or position 1060 of SEQ ID NO: 6611. In embodiments, the Cas9 molecule has a mutation only at position 810, position 1003, and position 1060 of SEQ ID NO: 6611, relative to SEQ ID NO: 6611, e.g., where each mutation is to an uncharged amino acid, for example, alanine. In embodiments, the

Cas9 molecule is a *S. pyogenes* Cas9 variant of SEQ ID NO: 6611 that includes a mutatation at position 848, a mutation at position 1003, and/or a mutation at position 1060 of SEQ ID NO: 6611, for example a mutation to alanine at position 848, position 1003, and/or position 1060 of SEQ ID NO: 6611. In embodiments, the Cas9 molecule has a mutation only at position 848, position 1003, and position 1060 of SEQ ID NO: 6611, relative to SEQ ID NO: 6611, e.g., where each mutation is to an uncharged amino acid, for example, alanine. In embodiments, the Cas9 molecule is a Cas9 molecule as described in Slaymaker et al., *Science Express*, available online December 1, 2015 at Science DOI: 10.1126/science.aad5227.

In embodiments, the Cas9 molecule is a *S. pyogenes* Cas9 variant of SEQ ID NO: 6611 that includes one or more mutations. In embodiments, the Cas9 variant comprises a mutation at position 80 of SEQ ID NO: 6611, e.g., includes a leucine at position 80 of SEQ ID NO: 6611 (i.e., comprises, e.g., consists of, SEQ ID NO: 6611 with a C80L mutation). In embodiments, the Cas9 variant comprises a mutation at position 574 of SEQ ID NO: 6611, e.g., includes a glutamic acid at position 574 of SEQ ID NO: 6611 (i.e., comprises, e.g., consists of, SEQ ID NO: 6611 with a C574E mutation). In embodiments, the Cas9 variant comprises a mutation at position 80 and a mutation at position 574 of SEQ ID NO: 6611, e.g., includes a leucine at position 80 of SEQ ID NO: 6611, and a glutamic acid at position 574 of SEQ ID NO: 6611 (i.e., comprises, e.g., consists of, SEQ ID NO: 6611 with a C80L mutation and a C574E mutation). Without being bound by theory, it is believed that such mutations improve the solution properties of the Cas9 molecule.

In embodiments, the Cas9 molecule is a *S. pyogenes* Cas9 variant of SEQ ID NO: 6611 that includes one or more mutations. In embodiments, the Cas9 variant comprises a mutation at position 147 of SEQ ID NO: 6611, e.g., includes a tyrosine at position 147 of SEQ ID NO: 6611 (i.e., comprises, e.g., consists of, SEQ ID NO: 6611 with a D147Y mutation). In embodiments, the Cas9 variant comprises a mutation at position 411 of SEQ ID NO: 6611, e.g., includes a threonine at position 411 of SEQ ID NO: 6611 (i.e., comprises, e.g., consists of, SEQ ID NO: 6611 with a P411T mutation). In embodiments, the Cas9 variant comprises a mutation at position 147 and a mutation at position 411 of SEQ ID NO: 6611, e.g., includes a tyrosine at position 147 of SEQ ID NO: 6611, and a threonine at position 411 of SEQ ID NO: 6611 (i.e., comprises, e.g., consists of, SEQ ID NO: 6611 with a D147Y mutation and a P411T mutation). Without being bound by theory, it is believed that such mutations improve the targeting efficiency of the Cas9 molecule, e.g., in yeast.

In embodiments, the Cas9 molecule is a *S. pyogenes* Cas9 variant of SEQ ID NO: 6611 that includes one or more mutations. In embodiments, the Cas9 variant comprises a mutation at position 1135 of SEQ ID NO: 6611, e.g., includes a glutamic acid at position 1135 of SEQ ID NO: 6611 (i.e., comprises, e.g., consists of, SEQ ID NO: 6611 with a D1135E mutation). Without being bound by

theory, it is believed that such mutations improve the selectivity of the Cas9 molecule for the NGG PAM sequence versus the NAG PAM sequence.

In embodiments, the Cas9 molecule is a *S. pyogenes* Cas9 variant of SEQ ID NO: 6611 that includes one or more mutations that introduce an uncharged or nonpolar amino acid, e.g., alanine, at certain positions. In embodiments, the Cas9 molecule is a *S. pyogenes* Cas9 variant of SEQ ID NO: 6611 that includes a mutatation at position 497, a mutation at position 661, a mutation at position 695 and/or a mutation at position 926 of SEQ ID NO: 6611, for example a mutation to alanine at position 497, position 661, position 695 and/or position 926 of SEQ ID NO: 6611. In embodiments, the Cas9 molecule has a mutation only at position 497, position 661, position 695, and position 926 of SEQ ID NO: 6611, relative to SEQ ID NO: 6611, e.g., where each mutation is to an uncharged amino acid, for example, alanine. Without being bound by theory, it is believed that such mutations reduce the cutting by the Cas9 molecule at off-target sites

It will be understood that the mutations described herein to the Cas9 molecule may be combined, and may be combined with any of the fusions or other modifications described herein, and the Cas9 molecule tested in the assays described herein.

Various types of Cas molecules can be used to practice the inventions disclosed herein. In some embodiments, Cas molecules of Type II Cas systems are used. In other embodiments, Cas molecules of other Cas systems are used. For example, Type I or Type III Cas molecules may be used. Exemplary Cas molecules (and Cas systems) are described, e.g., in Haft et ai, PLoS COMPUTATIONAL BIOLOGY 2005, 1(6): e60 and Makarova et al , NATURE REVIEW MICROBIOLOGY 201 1 , 9:467-477, the contents of both references are incorporated herein by reference in their entirety.

In an embodiment, the Cas9 molecule comprises one or more of the following activities: a nickase activity; a double stranded cleavage activity (e.g., an endonuclease and/or exonuclease activity); a helicase activity; or the ability, together with a gRNA molecule, to localize to a target nucleic acid.

Altered Cas9 Molecules

Naturally occurring Cas9 molecules possess a number of properties, including: nickase activity, nuclease activity (e.g., endonuclease and/or exonuclease activity); helicase activity; the ability to associate functionally with a gRNA molecule; and the ability to target (or localize to) a site on a nucleic acid (e.g., PAM recognition and specificity). In an embodiment, a Cas9 molecules can include all or a subset of these properties. In typical embodiments, Cas9 molecules have the ability to interact with a gRNA molecule and, in concert with the gRNA molecule, localize to a site in a nucleic acid. Other activities, e.g., PAM specificity, cleavage activity, or helicase activity can vary more widely in Cas9 molecules.

Cas9 molecules with desired properties can be made in a number of ways, e.g., by alteration of a parental, e.g., naturally occurring Cas9 molecules to provide an altered Cas9 molecule having a desired property. For example, one or more mutations or differences relative to a parental Cas9 molecule can be introduced. Such mutations and differences comprise: substitutions (e.g., conservative substitutions or substitutions of non-essential amino acids); insertions; or deletions. In an embodiment, a Cas9 molecule can comprises one or more mutations or differences, e.g., at least 1 , 2, 3, 4, 5, 10, 15, 20, 30, 40 or 50 mutations but less than 200, 100, or 80 mutations relative to a reference Cas9 molecule.

In an embodiment, a mutation or mutations do not have a substantial effect on a Cas9 activity, e.g. a Cas9 activity described herein. In an embodiment, a mutation or mutations have a substantial effect on a Cas9 activity, e.g. a Cas9 activity described herein. In an embodiment, exemplary activities comprise one or more of PAM specificity, cleavage activity, and helicase activity. A mutation(s) can be present, e.g., in: one or more RuvC-like domain, e.g., an N- terminal RuvC-like domain; an HNH-like domain; a region outside the RuvC-like domains and the HNH-like domain. In some embodiments, a mutation(s) is present in an N-terminal RuvC- like domain. In some embodiments, a mutation(s) is present in an HNH-like domain. In some embodiments, mutations are present in both an N-terminal RuvC-like domain and an HNH-like domain.

Whether or not a particular sequence, e.g., a substitution, may affect one or more activity, such as targeting activity, cleavage activity, etc, can be evaluated or predicted, e.g., by evaluating whether the mutation is conservative or by the method described in Section III. In an embodiment, a "non-essential" amino acid residue, as used in the context of a Cas9 molecule, is a residue that can be altered from the wild-type sequence of a Cas9 molecule, e.g., a naturally occurring Cas9 molecule, e.g., an active Cas9 molecule, without abolishing or more preferably, without substantially altering a Cas9 activity (e.g., cleavage activity), whereas changing an "essential" amino acid residue results in a substantial loss of activity (e.g., cleavage activity).

Cas9 Molecules with altered PAM recognition or no PAM recognition

Naturally occurring Cas9 molecules can recognize specific PAM sequences, for example the PAM recognition sequences described above for S. pyogenes, S. thermophilus, S. mutans, S. aureus and N. meningitidis.

In an embodiment, 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, or a PAM specificity 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, e.g., to alter PAM recognition, e.g., to alter the PAM sequence that the Cas9 molecule recognizes to decrease off target sites and/or improve specificity; or eliminate a PAM

recognition requirement. In an embodiment, a Cas9 molecule can be altered, e.g., to increase length of PAM recognition sequence and/or improve Cas9 specificity to high level of identity to decrease off target sites and 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. Cas9 molecules that recognize different PAM sequences and/or have reduced off- target activity can be generated using directed evolution. Exemplary methods and systems that can be used for directed evolution of Cas9 molecules are described, e.g., in Esvelt el al , Nature 2011, 472(7344): 499-503. Candidate Cas9 molecules can be evaluated, e.g., by methods described herein.

Non-Cleaving and Modified-Cleavage Cas9 Molecules

In an embodiment, a Cas9 molecule comprises a cleavage property that differs from naturally occurring Cas9 molecules, e.g., that differs from the naturally occurring Cas9 molecule having the closest homology. For example, a Cas9 molecule can differ from naturally occurring Cas9 molecules, e.g., a Cas9 molecule of S. pyogenes, as follows: its ability to modulate, e.g., decreased or increased, cleavage of a double stranded break (endonuclease and/or exonuclease activity), e.g., as compared to a naturally occurring Cas9 molecule (e.g., a Cas9 molecule of S. pyogenes); its ability to modulate, e.g., decreased or increased, cleavage of a single strand of a nucleic acid, e.g., a non-complimentary strand of a nucleic acid molecule or a complementary strand of a nucleic acid molecule (nickase activity), e.g., as compared to a naturally occurring Cas9 molecule (e.g., a Cas9 molecule of S. pyogenes); or the ability to cleave a nucleic acid molecule, e.g., a double stranded or single stranded nucleic acid molecule, can be eliminated.

Modified Cleavage active Cas9 Molecules

In an embodiment, an active Cas9 molecule comprises one or more of the following activities: cleavage activity associated with an N-terminal RuvC-like domain; cleavage activity associated with an HNH-like domain; cleavage activity associated with an HNH domain and cleavage activity associated with an N-terminal RuvC-like domain.

In an embodiment, the Cas9 molecule is a Cas9 nickase, e.g., cleaves only a single strand of DNA. In an embodiment, the Cas9 nickase includes a mutation at position 10 and/or a mutation at position 840 of SEQ ID NO: 6611, e.g., comprises a D10A and/or H840A mutation to SEQ ID NO: 6611.

Non-Cleaving inactive Cas9 Molecules

In an embodiment, the altered Cas9 molecule is an inactive Cas9 molecule which does not cleave a nucleic acid molecule (either double stranded or single stranded nucleic acid molecules) or cleaves a nucleic acid molecule with significantly less efficiency, e.g., less than 20, 10, 5, 1 or 0.1 % of the cleavage activity of a reference Cas9 molecule, e.g., as measured by an assay described herein. The reference Cas9 molecule can by a naturally occurring unmodified Cas9 molecule, e.g., a naturally

occurring Cas9 molecule such as a Cas9 molecule of S. pyogenes, S. thermophilus, S. aureus or N. meningitidis. In an embodiment, the reference Cas9 molecule is the naturally occurring Cas9 molecule having the closest sequence identity or homology. In an embodiment, the inactive Cas9 molecule lacks substantial cleavage activity associated with an N- terminal RuvC-like domain and cleavage activity associated with an HNH-like domain.

In an embodiment, the Cas9 molecule is dCas9. Tsai et al. (2014), Nat. Biotech. 32:569-577.

A catalytically inactive Cas9 molecule may be fused with a transcription repressor. An inactive Cas9 fusion protein complexes with a gRNA and localizes to a DNA sequence specified by gRNA's targeting domain, but, unlike an active Cas9, it will not cleave the target DNA. Fusion of an effector domain, such as a transcriptional repression domain, to an inactive Cas9 enables recruitment of the effector to any DNA site specified by the gRNA. Site specific targeting of a Cas9 fusion protein to a promoter region of a gene can block or affect polymerase binding to the promoter region, for example, a Cas9 fusion with a transcription factor (e.g., a transcription activator) and/or a transcriptional enhancer binding to the nucleic acid to increase or inhibit transcription activation. Alternatively, site specific targeting of a a Cas9- fusion to a transcription repressor to a promoter region of a gene can be used to decrease transcription activation.

Transcription repressors or transcription repressor domains that may be fused to an inactive Cas9 molecule can include ruppel associated box (KRAB or SKD), the Mad mSIN3 interaction domain (SID) or the ERF repressor domain (ERD).

In another embodiment, an inactive Cas9 molecule may be fused with a protein that modifies chromatin. For example, an inactive Cas9 molecule may be fused to heterochromatin protein 1 (HPl), a histone lysine methyltransferase (e.g., SUV39H 1 , SUV39H2, G9A, ESET/SETDB 1 , Pr-SET7/8, SUV4-20H 1,RIZ1), a histone lysine demethylates (e.g., LSD1/BHC1 10, SpLsdl/Sw, l/Safl 10, Su(var)3-3, JMJD2A/JHDM3A, JMJD2B, JMJD2C/GASC1 , JMJD2D, Rph 1 , JARID 1 A/RBP2, JARI DIB/PLU-I, JAR1D 1C/SMCX, JARID1 D/SMCY, Lid, Jhn2, Jmj2), a histone lysine deacetylases (e.g., HDAC1, HDAC2, HDAC3, HDAC8, Rpd3, Hos 1 , Cir6, HDAC4, HDAC5, HDAC7, HDAC9, Hdal , Cir3, SIRT 1 , SIRT2, Sir2, Hst 1 , Hst2, Hst3, Hst4, HDAC 1 1) and a DNA methylases (DNMT1,DNMT2a/DMNT3b, MET1). An inactive Cas9-chomatin modifying molecule fusion protein can be used to alter chromatin status to reduce expression a target gene.

The heterologous sequence (e.g., the transcription repressor domain) may be fused to the N- or C-terminus of the inactive Cas9 protein. In an alternative embodiment, the heterologous sequence (e.g., the transcription repressor domain) may be fused to an internal portion (i.e., a portion other than the N-terminus or C-terminus) of the inactive Cas9 protein.

The ability of a Cas9 molecule/gRNA molecule complex to bind to and cleave a target nucleic acid can be evaluated, e.g., by the methods described herein in Section ΠΙ. The activity of a Cas9 molecule, e.g., either an active Cas9 or a inactive Cas9, alone or in a complex with a gRNA molecule may also be evaluated by methods well-known in the art, including, gene expression assays and chromatin-based assays, e.g., chromatin immunoprecipitation (ChiP) and chromatin in vivo assay (CiA).

Other Cas9 Molecule Fusions

In embodiments, the Cas9 molecule, e.g, a Cas9 of *S. pyogenes*, may additionally comprise one or more amino acid sequences that confer additional activity.

In some aspects, the Cas9 molecule may comprise one or more nuclear localization sequences (NLSs), such as at least 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, or more NLSs. In some embodiments, the Cas9 molecule comprises at least 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, or more NLSs at or near the amino-terminus, at least 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, or more NLSs at or near the carboxy-terminus, or a combination of these (e.g. one or more NLS at the amino-terminus and one or more NLS at the carboxy terminus). When more than one NLS is present, each may be selected independently of the others, such that a single NLS may be present in more than one copy and/or in combination with one or more other NLSs present in one or more copies. In some embodiments, an NLS is considered near the N- or C-terminus when the nearest amino acid of the NLS is within about 1, 2, 3, 4, 5, 10, 15, 20, 25, 30, 40, 50, or more amino acids along the polypeptide chain from the N- or C-terminus. Typically, an NLS consists of one or more short sequences of positively charged lysines or arginines exposed on the protein surface, but other types of NLS are known. Non-limiting examples of NLSs include an NLS sequence comprising or derived from: the NLS of the SV40 virus large T-antigen, having the amino acid sequence PKKKRKV (SEQ ID NO: 6612); the NLS from nucleoplasmin (e.g. the nucleoplasmin bipartite NLS with the sequence KRPAATKKAGQAKKKK (SEQ ID NO: 6613); the c-myc NLS having the amino acid sequence PAAKRVKLD (SEQ ID NO: 6614) or RQRRNELKRSP (SEQ ID NO: 6615); the hRNPA1 M9 NLS having the sequence NQSSNFGPMKGGNFGGRSSGPYGGGGQYFAKPRNQGGY (SEQ ID NO: 6616); the sequence RMRIZFKNKGKDTAELRRRRVEVSVELRKAKKDEQILKRRNV (SEQ ID NO: 6617) of the IBB domain from importin-alpha; the sequences VSRKRPRP (SEQ ID NO: 6618) and PPKKARED (SEQ ID NO: 6619) of the myoma T protein; the sequence PQPKKKPL (SEQ ID NO: 6620) of human p53; the sequence SALIKKKKKMAP (SEQ ID NO: 6621) of mouse c-ab1 IV; the sequences DRLRR (SEQ ID NO: 6622) and PKQKKRK (SEQ ID NO: 6623) of the influenza virus NS1; the sequence RKLKKKIKKL (SEQ ID NO: 6624) of the Hepatitis virus delta antigen; the sequence REKKKFLKRR (SEQ ID NO: 6625) of the mouse Mx1 protein; the sequence KRKGDEVDGVDEVAKKKSKK (SEQ ID NO: 6626) of the human poly(ADP-ribose) polymerase;

and the sequence RKCLQAGMNLEARKTKK (SEQ ID NO: 6627) of the steroid hormone receptors (human) glucocorticoid. Other suitable NLS sequences are known in the art (e.g., Sorokin, Biochemistry (Moscow) (2007) 72:13, 1439-1457; Lange J Biol Chem. (2007) 282:8, 5101-5).

In an embodiment, the Cas9 molecule, e.g., *S. pyogenes* Cas9 molecule, comprises a NLS sequence of SV40, e.g., disposed N terminal to the Cas9 molecule. In an embodiment, the Cas9 molecule, e.g., *S. pyogenes* Cas9 molecule, comprises a NLS sequence of SV40 disposed N-terminal to the Cas9 molecule and a NLS sequence of SV40 disposed C terminal to the Cas9 molecule. In an embodiment, the Cas9 molecule, e.g., *S. pyogenes* Cas9 molecule, comprises a NLS sequence of SV40 disposed N-terminal to the Cas9 molecule and a NLS sequence of nucleoplasmin disposed C-terminal to the Cas9 molecule. In any of the aforementioned embodiments, the molecule may additionally comprise a tag, e.g., a His tag, e.g., a His(6) tag or His(8) tag (SEQ ID NOS 2969 and 2970, respectively), e.g., at the N terminus or the C terminus.

In some aspects, the Cas9 molecule may comprise one or more amino acid sequences that allow the Cas9 molecule to be specifically recognized, for example a tag. In one embodiment, the tag is a Histidine tag, e.g., a histidine tag comprising at least 3, 4, 5, 6, 7, 8, 9, 10 or more histidine amino acids (SEQ ID NO: 2971). In embodiments, the histidine tag is a His6 tag (six histidines) (SEQ ID NO: 2969). In other embodiments, the histidine tag is a His8 tag (eight histidines) (SEQ ID NO: 2970). In embodiments, the histidine tag may be separated from one or more other portions of the Cas9 molecule by a linker. In embodiments, the linker is GGS. An example of such a fusion is the Cas9 molecule iProt106520.

In some aspects, the Cas9 molecule may comprise one or more amino acid sequences that are recognized by a protease (e.g., comprise a protease cleavage site). In embodiments, the cleavage site is the tobacco etch virus (TEV) cleavage site, e.g., comprises the sequence ENLYFQG (SEQ ID NO: 7810). In some aspects the protease cleavage site, e.g., the TEV cleavage site is disposed between a tag, e.g., a His tag, e.g., a His6 or His8 tag (SEQ ID NOS 2969 and 2970, respectively), and the remainder of the Cas9 molecule. Without being bound by theory it is believed that such introduction will allow for the use of the tag for, e.g., purification of the Cas9 molecule, and then subsequent cleavage so the tag does not interfere with the Cas9 molecule function.

In embodiments, the Cas9 molecule (e.g., a Cas9 molecule as described herein) comprises an N-terminal NLS, and a C-terminal NLS (e.g., comprises, from N- to C-terminal NLS-Cas9-NLS), e.g., wherein each NLS is an SV40 NLS (PKKKRKV (SEQ ID NO: 6612)). In embodiments, the Cas9 molecule (e.g., a Cas9 molecule as described herein) comprises an N-terminal NLS, a C-terminal NLS, and a C-terminal His6 tag (SEQ ID NO: 2969) (e.g., comprises, from N- to C-terminal NLS-Cas9-NLS-His tag), e.g., wherein each NLS is an SV40 NLS (PKKKRKV (SEQ ID NO: 6612)). In embodiments, the Cas9 molecule (e.g., a Cas9 molecule as described herein) comprises an N-terminal

His tag (e.g., His6 tag (SEQ ID NO: 2969)), an N-terminal NLS, and a C-terminal NLS (e.g., comprises, from N- to C-terminal His tag-NLS-Cas9-NLS), e.g., wherein each NLS is an SV40 NLS (PKKKRKV (SEQ ID NO: 6612)). In embodiments, the Cas9 molecule (e.g., a Cas9 molecule as described herein) comprises an N-terminal NLS and a C-terminal His tag (e.g., His6 tag (SEQ ID NO: 2969)) (e.g., comprises from N- to C- terminal His tag-Cas9-NLS), e.g., wherein the NLS is an SV40 NLS (PKKKRKV (SEQ ID NO: 6612)). In embodiments, the Cas9 molecule (e.g., a Cas9 molecule as described herein) comprises an N-terminal NLS and a C-terminal His tag (e.g., His6 tag (SEQ ID NO: 2969)) (e.g., comprises from N- to C- terminal NLS-Cas9-His tag), e.g., wherein the NLS is an SV40 NLS (PKKKRKV (SEQ ID NO: 6612)). In embodiments, the Cas9 molecule (e.g., a Cas9 molecule as described herein) comprises an N-terminal His tag (e.g., His8 tag (SEQ ID NO: 2970)), an N-terminal cleavage domain (e.g., a tobacco etch virus (TEV) cleavage domain (e.g., comprises the sequence ENLYFQG (SEQ ID NO: 7810))), an N-terminal NLS (e.g., an SV40 NLS; SEQ ID NO: 6612), and a C-terminal NLS (e.g., an SV40 NLS; SEQ ID NO: 6612) (e.g., comprises from N- to C-terminal His tag-TEV-NLS-Cas9-NLS). In any of the aforementioned embodiments the Cas9 has the sequence of SEQ ID NO: 6611. Alternatively, in any of the aforementioned embodiments, the Cas9 has a sequence of a Cas9 variant of SEQ ID NO: 6611, e.g., as described herein. In any of the aforementioned embodiments, the Cas9 molecule comprises a linker between the His tag and another portion of the molecule, e.g., a GGS linker. Amino acid sequences of exemplary Cas9 molecules described above are provided below. "iProt" identifiers match those in Figure 60.

iProt105026 (also referred to as iProt106154, iProt106331, iProt106545, and PID426303, depending on the preparation of the protein) (SEQ ID NO: 7821):

MAPKKKRKVD KKYSIGLDIG TNSVGWAVIT DEYKVPSKKF KVLGNTDRHS IKKNLIGALL
FDSGETAEAT RLKRTARRRY TRRKNRICYL QEIFSNEMAK VDDSFFHRLE ESFLVEEDKK
HERHPIFGNI VDEVAYHEKY PTIYHLRKKL VDSTDKADLR LIYLALAHMI KFRGHFLIEG
DLNPDNSDVD KLFIQLVQTY NQLFEENPIN ASGVDAKAIL SARLSKSRRL ENLIAQLPGE
KKNGLFGNLI ALSLGLTPNF KSNFDLAEDA KLQLSKDTYD DDLDNLLAQI GDQYADLFLA
AKNLSDAILL SDILRVNTEI TKAPLSASMI KRYDEHHQDL TLLKALVRQQ LPEKYKEIFF
DQSKNGYAGY IDGGASQEEF YKFIKPILEK MDGTEELLVK LNREDLLRKQ RTFDNGSIPH
QIHLGELHAI LRRQEDFYPF LKDNREKIEK ILTFRIPYYV GPLARGNSRF AWMTRKSEET
ITPWNFEEVV DKGASAQSFI ERMTNFDKNL PNEKVLPKHS LLYEYFTVYN ELTKVKYVTE
GMRKPAFLSG EQKKAIVDLL FKTNRKVTVK QLKEDYFKKI ECFDSVEISG VEDRFNASLG
TYHDLLKIIK DKDFLDNEEN EDILEDIVLT LTLFEDREMI EERLKTYAHL FDDKVMKQLK
RRRYTGWGRL SRKLINGIRD KQSGKTILDF LKSDGFANRN FMQLIHDDSL TFKEDIQKAQ
VSGQGDSLHE HIANLAGSPA IKKGILQTVK VVDELVKVMG RHKPENIVIE MARENQTTQK
GQKNSRERMK RIEEGIKELG SQILKEHPVE NTQLQNEKLY LYYLQNGRDM YVDQELDINR
LSDYDVDHIV PQSFLKDDSI DNKVLTRSDK NRGKSDNVPS EEVVKKMKNY
WRQLLNAKLI TQRKFDNLTK AERGGLSELD KAGFIKRQLV ETRQITKHVA QILDSRMNTK
YDENDKLIRE VKVITLKSKL VSDFRKDFQF YKVREINNYH HAHDAYLNAV VGTALIKKYP
KLESEFVYGD YKVYDVRKMI AKSEQEIGKA TAKYFFYSNI MNFFKTEITL ANGEIRKRPL
IETNGETGEI VWDKGRDFAT VRKVLSMPQV NIVKKTEVQT GGFSKESILP KRNSDKLIAR
KKDWDPKKYG GFDSPTVAYS VLVVAKVEKG KSKKLKSVKE LLGITIMERS SFEKNPIDFL
EAKGYKEVKK DLIIKLPKYS LFELENGRKR MLASAGELQK GNELALPSKY VNFLYLASHY
EKLKGSPEDN EQKQLFVEQH KHYLDEIIEQ ISEFSKRVIL ADANLDKVLS AYNKHRDKPI

REQAENIIHL FTLTNLGAPA AFKYFDTTID RKRYTSTKEV LDATLIHQSI TGLYETRIDL SQLGGDSRAD PKKKRKVHHH HHH

iProt106518 (SEQ ID NO: 7822):

MAPKKKRKVD KKYSIGLDIG TNSVGWAVIT DEYKVPSKKF KVLGNTDRHS IKKNLIGALL FDSGETAEAT RLKRTARRRY TRRKNRILYL QEIFSNEMAK VDDSFFHRLE ESFLVEEDKK HERHPIFGNI VDEVAYHEKY PTIYHLRKKL VDSTDKADLR LIYLALAHMI KFRGHFLIEG DLNPDNSDVD KLFIQLVQTY NQLFEENPIN ASGVDAKAIL SARLSKSRRL ENLIAQLPGE KKNGLFGNLI ALSLGLTPNF KSNFDLAEDA KLQLSKDTYD DDLDNLLAQI GDQYADLFLA AKNLSDAILL SDILRVNTEI TKAPLSASMI KRYDEHHQDL TLLKALVRQQ LPEKYKEIFF DQSKNGYAGY IDGGASQEEF YKFIKPILEK MDGTEELLVK LNREDLLRKQ RTFDNGSIPH QIHLGELHAI LRRQEDFYPF LKDNREKIEK ILTFRIPYYV GPLARGNSRF AWMTRKSEET ITPWNFEEVV DKGASAQSFI ERMTNFDKNL PNEKVLPKHS LLYEYFTVYN ELTKVKYVTE GMRKPAFLSG EQKKAIVDLL FKTNRKVTVK QLKEDYFKKI EEFDSVEISG VEDRFNASLG TYHDLLKIIK DKDFLDNEEN EDILEDIVLT LTLFEDREMI EERLKTYAHL FDDKVMKQLK RRRYTGWGRL SRKLINGIRD KQSGKTILDF LKSDGFANRN FMQLIHDDSL TFKEDIQKAQ VSGQGDSLHE HIANLAGSPA IKKGILQTVK VVDELVKVMG RHKPENIVIE MARENQTTQK GQKNSRERMK RIEEGIKELG SQILKEHPVE NTQLQNEKLY LYYLQNGRDM YVDQELDINR LSDYDVDHIV PQSFLKDDSI DNKVLTRSDK NRGKSDNVPS EEVVKKMKNY WRQLLNAKLI TQRKFDNLTK AERGGLSELD KAGFIKRQLV ETRQITKHVA QILDSRMNTK YDENDKLIRE VKVITLKSKL VSDFRKDFQF YKVREINNYH HAHDAYLNAV VGTALIKKYP KLESEFVYGD YKVYDVRKMI AKSEQEIGKA TAKYFFYSNI MNFFKTEITL ANGEIRKRPL IETNGETGEI VWDKGRDFAT VRKVLSMPQV NIVKKTEVQT GGFSKESILP KRNSDKLIAR KKDWDPKKYG GFDSPTVAYS VLVVAKVEKG KSKKLKSVKE LLGITIMERS SFEKNPIDFL EAKGYKEVKK DLIIKLPKYS LFELENGRKR MLASAGELQK GNELALPSKY VNFLYLASHY EKLKGSPEDN EQKQLFVEQH KHYLDEIIEQ ISEFSKRVIL ADANLDKVLS AYNKHRDKPI REQAENIIHL FTLTNLGAPA AFKYFDTTID RKRYTSTKEV LDATLIHQSI TGLYETRIDL SQLGGDSRAD PKKKRKVHHH HHH

iProt106519 (SEQ ID NO: 7823):

MGSSHHHHHH HHENLYFQGS MDKKYSIGLD IGTNSVGWAV ITDEYKVPSK KFKVLGNTDR HSIKKNLIGA LLFDSGETAE ATRLKRTARR RYTRRKNRIC YLQEIFSNEM AKVDDSFFHR LEESFLVEED KKHERHPIFG NIVDEVAYHE KYPTIYHLRK KLVDSTDKAD LRLIYLALAH MIKFRGHFLI EGDLNPDNSD VDKLFIQLVQ TYNQLFEENP INASGVDAKA ILSARLSKSR RLENLIAQLP GEKKNGLFGN LIALSLGLTP NFKSNFDLAE DAKLQLSKDT YDDDLDNLLA QIGDQYADLF LAAKNLSDAI LLSDILRVNT EITKAPLSAS MIKRYDEHHQ DLTLLKALVR QQLPEKYKEI FFDQSKNGYA GYIDGGASQE EFYKFIKPIL EKMDGTEELL VKLNREDLLR KQRTFDNGSI PHQIHLGELH AILRRQEDFY PFLKDNREKI EKILTFRIPY YVGPLARGNS RFAWMTRKSE ETITPWNFEE VVDKGASAQS FIERMTNFDK NLPNEKVLPK HSLLYEYFTV YNELTKVKYV TEGMRKPAFL SGEQKKAIVD LLFKTNRKVT VKQLKEDYFK KIECFDSVEI SGVEDRFNAS LGTYHDLLKI IKDKDFLDNE ENEDILEDIV LTLTLFEDRE MIEERLKTYA HLFDDKVMKQ LKRRRYTGWG RLSRKLINGI RDKQSGKTIL DFLKSDGFAN RNFMQLIHDD SLTFKEDIQK AQVSGQGDSL HEHIANLAGS PAIKKGILQT VKVVDELVKV MGRHKPENIV IEMARENQTT QKGQKNSRER MKRIEEGIKE LGSQILKEHP VENTQLQNEK LYLYYLQNGR DMYVDQELDI NRLSDYDVDH IVPQSFLKDD SIDNKVLTRS DKNRGKSDNV PSEEVVKKMK NYWRQLLNAK LITQRKFDNL TKAERGGLSE LDKAGFIKRQ LVETRQITKH VAQILDSRMN TKYDENDKLI REVKVITLKS KLVSDFRKDF QFYKVREINN YHHAHDAYLN AVVGTALIKK YPKLESEFVY GDYKVYDVRK MIAKSEQEIG KATAKYFFYS NIMNFFKTEI TLANGEIRKR PLIETNGETG EIVWDKGRDF ATVRKVLSMP QVNIVKKTEV QTGGFSKESI LPKRNSDKLI ARKKDWDPKK YGGFDSPTVA YSVLVVAKVE KGKSKKLKSV KELLGITIME RSSFEKNPID FLEAKGYKEV KKDLIIKLPK YSLFELENGR KRMLASAGEL QKGNELALPS KYVNFLYLAS HYEKLKGSPE DNEQKQLFVE QHKHYLDEII EQISEFSKRV ILADANLDKV LSAYNKHRDK PIREQAENII HLFTLTNLGA PAAFKYFDTT IDRKRYTSTK EVLDATLIHQ SITGLYETRI DLSQLGGDGG GSPKKKRKV

iProt106520 (SEQ ID NO: 7824):

MAHHHHHHGG SPKKKRKVDK KYSIGLDIGT NSVGWAVITD EYKVPSKKFK
VLGNTDRHSI KKNLIGALLF DSGETAEATR LKRTARRRYT RRKNRICYLQ EIFSNEMAKV
DDSFFHRLEE SFLVEEDKKH ERHPIFGNIV DEVAYHEKYP TIYHLRKKLV DSTDKADLRL
IYLALAHMIK FRGHFLIEGD LNPDNSDVDK LFIQLVQTYN QLFEENPINA SGVDAKAILS
ARLSKSRRLE NLIAQLPGEK KNGLFGNLIA LSLGLTPNFK SNFDLAEDAK LQLSKDTYDD
DLDNLLAQIG DQYADLFLAA KNLSDAILLS DILRVNTEIT KAPLSASMIK RYDEHHQDLT
LLKALVRQQL PEKYKEIFFD QSKNGYAGYI DGGASQEEFY KFIKPILEKM DGTEELLVKL
NREDLLRKQR TFDNGSIPHQ IHLGELHAIL RRQEDFYPFL KDNREKIEKI LTFRIPYYVG
PLARGNSRFA WMTRKSEETI TPWNFEEVVD KGASAQSFIE RMTNFDKNLP NEKVLPKHSL
LYEYFTVYNE LTKVKYVTEG MRKPAFLSGE QKKAIVDLLF KTNRKVTVKQ LKEDYFKKIE
CFDSVEISGV EDRFNASLGT YHDLLKIIKD KDFLDNEENE DILEDIVLTL TLFEDREMIE
ERLKTYAHLF DDKVMKQLKR RRYTGWGRLS RKLINGIRDK QSGKTILDFL KSDGFANRNF
MQLIHDDSLT FKEDIQKAQV SGQGDSLHEH IANLAGSPAI KKGILQTVKV VDELVKVMGR
HKPENIVIEM ARENQTTQKG QKNSRERMKR IEEGIKELGS QILKEHPVEN TQLQNEKLYL
YYLQNGRDMY VDQELDINRL SDYDVDHIVP QSFLKDDSID NKVLTRSDKN RGKSDNVPSE
EVVKKMKNYW RQLLNAKLIT QRKFDNLTKA ERGGLSELDK AGFIKRQLVE
TRQITKHVAQ ILDSRMNTKY DENDKLIREV KVITLKSKLV SDFRKDFQFY KVREINNYHH
AHDAYLNAVV GTALIKKYPK LESEFVYGDY KVYDVRKMIA KSEQEIGKAT
AKYFFYSNIM NFFKTEITLA NGEIRKRPLI ETNGETGEIV WDKGRDFATV RKVLSMPQVN
IVKKTEVQTG GFSKESILPK RNSDKLIARK KDWDPKKYGG FDSPTVAYSV LVVAKVEKGK
SKKLKSVKEL LGITIMERSS FEKNPIDFLE AKGYKEVKKD LIIKLPKYSL FELENGRKRM
LASAGELQKG NELALPSKYV NFLYLASHYE KLKGSPEDNE QKQLFVEQHK HYLDEIIEQI
SEFSKRVILA DANLDKVLSA YNKHRDKPIR EQAENIIHLF TLTNLGAPAA FKYFDTTIDR
KRYTSTKEVL DATLIHQSIT GLYETRIDLS QLGGDSRADP KKKRKV

iProt106521 (SEQ ID NO: 7825):

MAPKKKRKVD KKYSIGLDIG TNSVGWAVIT DEYKVPSKKF KVLGNTDRHS IKKNLIGALL
FDSGETAEAT RLKRTARRRY TRRKNRICYL QEIFSNEMAK VDDSFFHRLE ESFLVEEDKK
HERHPIFGNI VDEVAYHEKY PTIYHLRKKL VDSTDKADLR LIYLALAHMI KFRGHFLIEG
DLNPDNSDVD KLFIQLVQTY NQLFEENPIN ASGVDAKAIL SARLSKSRRL ENLIAQLPGE
KKNGLFGNLI ALSLGLTPNF KSNFDLAEDA KLQLSKDTYD DDLDNLLAQI GDQYADLFLA
AKNLSDAILL SDILRVNTEI TKAPLSASMI KRYDEHHQDL TLLKALVRQQ LPEKYKEIFF
DQSKNGYAGY IDGGASQEEF YKFIKPILEK MDGTEELLVK LNREDLLRKQ RTFDNGSIPH
QIHLGELHAI LRRQEDFYPF LKDNREKIEK ILTFRIPYYV GPLARGNSRF AWMTRKSEET
ITPWNFEEVV DKGASAQSFI ERMTNFDKNL PNEKVLPKHS LLYEYFTVYN ELTKVKYVTE
GMRKPAFLSG EQKKAIVDLL FKTNRKVTVK QLKEDYFKKI ECFDSVEISG VEDRFNASLG
TYHDLLKIIK DKDFLDNEEN EDILEDIVLT LTLFEDREMI EERLKTYAHL FDDKVMKQLK
RRRYTGWGRL SRKLINGIRD KQSGKTILDF LKSDGFANRN FMQLIHDDSL TFKEDIQKAQ
VSGQGDSLHE HIANLAGSPA IKKGILQTVK VVDELVKVMG RHKPENIVIE MARENQTTQK
GQKNSRERMK RIEEGIKELG SQILKEHPVE NTQLQNEKLY LYYLQNGRDM YVDQELDINR
LSDYDVDHIV PQSFLKDDSI DNKVLTRSDK NRGKSDNVPS EEVVKKMKNY
WRQLLNAKLI TQRKFDNLTK AERGGLSELD KAGFIKRQLV ETRQITKHVA QILDSRMNTK
YDENDKLIRE VKVITLKSKL VSDFRKDFQF YKVREINNYH HAHDAYLNAV VGTALIKKYP
KLESEFVYGD YKVYDVRKMI AKSEQEIGKA TAKYFFYSNI MNFFKTEITL ANGEIRKRPL
IETNGETGEI VWDKGRDFAT VRKVLSMPQV NIVKKTEVQT GGFSKESILP KRNSDKLIAR
KKDWDPKKYG GFDSPTVAYS VLVVAKVEKG KSKKLKSVKE LLGITIMERS SFEKNPIDFL
EAKGYKEVKK DLIIKLPKYS LFELENGRKR MLASAGELQK GNELALPSKY VNFLYLASHY
EKLKGSPEDN EQKQLFVEQH KHYLDEIIEQ ISEFSKRVIL ADANLDKVLS AYNKHRDKPI
REQAENIIHL FTLTNLGAPA AFKYFDTTID RKRYTSTKEV LDATLIHQSI TGLYETRIDL
SQLGGDSRAD HHHHHH

iProt106522 (SEQ ID NO: 7826):

MAHHHHHHGG SDKKYSIGLD IGTNSVGWAV ITDEYKVPSK KFKVLGNTDR HSIKKNLIGA
LLFDSGETAE ATRLKRTARR RYTRRKNRIC YLQEIFSNEM AKVDDSFFHR LEESFLVEED
KKHERHPIFG NIVDEVAYHE KYPTIYHLRK KLVDSTDKAD LRLIYLALAH MIKFRGHFLI
EGDLNPDNSD VDKLFIQLVQ TYNQLFEENP INASGVDAKA ILSARLSKSR RLENLIAQLP
GEKKNGLFGN LIALSLGLTP NFKSNFDLAE DAKLQLSKDT YDDDLDNLLA QIGDQYADLF
LAAKNLSDAI LLSDILRVNT EITKAPLSAS MIKRYDEHHQ DLTLLKALVR QQLPEKYKEI
FFDQSKNGYA GYIDGGASQE EFYKFIKPIL EKMDGTEELL VKLNREDLLR KQRTFDNGSI
PHQIHLGELH AILRRQEDFY PFLKDNREKI EKILTFRIPY YVGPLARGNS RFAWMTRKSE
ETITPWNFEE VVDKGASAQS FIERMTNFDK NLPNEKVLPK HSLLYEYFTV YNELTKVKYV
TEGMRKPAFL SGEQKKAIVD LLFKTNRKVT VKQLKEDYFK KIECFDSVEI SGVEDRFNAS
LGTYHDLLKI IKDKDFLDNE ENEDILEDIV LTLTLFEDRE MIEERLKTYA HLFDDKVMKQ
LKRRRYTGWG RLSRKLINGI RDKQSGKTIL DFLKSDGFAN RNFMQLIHDD SLTFKEDIQK
AQVSGQGDSL HEHIANLAGS PAIKKGILQT VKVVDELVKV MGRHKPENIV IEMARENQTT
QKGQKNSRER MKRIEEGIKE LGSQILKEHP VENTQLQNEK LYLYYLQNGR DMYVDQELDI
NRLSDYDVDH IVPQSFLKDD SIDNKVLTRS DKNRGKSDNV PSEEVVKKMK
NYWRQLLNAK LITQRKFDNL TKAERGGLSE LDKAGFIKRQ LVETRQITKH VAQILDSRMN
TKYDENDKLI REVKVITLKS KLVSDFRKDF QFYKVREINN YHHAHDAYLN AVVGTALIKK
YPKLESEFVY GDYKVYDVRK MIAKSEQEIG KATAKYFFYS NIMNFFKTEI TLANGEIRKR
PLIETNGETG EIVWDKGRDF ATVRKVLSMP QVNIVKKTEV QTGGFSKESI LPKRNSDKLI
ARKKDWDPKK YGGFDSPTVA YSVLVVAKVE KGKSKKLKSV KELLGITIME RSSFEKNPID
FLEAKGYKEV KKDLIIKLPK YSLFELENGR KRMLASAGEL QKGNELALPS KYVNFLYLAS
HYEKLKGSPE DNEQKQLFVE QHKHYLDEII EQISEFSKRV ILADANLDKV LSAYNKHRDK
PIREQAENII HLFTLTNLGA PAAFKYFDTT IDRKRYTSTK EVLDATLIHQ SITGLYETRI
DLSQLGGDSR ADPKKKRKV

iProt106658 (SEQ ID NO: 7827):

MGSSHHHHHH HHENLYFQGS MDKKYSIGLD IGTNSVGWAV ITDEYKVPSK
KFKVLGNTDR HSIKKNLIGA LLFDSGETAE ATRLKRTARR RYTRRKNRIC YLQEIFSNEM
AKVDDSFFHR LEESFLVEED KKHERHPIFG NIVDEVAYHE KYPTIYHLRK KLVDSTDKAD
LRLIYLALAH MIKFRGHFLI EGDLNPDNSD VDKLFIQLVQ TYNQLFEENP INASGVDAKA
ILSARLSKSR RLENLIAQLP GEKKNGLFGN LIALSLGLTP NFKSNFDLAE DAKLQLSKDT
YDDDLDNLLA QIGDQYADLF LAAKNLSDAI LLSDILRVNT EITKAPLSAS MIKRYDEHHQ
DLTLLKALVR QQLPEKYKEI FFDQSKNGYA GYIDGGASQE EFYKFIKPIL EKMDGTEELL
VKLNREDLLR KQRTFDNGSI PHQIHLGELH AILRRQEDFY PFLKDNREKI EKILTFRIPY
YVGPLARGNS RFAWMTRKSE ETITPWNFEE VVDKGASAQS FIERMTNFDK NLPNEKVLPK
HSLLYEYFTV YNELTKVKYV TEGMRKPAFL SGEQKKAIVD LLFKTNRKVT
VKQLKEDYFK KIECFDSVEI SGVEDRFNAS LGTYHDLLKI IKDKDFLDNE ENEDILEDIV
LTLTLFEDRE MIEERLKTYA HLFDDKVMKQ LKRRRYTGWG RLSRKLINGI RDKQSGKTIL
DFLKSDGFAN RNFMQLIHDD SLTFKEDIQK AQVSGQGDSL HEHIANLAGS PAIKKGILQT
VKVVDELVKV MGRHKPENIV IEMARENQTT QKGQKNSRER MKRIEEGIKE LGSQILKEHP
VENTQLQNEK LYLYYLQNGR DMYVDQELDI NRLSDYDVDH IVPQSFLKDD SIDNKVLTRS
DKNRGKSDNV PSEEVVKKMK NYWRQLLNAK LITQRKFDNL TKAERGGLSE
LDKAGFIKRQ LVETRQITKH VAQILDSRMN TKYDENDKLI REVKVITLKS KLVSDFRKDF
QFYKVREINN YHHAHDAYLN AVVGTALIKK YPKLESEFVY GDYKVYDVRK
MIAKSEQEIG KATAKYFFYS NIMNFFKTEI TLANGEIRKR PLIETNGETG EIVWDKGRDF
ATVRKVLSMP QVNIVKKTEV QTGGFSKESI LPKRNSDKLI ARKKDWDPKK YGGFDSPTVA
YSVLVVAKVE KGKSKKLKSV KELLGITIME RSSFEKNPID FLEAKGYKEV KKDLIIKLPK
YSLFELENGR KRMLASAGEL QKGNELALPS KYVNFLYLAS HYEKLKGSPE DNEQKQLFVE
QHKHYLDEII EQISEFSKRV ILADANLDKV LSAYNKHRDK PIREQAENII HLFTLTNLGA
PAAFKYFDTT IDRKRYTSTK EVLDATLIHQ SITGLYETRI DLSQLGGDGG GSPKKKRKV

iProt106745 (SEQ ID NO: 7828):

MAPKKKRKVD KKYSIGLDIG TNSVGWAVIT DEYKVPSKKF KVLGNTDRHS IKKNLIGALL
FDSGETAEAT RLKRTARRRY TRRKNRICYL QEIFSNEMAK VDDSFFHRLE ESFLVEEDKK

HERHPIFGNI VDEVAYHEKY PTIYHLRKKL VDSTDKADLR LIYLALAHMI KFRGHFLIEG
DLNPDNSDVD KLFIQLVQTY NQLFEENPIN ASGVDAKAIL SARLSKSRRL ENLIAQLPGE
KKNGLFGNLI ALSLGLTPNF KSNFDLAEDA KLQLSKDTYD DDLDNLLAQI GDQYADLFLA
AKNLSDAILL SDILRVNTEI TKAPLSASMI KRYDEHHQDL TLLKALVRQQ LPEKYKEIFF
DQSKNGYAGY IDGGASQEEF YKFIKPILEK MDGTEELLVK LNREDLLRKQ RTFDNGSIPH
QIHLGELHAI LRRQEDFYPF LKDNREKIEK ILTFRIPYYV GPLARGNSRF AWMTRKSEET
ITPWNFEEVV DKGASAQSFI ERMTNFDKNL PNEKVLPKHS LLYEYFTVYN ELTKVKYVTE
GMRKPAFLSG EQKKAIVDLL FKTNRKVTVK QLKEDYFKKI ECFDSVEISG VEDRFNASLG
TYHDLLKIIK DKDFLDNEEN EDILEDIVLT LTLFEDREMI EERLKTYAHL FDDKVMKQLK
RRRYTGWGRL SRKLINGIRD KQSGKTILDF LKSDGFANRN FMQLIHDDSL TFKEDIQKAQ
VSGQGDSLHE HIANLAGSPA IKKGILQTVK VVDELVKVMG RHKPENIVIE MARENQTTQK
GQKNSRERMK RIEEGIKELG SQILKEHPVE NTQLQNEKLY LYYLQNGRDM YVDQELDINR
LSDYDVDHIV PQSFLKDDSI DNAVLTRSDK NRGKSDNVPS EEVVKKMKNY
WRQLLNAKLI TQRKFDNLTK AERGGLSELD KAGFIKRQLV ETRQITKHVA QILDSRMNTK
YDENDKLIRE VKVITLKSKL VSDFRKDFQF YKVREINNYH HAHDAYLNAV VGTALIKKYP
KLESEFVYGD YKVYDVRKMI AKSEQEIGKA TAKYFFYSNI MNFFKTEITL ANGEIRKRPL
IETNGETGEI VWDKGRDFAT VRKVLSMPQV NIVKKTEVQT GGFSKESILP KRNSDKLIAR
KKDWDPKKYG GFDSPTVAYS VLVVAKVEKG KSKKLKSVKE LLGITIMERS SFEKNPIDFL
EAKGYKEVKK DLIIKLPKYS LFELENGRKR MLASAGELQK GNELALPSKY VNFLYLASHY
EKLKGSPEDN EQKQLFVEQH KHYLDEIIEQ ISEFSKRVIL ADANLDKVLS AYNKHRDKPI
REQAENIIHL FTLTNLGAPA AFKYFDTTID RKRYTSTKEV LDATLIHQSI TGLYETRIDL
SQLGGDSRAD PKKKRKVHHH HHH

iProt106746 (SEQ ID NO: 7829):

MAPKKKRKVD KKYSIGLDIG TNSVGWAVIT DEYKVPSKKF KVLGNTDRHS IKKNLIGALL
FDSGETAEAT RLKRTARRRY TRRKNRICYL QEIFSNEMAK VDDSFFHRLE ESFLVEEDKK
HERHPIFGNI VDEVAYHEKY PTIYHLRKKL VDSTDKADLR LIYLALAHMI KFRGHFLIEG
DLNPDNSDVD KLFIQLVQTY NQLFEENPIN ASGVDAKAIL SARLSKSRRL ENLIAQLPGE
KKNGLFGNLI ALSLGLTPNF KSNFDLAEDA KLQLSKDTYD DDLDNLLAQI GDQYADLFLA
AKNLSDAILL SDILRVNTEI TKAPLSASMI KRYDEHHQDL TLLKALVRQQ LPEKYKEIFF
DQSKNGYAGY IDGGASQEEF YKFIKPILEK MDGTEELLVK LNREDLLRKQ RTFDNGSIPH
QIHLGELHAI LRRQEDFYPF LKDNREKIEK ILTFRIPYYV GPLARGNSRF AWMTRKSEET
ITPWNFEEVV DKGASAQSFI ERMTNFDKNL PNEKVLPKHS LLYEYFTVYN ELTKVKYVTE
GMRKPAFLSG EQKKAIVDLL FKTNRKVTVK QLKEDYFKKI ECFDSVEISG VEDRFNASLG
TYHDLLKIIK DKDFLDNEEN EDILEDIVLT LTLFEDREMI EERLKTYAHL FDDKVMKQLK
RRRYTGWGRL SRKLINGIRD KQSGKTILDF LKSDGFANRN FMQLIHDDSL TFKEDIQKAQ
VSGQGDSLHE HIANLAGSPA IKKGILQTVK VVDELVKVMG RHKPENIVIE MARENQTTQK
GQKNSRERMK RIEEGIKELG SQILKEHPVE NTQLQNEALY LYYLQNGRDM YVDQELDINR
LSDYDVDHIV PQSFLKDDSI DNKVLTRSDK NRGKSDNVPS EEVVKKMKNY
WRQLLNAKLI TQRKFDNLTK AERGGLSELD KAGFIKRQLV ETRQITKHVA QILDSRMNTK
YDENDKLIRE VKVITLKSKL VSDFRKDFQF YKVREINNYH HAHDAYLNAV VGTALIKKYP
ALESEFVYGD YKVYDVRKMI AKSEQEIGKA TAKYFFYSNI MNFFKTEITL ANGEIRKAPL
IETNGETGEI VWDKGRDFAT VRKVLSMPQV NIVKKTEVQT GGFSKESILP KRNSDKLIAR
KKDWDPKKYG GFDSPTVAYS VLVVAKVEKG KSKKLKSVKE LLGITIMERS SFEKNPIDFL
EAKGYKEVKK DLIIKLPKYS LFELENGRKR MLASAGELQK GNELALPSKY VNFLYLASHY
EKLKGSPEDN EQKQLFVEQH KHYLDEIIEQ ISEFSKRVIL ADANLDKVLS AYNKHRDKPI
REQAENIIHL FTLTNLGAPA AFKYFDTTID RKRYTSTKEV LDATLIHQSI TGLYETRIDL
SQLGGDSRAD PKKKRKVHHH HHH

iProt106747 (SEQ ID NO: 7830):

MAPKKKRKVD KKYSIGLDIG TNSVGWAVIT DEYKVPSKKF KVLGNTDRHS IKKNLIGALL
FDSGETAEAT RLKRTARRRY TRRKNRICYL QEIFSNEMAK VDDSFFHRLE ESFLVEEDKK
HERHPIFGNI VDEVAYHEKY PTIYHLRKKL VDSTDKADLR LIYLALAHMI KFRGHFLIEG
DLNPDNSDVD KLFIQLVQTY NQLFEENPIN ASGVDAKAIL SARLSKSRRL ENLIAQLPGE

KKNGLFGNLI ALSLGLTPNF KSNFDLAEDA KLQLSKDTYD DDLDNLLAQI GDQYADLFLA
AKNLSDAILL SDILRVNTEI TKAPLSASMI KRYDEHHQDL TLLKALVRQQ LPEKYKEIFF
DQSKNGYAGY IDGGASQEEF YKFIKPILEK MDGTEELLVK LNREDLLRKQ RTFDNGSIPH
QIHLGELHAI LRRQEDFYPF LKDNREKIEK ILTFRIPYYV GPLARGNSRF AWMTRKSEET
ITPWNFEEVV DKGASAQSFI ERMTNFDKNL PNEKVLPKHS LLYEYFTVYN ELTKVKYVTE
GMRKPAFLSG EQKKAIVDLL FKTNRKVTVK QLKEDYFKKI ECFDSVEISG VEDRFNASLG
TYHDLLKIIK DKDFLDNEEN EDILEDIVLT LTLFEDREMI EERLKTYAHL FDDKVMKQLK
RRRYTGWGRL SRKLINGIRD KQSGKTILDF LKSDGFANRN FMQLIHDDSL TFKEDIQKAQ
VSGQGDSLHE HIANLAGSPA IKKGILQTVK VVDELVKVMG RHKPENIVIE MARENQTTQK
GQKNSRERMK RIEEGIKELG SQILKEHPVE NTQLQNEKLY LYYLQNGRDM YVDQELDINR
LSDYDVDHIV PQSFLADDSI DNKVLTRSDK NRGKSDNVPS EEVVKKMKNY
WRQLLNAKLI TQRKFDNLTK AERGGLSELD KAGFIKRQLV ETRQITKHVA QILDSRMNTK
YDENDKLIRE VKVITLKSKL VSDFRKDFQF YKVREINNYH HAHDAYLNAV VGTALIKKYP
ALESEFVYGD YKVYDVRKMI AKSEQEIGKA TAKYFFYSNI MNFFKTEITL ANGEIRKAPL
IETNGETGEI VWDKGRDFAT VRKVLSMPQV NIVKKTEVQT GGFSKESILP KRNSDKLIAR
KKDWDPKKYG GFDSPTVAYS VLVVAKVEKG KSKKLKSVKE LLGITIMERS SFEKNPIDFL
EAKGYKEVKK DLIIKLPKYS LFELENGRKR MLASAGELQK GNELALPSKY VNFLYLASHY
EKLKGSPEDN EQKQLFVEQH KHYLDEIIEQ ISEFSKRVIL ADANLDKVLS AYNKHRDKPI
REQAENIIHL FTLTNLGAPA AFKYFDTTID RKRYTSTKEV LDATLIHQSI TGLYETRIDL
SQLGGDSRAD PKKKRKVHHH HHH

iProt106884 (SEQ ID NO: 7831):

MAPKKKRKVD KKYSIGLDIG TNSVGWAVIT DEYKVPSKKF KVLGNTDRHS IKKNLIGALL
FDSGETAEAT RLKRTARRRY TRRKNRICYL QEIFSNEMAK VDDSFFHRLE ESFLVEEDKK
HERHPIFGNI VDEVAYHEKY PTIYHLRKKL VDSTDKADLR LIYLALAHMI KFRGHFLIEG
DLNPDNSDVD KLFIQLVQTY NQLFEENPIN ASGVDAKAIL SARLSKSRRL ENLIAQLPGE
KKNGLFGNLI ALSLGLTPNF KSNFDLAEDA KLQLSKDTYD DDLDNLLAQI GDQYADLFLA
AKNLSDAILL SDILRVNTEI TKAPLSASMI KRYDEHHQDL TLLKALVRQQ LPEKYKEIFF
DQSKNGYAGY IDGGASQEEF YKFIKPILEK MDGTEELLVK LNREDLLRKQ RTFDNGSIPH
QIHLGELHAI LRRQEDFYPF LKDNREKIEK ILTFRIPYYV GPLARGNSRF AWMTRKSEET
ITPWNFEEVV DKGASAQSFI ERMTAFDKNL PNEKVLPKHS LLYEYFTVYN ELTKVKYVTE
GMRKPAFLSG EQKKAIVDLL FKTNRKVTVK QLKEDYFKKI ECFDSVEISG VEDRFNASLG
TYHDLLKIIK DKDFLDNEEN EDILEDIVLT LTLFEDREMI EERLKTYAHL FDDKVMKQLK
RRRYTGWGAL SRKLINGIRD KQSGKTILDF LKSDGFANRN FMALIHDDSL TFKEDIQKAQ
VSGQGDSLHE HIANLAGSPA IKKGILQTVK VVDELVKVMG RHKPENIVIE MARENQTTQK
GQKNSRERMK RIEEGIKELG SQILKEHPVE NTQLQNEKLY LYYLQNGRDM YVDQELDINR
LSDYDVDHIV PQSFLKDDSI DNKVLTRSDK NRGKSDNVPS EEVVKKMKNY
WRQLLNAKLI TQRKFDNLTK AERGGLSELD KAGFIKRQLV ETRAITKHVA QILDSRMNTK
YDENDKLIRE VKVITLKSKL VSDFRKDFQF YKVREINNYH HAHDAYLNAV VGTALIKKYP
KLESEFVYGD YKVYDVRKMI AKSEQEIGKA TAKYFFYSNI MNFFKTEITL ANGEIRKRPL
IETNGETGEI VWDKGRDFAT VRKVLSMPQV NIVKKTEVQT GGFSKESILP KRNSDKLIAR
KKDWDPKKYG GFDSPTVAYS VLVVAKVEKG KSKKLKSVKE LLGITIMERS SFEKNPIDFL
EAKGYKEVKK DLIIKLPKYS LFELENGRKR MLASAGELQK GNELALPSKY VNFLYLASHY
EKLKGSPEDN EQKQLFVEQH KHYLDEIIEQ ISEFSKRVIL ADANLDKVLS AYNKHRDKPI
REQAENIIHL FTLTNLGAPA AFKYFDTTID RKRYTSTKEV LDATLIHQSI TGLYETRIDL
SQLGGDSRAD PKKKRKVHHH HHH

Nucleic Acids Encoding Cas9 Molecules

Nucleic acids encoding the Cas9 molecules, e.g., an active Cas9 molecule or an inactive Cas9 molecule are provided herein.

Exemplary nucleic acids encoding Cas9 molecules are described in Cong et al , SCIENCE 2013, 399(6121):819-823; Wang et al , CELL 2013, 153(4):910-918; Mali et al. , SCIENCE 2013, 399(6121):823-826; Jinek et al, SCIENCE 2012, 337(6096):816-821.

In an embodiment, a nucleic acid encoding a Cas9 molecule can be a synthetic nucleic acid sequence. For example, the synthetic nucleic acid molecule can be chemically modified, e.g., as described in Section XIII. In an embodiment, the Cas9 mRNA has one or more of, e.g., all of the following properties: it is capped, polyadenylated, substituted with 5-methylcytidine and/or pseudouridine.

In addition or alternatively, the synthetic nucleic acid sequence can be codon optimized, e.g., at least one non-common codon or less-common codon has been replaced by a common codon. For example, the synthetic nucleic acid can direct the synthesis of an optimized messenger mRNA, e.g., optimized for expression in a mammalian expression system, e.g., described herein.

Provided below is an exemplary codon optimized nucleic acid sequence encoding a Cas9 molecule of S. pyogenes.

atggataaaa agtacagcat cgggctggac atcggtacaa actcagtggg gtgggccgtg 60

attacggacg agtacaaggt accctccaaa aaatttaaag tgctgggtaa cacggacaga 120

cactctataa agaaaaatct tattggagcc ttgctgttcg actcaggcga gacagccgaa 180

gccacaaggt tgaagcggac cgccaggagg cggtatacca ggagaaagaa ccgcatatgc 240

tacctgcaag aaatcttcag taacgagatg gcaaaggttg acgatagctt tttccatcgc 300

ctggaagaat cctttcttgt tgaggaagac aagaagcacg aacggcaccc catctttggc 360

aatattgtcg acgaagtggc atatcacgaa aagtacccga ctatctacca cctcaggaag 420

aagctggtgg actctaccga taaggcggac ctcagactta tttatttggc actcgcccac 480

atgattaaat ttagaggaca tttcttgatc gagggcgacc tgaacccgga caacagtgac 540

gtcgataagc tgttcatcca acttgtgcag acctacaatc aactgttcga agaaaaccct 600

ataaatgctt caggagtcga cgctaaagca atcctgtccg cgcgcctctc aaaatctaga 660

agacttgaga atctgattgc tcagttgccc ggggaaaaga aaaatggatt gtttggcaac 720

ctgatcgccc tcagtctcgg actgacccca aatttcaaaa gtaacttcga cctggccgaa 780

gacgctaagc tccagctgtc caaggacaca tacgatgacg acctcgacaa tctgctggcc 840

cagattgggg atcagtacgc cgatctcttt ttggcagcaa agaacctgtc cgacgccatc 900

ctgttgagcg atatcttgag agtgaacacc gaaattacta aagcacccct tagcgcatct 960

atgatcaagc ggtacgacga gcatcatcag gatctgaccc tgctgaaggc tcttgtgagg 1020

caacagctcc ccgaaaaata caaggaaatc ttctttgacc agagcaaaaa cggctacgct 1080

ggctatatag atggtggggc cagtcaggag gaattctata aattcatcaa gcccattctc 1140

gagaaaatgg acggcacaga ggagttgctg gtcaaactta acagggagga cctgctgcgg 1200

aagcagcgga cctttgacaa cgggtctatc ccccaccaga ttcatctggg cgaactgcac 1260

gcaatcctga ggaggcagga ggatttttat cctttcctta aagataaccg cgagaaaata 1320

gaaaagattc ttacattcag gatcccgtac tacgtgggac ctctcgcccg gggcaattca 1380

cggtttgcct ggatgacaag gaagtcagag gagactatta caccttggaa cttcgaagaa 1440

gtggtggaca agggtgcatc tgcccagtct ttcatcgagc ggatgacaaa ttttgacaag 1500

aacctcccta atgagaaggt gctgcccaaa cattctctgc tctacgagta ctttaccgtc 1560

tacaatgaac tgactaaagt caagtacgtc accgagggaa tgaggaagcc ggcattcctt 1620

agtggagaac agaagaaggc gattgtagac ctgttgttca agaccaacag gaaggtgact 1680

gtgaagcaac ttaaagaaga ctactttaag aagatcgaat gttttgacag tgtggaaatt 1740

tcagggttg aagaccgctt caatgcgtca ttggggactt accatgatct tctcaagatc 1800

ataaaggaca aagacttcct ggacaacgaa gaaaatgagg atattctcga agacatcgtc 1860

ctcaccctga ccctgttcga agacagggaa atgatagaag agcgcttgaa aacctatgcc 1920

cacctcttcg acgataaagt tatgaagcag ctgaagcgca ggagatacac aggatgggga 1980

agattgtcaa ggaagctgat caatggaatt agggataaac agagtggcaa gaccatactg 2040

gatttcctca aatctgatgg cttcgccaat aggaacttca tgcaactgat tcacgatgac 2100

tctcttacct tcaaggagga cattcaaaag gctcaggtga gcgggcaggg agactccctt 2160

catgaacaca tcgcgaattt ggcaggttcc cccgctatta aaaagggcat ccttcaaact 2220

gtcaaggtgg tggatgaatt ggtcaaggta atgggcagac ataagccaga aaatattgtg 2280

atcgagatgg cccgcgaaaa ccagaccaca cagaagggcc agaaaaatag tagagagcgg 2340

atgaagagga tcgaggaggg catcaaagag ctgggatctc agattctcaa agaacacccc 2400

gtagaaaaca cacagctgca gaacgaaaaa ttgtacttgt actatctgca gaacggcaga 2460

gacatgtacg tcgaccaaga acttgatatt aatagactgt ccgactatga cgtagaccat 2520

atcgtgcccc agtccttcct gaaggacgac tccattgata acaaagtctt gacaagaagc 2580

gacaagaaca ggggtaaaag tgataatgtg cctagcgagg aggtggtgaa aaaaatgaag 2640

aactactggc gacagctgct taatgcaaag ctcattacac aacggaagtt cgataatctg 2700

acgaaagcag agagaggtgg cttgtctgag ttggacaagg cagggtttat taagcggcag 2760

ctggtggaaa ctaggcagat cacaaagcac gtggcgcaga ttttggacag ccggatgaac 2820

acaaaatacg acgaaaatga taaactgata cgagaggtca aagttatcac gctgaaaagc 2880

aagctggtgt ccgattttcg gaaagacttc cagttctaca aagttcgcga gattaataac 2940

taccatcatg ctcacgatgc gtacctgaac gctgttgtcg ggaccgcctt gataaagaag 3000

tacccaaagc tggaatccga gttcgtatac ggggattaca aagtgtacga tgtgaggaaa 3060

atgatagcca agtccgagca ggagattgga aaggccacag ctaagtactt cttttattct 3120

aacatcatga attttttaa gacggaaatt accctggcca acggagagat cagaaagcgg 3180

ccccttatag agacaaatgg tgaaacaggt gaaatcgtct gggataaggg cagggatttc 3240

gctactgtga ggaaggtgct gagtatgcca caggtaaata tcgtgaaaaa aaccgaagta 3300

cagaccggag gattttccaa ggaaagcatt ttgcctaaaa gaaactcaga caagctcatc 3360

gcccgcaaga aagattggga ccctaagaaa tacgggggat ttgactcacc caccgtagcc 3420

tattctgtgc tggtggtagc taaggtggaa aaaggaaagt ctaagaagct gaagtccgtg 3480

aaggaactct tgggaatcac tatcatggaa agatcatcct ttgaaaagaa ccctatcgat 3540

ttcctggagg ctaagggtta caaggaggtc aagaaagacc tcatcattaa actgccaaaa 3600

tactctctct tcgagctgga aaatggcagg aagagaatgt tggccagcgc cggagagctg 3660

caaaagggaa acgagcttgc tctgccctcc aaatatgtta attttctcta tctcgcttcc 3720

cactatgaaa agctgaaagg gtctcccgaa gataacgagc agaagcagct gttcgtcgaa 3780

cagcacaagc actatctgga tgaaataatc gaacaaataa gcgagttcag caaaagggtt 3840

atcctggcgg atgctaattt ggacaaagta ctgtctgctt ataacaagca ccgggataag 3900

cctattaggg aacaagccga gaatataatt cacctcttta cactcacgaa tctcggagcc 3960

cccgccgcct tcaaatactt tgatacgact atcgaccgga aacggtatac cagtaccaaa 4020

gaggtcctcg atgccaccct catccaccag tcaattactg gcctgtacga aacacggatc 4080

gacctctctc aactgggcgg cgactag 4107

(SEQ ID NO: 6628)

If the above Cas9 sequences are fused with a peptide or polypeptide at the C-terminus (e.g., an inactive Cas9 fused with a transcription repressor at the C-terminus), it is understood that the stop codon will be removed.

VI. Functional Analysis of Candidate Molecules

Candidate Cas9 molecules, candidate gRNA molecules, candidate Cas9 molecule/gRNA molecule complexes, can be evaluated by art-known methods or as described herein. For example, exemplary methods for evaluating the endonuclease activity of Cas9 molecule are described, e.g., in Jinek el al., SCIENCE 2012; 337(6096):8 16-821.

VII. Template Nucleic Acids (For Introduction of Nucleic Acids)

The term "template nucleic acid" or “donor template” as used herein refers to a nucleic acid to be inserted at or near a target sequence that has been modified, e.g., cleaved, by a CRISPR system of the present invention. In an embodiment, nucleic acid sequence at or near the target sequence is modified to have some or all of the sequence of the template nucleic acid, typically at or near cleavage site(s). In an embodiment, the template nucleic acid is single stranded. In an alternate embodiment, the template nucleic acid is double stranded. In an embodiment, the template nucleic acid is DNA, e.g., double stranded DNA. In an alternate embodiment, the template nucleic acid is single stranded DNA.

In embodiments, the template nucleic acid comprises sequence encoding a globin protein, e.g., a beta globin, e.g., comprises a beta globin gene. In an embodiment, the beta globin encoded by the nucleic acid comprises one or more mutations, e.g., anti-sickling mutations. In an embodiment, the beta globin encoded by the nucleic acid comprises the mutation T87Q. In an embodiment, the beta globin encoded by the nucleic acid comprises the mutation G16D. In an embodiment, the beta globin encoded by the nucleic acid comprises the mutation E22A. In an embodiment, the beta globin gene comprises the mutations G16D, E22A and T87Q. In embodiments, the template nucleic acid further comprises one or more regulatory elements, e.g., a promoter (e.g., a human beta globin promoter), a 3’ enhancer, and/or at least a portion of a globin locus control regoin (e.g., one or more DNAseI hypersensitivity sites (e.g., HS2, HS3 and/or HS4 of the human globin locus)).

In other embodiments, the template nucleic acid comprises sequence encoding a gamma globin, e.g., comprises a gamma globin gene. In embodiments, the template nucleic acid comprises sequence encoding more than one copy of a gamma globin protein, e.g., comprises two or more, e.g., two, gamma globin gene sequences. In embodiments, the template nucleic acid further comprises one or more regulatory elements, e.g., a promotor and/or enhancer.

In an embodiment, the template nucleic acid alters the structure of the target position by participating in a homology directed repair event. In an embodiment, the template nucleic acid alters the sequence of the target position. In an embodiment, the template nucleic acid results in the incorporation of a modified, or non-naturally occurring base into the target nucleic acid.

Mutations in a gene or pathway described herein may be corrected using one of the approaches discussed herein. In an embodiment, a mutation in a gene or pathway described herein is corrected by homology directed repair (HDR) using a template nucleic acid. In an embodiment, a mutation in a gene or pathway described herein is corrected by homologous recombination (HR) using a template nucleic acid. In an embodiment, a mutation in a gene or pathway described herein is corrected by Non-Homologous End Joining (NHEJ) repair using a template nucleic acid. In other embodiments, nucleic acid encoding molecules of interest may be inserted at or near a site modified by a CRISPR system of the present invention. In embodiments, the template nucleic acid comprises regulatory elements, e.g., one or more promotors and/or enhancers, operably linked to the nucleic acid sequence encoding a molecule of interest, e.g., as described herein.

HDR or HR Repair and Template Nucleic Acids

As described herein, nuclease-induced homology directed repair (HDR) or homologous recombination (HR) can be used to alter a target sequence and correct (e.g., repair or edit) a mutation in the genome. While not wishing to be bound by theory, it is believed that alteration of the target sequence occurs by repair based on a donor template or template nucleic acid. For example, the donor template or the template nucleic acid provides for alteration of the target sequence. It is contemplated that a plasmid donor or linear double stranded template can be used as a template for homologous recombination. It is further contemplated that a single stranded donor template can be used as a template for alteration of the target sequence by alternate methods of homology directed repair (e.g., single strand annealing) between the target sequence and the donor template. Donor template-effected alteration of a target sequence may depend on cleavage by a Cas9 molecule. Cleavage by Cas9 can comprise a double strand break, one single strand break, or two single strand breaks.

In an embodiment, a mutation can be corrected by either a single double-strand break or two single strand breaks. In an embodiment, a mutation can be corrected by providing a template and a CRISPR/Cas9 system that creates (1) one double strand break, (2) two single strand breaks, (3) two double stranded breaks with a break occurring on each side of the target sequence, (4) one double stranded break and two single strand breaks with the double strand break and two single strand breaks occurring on each side of the target sequence, (5) four single stranded breaks with a pair of single stranded breaks occurring on each side of the target sequence, or (6) one single strand break.

Double strand break mediated correction

In an embodiment, double strand cleavage is effected by a Cas9 molecule having cleavage activity associated with an HNH-like domain and cleavage activity associated with a RuvC-like domain, e.g., an N-terminal RuvC-like domain, e.g., a wild type Cas9. Such embodiments require only a single gRNA.

Single strand break mediated correction

In other embodiments, two single strand breaks, or nicks, are effected by a Cas9 molecule having nickase activity, e.g., cleavage activity associated with an HNH-like domain or cleavage activity associated with an N-terminal RuvC-like domain. Such embodiments require two gRNAs, one for placement of each single strand break. In an embodiment, the Cas9 molecule having nickase activity cleaves the strand to which the gRNA hybridizes, but not the strand that is complementary to the strand to which the gRNA hybridizes. In an embodiment, the Cas9 molecule having nickase activity does not cleave the strand to which the gRNA hybridizes, but rather cleaves the strand that is complementary to the strand to which the gRNA hybridizes.

In an embodiment, the nickase has HNH activity, e.g., a Cas9 molecule having the RuvC activity inactivated, e.g., a Cas9 molecule having a mutation at D10, e.g., the D10A mutation. D10A inactivates RuvC; therefore, the Cas9 nickase has (only) HN H activity and will cut on the strand to which the gRNA hybridizes (e.g., the complementary strand, which does not have the NGG PAM on it). In other embodiments, a Cas9 molecule having an H840, e.g., an H840A, mutation can be used as a nickase. H840A inactivates HNH; therefore, the Cas9 nickase has (only) RuvC activity and cuts on the non-complementary strand (e.g., the strand that has the NGG PAM and whose sequence is identical to the gRNA).

In an embodiment, in which a nickase and two gRNAs are used to position two single strand nicks, one nick is on the + strand and one nick is on the - strand of the target nucleic acid. The PAMs are outwardly facing. The gRNAs can be selected such that the gRNAs are separated by, from about 0-50, 0- 100, or 0-200 nucleotides. In an embodiment, there is no overlap between the target sequence that is complementary to the targeting domains of the two gRNAs. In an embodiment, the gRNAs do not overlap and are separated by as much as 50, 100, or 200 nucleotides. In an embodiment, the use of two gRNAs can increase specificity, e.g., by decreasing off-target binding (Ran el cil., CELL 2013).

In an embodiment, a single nick can be used to induce HDR. It is contemplated herein that a single nick can be used to increase the ratio of HDR, HR or NHEJ at a given cleavage site.

Placement of the double strand break or a single strand break relative to target position

The double strand break or single strand break in one of the strands should be sufficiently close to target position such that correction occurs. In an embodiment, the distance is not more than 50, 100, 200, 300, 350 or 400 nucleotides. While not wishing to be bound by theory, it is believed that the

break should be sufficiently close to target position such that the break is within the region that is subject to exonuclease-mediated removal during end resection. If the distance between the target position and a break is too great, the mutation may not be included in the end resection and, therefore, may not be corrected, as donor sequence may only be used to correct sequence within the end resection region.

In an embodiment, in which a gRNA (unimolecular (or chimeric) or modular gRNA) and Cas9 nuclease induce a double strand break for the purpose of inducing HDR- or HR-mediated correction, the cleavage site is between 0-200 bp (e.g., 0 to 175, 0 to 150, 0 to 125, 0 to 100, 0 to 75, 0 to 50, 0 to 25, 25 to 200, 25 to 175, 25 to 150, 25 to 125, 25 to 100, 25 to 75, 25 to 50, 50 to 200, 50 to 175, 50 to 150, 50 to 125, 50 to 100, 50 to 75, 75 to 200, 75 to 175, 75 to 150, 75 to 1 25, 75 to 100 bp) away from the target position. In an embodiment, the cleavage site is between 0- 100 bp (e.g., 0 to 75, 0 to 50, 0 to 25, 25 to 100, 25 to 75, 25 to 50, 50 to 100, 50 to 75 or 75 to 100 bp) away from the target position.

In an embodiment, in which two gRNAs (independently, unimolecular (or chimeric) or modular gRNA) complexing with Cas9 nickases induce two single strand breaks for the purpose of inducing HDR-mediated correction, the closer nick is between 0-200 bp (e.g., 0 to 175, 0 to 150, 0 to 125, 0 to 100, 0 to 75, 0 to 50, 0 to 25, 25 to 200, 25 to 175, 25 to 150, 25 to 125, 25 to 100, 25 to 75, 25 to 50, 50 to 200, 50 to 175, 50 to 150, 50 to 125, 50 to 100, 50 to 75, 75 to 200, 75 to 175, 75 to 150, 75 to 125, 75 to 100 bp) away from the target position and the two nicks will ideally be within 25-55 bp of each other (e.g., 25 to 50, 25 to 45, 25 to 40, 25 to 35, 25 to 30, 30 to 55, 30 to 50, 30 to 45, 30 to 40, 30 to 35, 35 to 55, 35 to 50, 35 to 45, 35 to 40, 40 to 55, 40 to 50, 40 to 45 bp) and no more than 100 bp away from each other (e.g., no more than 90, 80, 70, 60, 50, 40, 30, 20, 10 or 5 bp away from each other). In an embodiment, the cleavage site is between 0- 100 bp (e.g., 0 to 75, 0 to 50, 0 to 25, 25 to 100, 25 to 75, 25 to 50, 50 to 100, 50 to 75 or 75 to 100 bp) away from the target position.

In one embodiment, two gRNAs, e.g., independently, unimolecular (or chimeric) or modular gRNA, are configured to position a double-strand break on both sides of a target position. In an alternate embodiment, three gRNAs, e.g., independently, unimolecular (or chimeric) or modular gRNA, are configured to position a double strand break (i.e., one gRNA complexes with a Cas9 nuclease) and two single strand breaks or paired single stranded breaks (i.e., two gRNAs complex with Cas9 nickases) on either side of the target position (e.g., the first gRNA is used to target upstream (i.e., 5') of the target positionand the second gRNA is used to target downstream (i.e., 3') of the target position). In another embodiment, four gRNAs, e.g., independently, unimolecular (or chimeric) or modular gRNA, are configured to generate two pairs of single stranded breaks (i.e., two pairs of two gRNAs complex with Cas9 nickases) on either side of the target position (e.g., the first gRNA is used to target upstream (i.e., 5') of the target position and the second gRNA is used to target downstream

(i.e., 3') of the target position). The double strand break(s) or the closer of the two single strand nicks in a pair will ideally be within 0-500 bp of the target position (e.g., no more than 450, 400, 350, 300, 250, 200, 150, l00, 50 or 25 bp from the target position). When nickases are used, the two nicks in a pair are within 25-55 bp of each other (e.g., between 25 to 50, 25 to 45, 25 to 40, 25 to 35, 25 to 30, 50 to 55, 45 to 55, 40 to 55, 35 to 55, 30 to 55, 30 to 50, 35. to 50, 40 to 50 , 45 to 50, 35 to 45, or 40 to 45 bp) and no more than 100 bp away from each other (e.g., no more than 90, 80, 70, 60, 50, 40, 30, 20 or 10 bp).

In one embodiment, two gRNAs, e.g., independently, unimolecular (or chimeric) or modular gRNA, are configured to position a double-strand break on both sides of a target position. In an alternate embodiment, three gRNAs, e.g., independently, unimolecular (or chimeric) or modular gRNA, are configured to position a double strand break (i.e., one gRNA complexes with a Cas9 nuclease) and two single strand breaks or paired single stranded breaks (i.e., two gRNAs complex with Cas9 nickases) on two target sequences (e.g., the first gRNA is used to target an upstream (i.e., 5') target sequence and the second gRNA is used to target a downstream (i.e., 3') target sequence of an insertion site. In another embodiment, four gRNAs, e.g., independently, unimolecular (or chimeric) or modular gRNA, are configured to generate two pairs of single stranded breaks (i.e., two pairs of two gRNAs complex with Cas9 nickases) on either side of an insertion site (e.g., the first gRNA is used to target an upstream (i.e., 5') target sequence described herein, and the second gRNA is used to target a downstream (i.e., 3') target sequence described herein). The double strand break(s) or the closer of the two single strand nicks in a pair will ideally be within 0-500 bp of the target position (e.g., no more than 450, 400, 350, 300, 250, 200, 150, 100, 50 or 25 bp from the target position). When nickases are used, the two nicks in a pair are within 25-55 bp of each other (e.g., between 25 to 50, 25 to 45, 25 to 40, 25 to 35, 25 to 30, 50 to 55, 45 to 55, 40 to 55, 35 to 55, 30 to 55, 30 to 50, 35 to 50, 40 to 50 , 45 to 50, 35 to 45, or 40 to 45 bp) and no more than 100 bp away from each other (e.g., no more than 90, 80, 70, 60, 50, 40, 30, 20 or 10 bp).

Length of the homology arms

The homology arm should extend at least as far as the region in which end resection may occur, e.g., in order to allow the resected single stranded overhang to find a complementary region within the donor template. The overall length could be limited by parameters such as plasmid size or viral packaging limits. In an embodiment, a homology arm does not extend into repeated elements, e.g., ALU repeats, LINE repeats. A template may have two homology arms of the same or different lengths.

Exemplary homology arm lengths include at least 25, 50, 100, 250, 500, 750 or 1000 nucleotides.

Target position, as used herein, refers to a site on a target nucleic acid (e.g., the chromosome) that is modified by a Cas9 molecule-dependent process. For example, the target position can be a modified

Cas9 molecule cleavage of the target nucleic acid and template nucleic acid directed modification, e.g., correction, of the target position. In an embodiment, a target position can be a site between two nucleotides, e.g., adjacent nucleotides, on the target nucleic acid into which one or more nucleotides is added. The target position may comprise one or more nucleotides that are altered, e.g., corrected, by a template nucleic acid. In an embodiment, the target position is within a target sequence (e.g., the sequence to which the gRN A binds). In an embodiment, a target position is upstream or downstream of a target sequence (e.g., the sequence to which the gRNA binds).

Typically, the template sequence undergoes a breakage mediated or catalyzed recombination with the target sequence. In an embodiment, the template nucleic acid includes sequence that corresponds to a site on the target sequence that is cleaved by a Cas9 mediated cleavage event. In an embodiment, the template nucleic acid includes sequence that corresponds to both, a first site on the target sequence that is cleaved in a first Cas9 mediated event, and a second site on the target sequence that is cleaved in a second Cas9 mediated event.

In an embodiment, the template nucleic acid can include sequence which results in an alteration in the coding sequence of a translated sequence, e.g., one which results in the substitution of one amino acid for another in a protein product, e.g., transforming a mutant allele into a wild type allele, transforming a wild type allele into a mutant allele, and/or introducing a stop codon, insertion of an amino acid residue, deletion of an amino acid residue, or a nonsense mutation.

In other embodiments, the template nucleic acid can include sequence which results in an alteration in a non-coding sequence, e.g., an alteration in an exon or in a 5' or 3' non-translated or non-transcribed region. Such alterations include an alteration in a control element, e.g., a promoter, enhancer, and an alteration in a cis-acting or trans-acting control element.

The template nucleic acid can include sequence which, when integrated, results in:

decreasing the activity of a positive control element;

increasing the activity of a positive control element;

decreasing the activity of a negative control element;

increasing the activityof a negative control element;

decreasing the expression of a gene;

increasing the expression of a gene;

increasing resistance to a disorder or disease;

increasing resistance to viral entry;

correcting a mutation or altering an unwanted amino acid residue;

conferring, increasing, abolishing or decreasing a biological property of a gene product, e.g., increasing the enzymatic activity of an enzyme, or increasing the ability of a gene product to interact with another molecule.

The template nucleic acid can include sequence which results in:

a change in sequence of 1 , 2, 3, 4, 5, 6, 7, 8, 9, 10, 1 1 , 12 or more nucleotides of the target sequence.

In an embodiment, the template nucleic acid is 20+/- 10, 30+/- 10, 40+/- 10, 50+/- 10, 60+/- 10, 70+/- 10, 80+/- 10, 90+/- 10, 100+/- 10, 1 10+/- 10, 120+/- 10, 130+/- 10, 140+/- 10, 150+/- 10, 160+/- 10, 170+/- 10, 1 80+/- 10, 190+/- 10, 200+/- 10, 210+/-10, 220+/- 10, 200-300, 300-400, 400-500, 500-600, 600-700, 700-800, 800-900, 900-1000, 1000-2000, 2000-3000 or more than 3000 nucleotides in length.

A template nucleic acid comprises the following components:

[5' homology arm]-[insertion sequence]-[3' homology arm].

The homology arms provide for recombination into the chromosome, which can replace the undesired element, e.g., a mutation or signature, with the replacement sequence. In an embodiment, the homology arms flank the most distal cleavage sites.

In an embodiment, the 3' end of the 5' homology arm is the position next to the 5' end of the replacement sequence. In an embodiment, the 5' homology arm can extend at least 10, 20, 30, 40, 50, 60, 70, 80, 90, 100, 120, 150, 180, 200, 300, 400, 500, 600, 700, 800, 900, 1000, 1500, or 2000 nucleotides 5' from the 5' end of the replacement sequence.

In an embodiment, the 5' end of the 3' homology arm is the position next to the 3' end of the replacement sequence. In an embodiment, the 3' homology arm can extend at least 10, 20, 30, 40, 50, 60, 70, 80, 90, 100, 120, 150, 180, 200, 300, 400, 500, 600, 700, 800, 900, 1000, 1500, or 2000 nucleotides 3' from the 3' end of the replacement sequence.

It is contemplated herein that one or both homology arms may be shortened to avoid including certain sequence repeat elements, e.g., Alu repeats, LINE elements. For example, a 5' homology arm may be shortened to avoid a sequence repeat element. In other embodiments, a 3' homology arm may be shortened to avoid a sequence repeat element. In some embodiments, both the 5' and the 3' homology arms may be shortened to avoid including certain sequence repeat elements.

It is contemplated herein that template nucleic acids for correcting a mutation may designed for use as a single-stranded oligonucleotide (ssODN). When using a ssODN, 5' and 3' homology arms may range up to about 200 base pairs (bp) in length, e.g., at least 25, 50, 75, 100, 125, 150, 175, or 200 bp

in length. Longer homology arms are also contemplated for ssODNs as improvements in oligonucleotide synthesis continue to be made.

NHEJ Approaches for Gene Targeting

As described herein, nuclease-induced non-homologous end-joining (NHEJ) can be used to target gene-specific knockouts. Nuclease-induced NHEJ can also be used to remove (e.g., delete) sequence in a gene of interest.

While not wishing to be bound by theory, it is believed that, in an embodiment, the genomic alterations associated with the methods described herein rely on nuclease-induced NHEJ and the error-prone nature of the NHEJ repair pathway. NHEJ repairs a double-strand break in the DNA by joining together the two ends; however, generally, the original sequence is restored only if two compatible ends, exactly as they were formed by the double-strand break, are perfectly ligated. The DNA ends of the double-strand break are frequently the subject of enzymatic processing, resulting in the addition or removal of nucleotides, at one or both strands, prior to rejoining of the ends. This results in the presence of insertion and/or deletion (indel) mutations in the DNA sequence at the site of the NHEJ repair. Two-thirds of these mutations may alter the reading frame and, therefore, produce a non-functional protein. Additionally, mutations that maintain the reading frame, but which insert or delete a significant amount of sequence, can destroy functionality of the protein. This is locus dependent as mutations in critical functional domains are likely less tolerable than mutations in non-critical regions of the protein.

The indel mutations generated by NHEJ are unpredictable in nature; however, at a given break site certain indel sequences are favored and are over represented in the population. The lengths of deletions can vary widely; most commonly in the 1 -50 bp range, but they can easily reach greater than 100-200 bp. Insertions tend to be shorter and often include short duplications of the sequence immediately surrounding the break site. However, it is possible to obtain large insertions, and in these cases, the inserted sequence has often been traced to other regions of the genome or to plasmid DNA present in the cells.

Because NHEJ is a mutagenic process, it can also be used to delete small sequence motifs as long as the generation of a specific final sequence is not required. If a double-strand break is targeted near to a short target sequence, the deletion mutations caused by the NHEJ repair often span, and therefore remove, the unwanted nucleotides. For the deletion of larger DNA segments, introducing two double-strand breaks, one on each side of the sequence, can result in NHEJ between the ends with removal of the entire intervening sequence. Both of these approaches can be used to delete specific DNA sequences; however, the error-prone nature of NHEJ may still produce indel mutations at the site of repair.

Both double strand cleaving Cas9 molecules and single strand, or nickase, Cas9 molecules can be used in the methods and compositions described herein to generate NHEJ- mediated indels. NHEJ-mediated indels targeted to the gene, e.g., a coding region, e.g., an early coding region of a gene of interest can be used to knockout (i.e., eliminate expression of) a gene of interest. For example, early coding region of a gene of interest includes sequence immediately following a transcription start site, within a first exon of the coding sequence, or within 500 bp of the transcription start site (e.g., less than 500, 450, 400, 350, 300, 250, 200, 150, 100 or 50 bp).

Placement of double strand or single strand breaks relative to the target position

In an embodiment, in which a gRNA and Cas9 nuclease generate a double strand break for the purpose of inducing NHEJ-mediated indels, a gRNA, e.g., a unimolecular (or chimeric) or modular gRNA molecule, is configured to position one double-strand break in close proximity to a nucleotide of the target position. In an embodiment, the cleavage site is between 0-500 bp away from the target position (e.g., less than 500, 400, 300, 200, 100, 50, 40, 30, 25, 20, 15, 10, 9, 8, 7, 6, 5, 4, 3, 2 or 1 bp from the target position).

In an embodiment, in which two gRNAs complexing with Cas9 nickases induce two single strand breaks for the puipose of inducing NHEJ-mediated indels, two gRNAs, e.g., independently, unimolecular (or chimeric) or modular gRNA, are configured to position two single-strand breaks to provide for NHEJ repair a nucleotide of the target position. In an embodiment, the gRNAs are configured to position cuts at the same position, or within a few nucleotides of one another, on different strands, essentially mimicking a double strand break. In an embodiment, the closer nick is between 0-30 bp away from the target position (e.g., less than 30, 25, 20, 1 , 10, 9, 8, 7, 6, 5, 4, 3, 2 or 1 bp from the target position), and the two nicks are within 25-55 bp of each other (e.g., between 25 to 50, 25 to 45, 25 to 40, 25 to 35, 25 to 30, 50 to 55, 45 to 55, 40 to 55, 35 to 55, 30 to 55, 30 to 50, 35 to 50, 40 to 50 , 45 to 50, 35 to 45, or 40 to 45 bp) and no more than 100 bp away from each other (e.g., no more than 90, 80, 70, 60, 50, 40, 30, 20 or 10 bp). In an embodiment, the gRNAs are configured to place a single strand break on either side of a nucleotide of the target position.

Both double strand cleaving Cas9 molecules and single strand, or nickase, Cas9 molecules can be used in the methods and compositions described herein to generate breaks both sides of a target position. Double strand or paired single strand breaks may be generated on both sides of a target position to remove the nucleic acid sequence between the two cuts (e.g., the region between the two breaks is deleted). In one embodiment, two gRNAs, e.g., independently, unimolecular (or chimeric) or modular gRNA, are configured to position a double-strand break on both sides of a target position (e.g., the first gRNA is used to target upstream (i.e., 5') of the mutation in a gene or pathway described herein, and the second gRNA is used to target downstream (i.e., 3') of the mutation in a gene or pathway described herein). In an alternate embodiment, three gRNAs, e.g., independently,

unimolecular (or chimeric) or modular gRNA, are configured to position a double strand break (i.e., one gRNA complexes with a Cas9 nuclease) and two single strand breaks or paired single stranded breaks (i.e., two gRNAs complex with Cas9 nickases) on either side of a target position (e.g., the fu st gRNA is used to target upstream (i.e., 5') of the mutation in a gene or pathway described herein, and the second gRNA is used to target downstream (i.e., 3') of the mutation in a gene or pathway described herein). In another embodiment, four gRNAs, e.g., independently, unimolecular (or chimeric) or modular gRNA, are configured to generate two pairs of single stranded breaks (i.e., two pairs of two gRNAs complex with Cas9 nickases) on either side of the target position (e.g., the first gRNA is used to target upstream (i.e., 5') of the mutation in a gene or pathway described herein, and the second gRNA is used to target downstream (i.e., 3') of the mutation in a gene or pathway described herein). The double strand break(s) or the closer of the two single strand nicks in a pair will ideally be within 0-500 bp of the target position (e.g., no more than 450, 400, 350, 300, 250, 200, 150, 100, 50 or 25 bp from the target position). When nickases are used, the two nicks in a pair are within 25-55 bp of each other (e.g., between 25 to 50, 25 to 45, 25 to 40, 25 to 35, 25 to 30, 50 to 55, 45 to 55, 40 to 55, 35 to 55, 30 to 55, 30 to 50, 35 to 50, 40 to 50 , 45 to 50, 35 to 45, or 40 to 45 bp) and no more than 100 bp away from each other (e.g., no more than 90, 80, 70, 60, 50, 40, 30, 20 or 10 bp).

In other embodiments, the insertion of template nucleic acid may be mediated by microhomology end joining (MMEJ). See, e.g., Saksuma et al., "MMEJ-assisted gene knock-in using TALENs and CRISPR-Cas9 with the PITCh systems." *Nature Protocols* **11**, 118–133 (2016) doi:10.1038/nprot.2015.140 Published online 17 December 2015, the contents of which are incorporated by reference in their entirety.

VIII. Systems Comprising More Than One gRNA Molecule

While not intending to be bound by theory, it has been surprisingly shown herein that the targeting of two target sequences (e.g., by two gRNA molecule/Cas9 molecule complexes which each induce a single- or double-strand break at or near their respective target sequences) located in close proximity on a continuous nucleic acid induces excision (e.g., deletion) of the nucleic acid sequence (or at least 80%, 85%, 90%, 95%, 96%, 97%, 98%, 99% of the nucleic acid sequence) located between the two target sequences. In some aspects, the present disclosure provides for the use of two or more gRNA molecules that comprise targeting domains targeting target sequences in close proximity on a continuous nucleic acid, e.g., a chromosome, e.g., a gene or gene locus, including its introns, exons and regulatory elements. The use may be, for example, by introduction of the two or more gRNA molecules, together with one or more Cas9 molecules (or nucleic acid encoding the two or more gRNA molecules and/or the one or more Cas9 molecules) into a cell.

In some aspects, the target sequences of the two or more gRNA molecules are located at least 5, 6, 7, 8, 9, 10, 20, 30, 40, 50, 60, 70, 80, 90, 100, 200, 300, 400, 500, 600, 700, 800, 900, 1000, 2000, 3000,

4000, 5000, 6000, 7000, 8000, 9000, 10,000, 11,000, 12,000, 13,000, 14,000, or 15,000 nucleotides apart on a continuous nucleic acid, but not more than 25,000 nucleotides apart on a continuous nucleic acid. In an embodiment, the target sequences are located about 4000 nucleotides apart. In an embodiment, the target sequences are located about 6000 nucleotides apart.

In some aspects, the plurality of gRNA molecules each target sequences within the same gene or gene locus. In another aspect, the plurality of gRNA molecules each target sequences within 2 or more different genes.

In some aspects, the invention provides compositions and cells comprising a plurality, for example, 2 or more, for example, 2, gRNA molecules of the invention, wherein the plurality of gRNA molecules target sequences less than 15,000, less than 14,000, less than 13,000, less than 12,000, less than 11,000, less than 10,000, less than 9,000, less than 8,000, less than 7,000, less than 6,000, less than 5,000, less than 4,000, less than 3,000, less than 2,000, less than 1,000, less than 900, less than 800, less than 700, less than 600, less than 500, less than 400, less than 300, less than 200, less than 100, less than 90, less than 80, less than 70, less than 60, less than 50, less than 40, or less than 30 nucleotides apart. In an embodiment, the target sequences are on the same strand of duplex nulceic acid. In an embodiment, the target sequences are on different strands of duplex nucleic acid.

In one embodiment, the invention provides a method for excising (e.g., deleting) nucleic acid disposed between two gRNA binding sites disposed less than 25,000, less than 20,000, less than 15,000, less than 14,000, less than 13,000, less than 12,000, less than 11,000, less than 10,000, less than 9,000, less than 8,000, less than 7,000, less than 6,000, less than 5,000, less than 4,000, less than 3,000, less than 2,000, less than 1,000, less than 900, less than 800, less than 700, less than 600, less than 500, less than 400, less than 300, less than 200, less than 100, less than 90, less than 80, less than 70, less than 60, less than 50, less than 40, or less than 30 nucleotides apart on the same or different strands of duplex nucleic acid. In an embodiment, the method provides for deletion of more than 50%, more than 60%, more than 70%, more than 80%, more than 85%, more than 86%, more than 87%, more than 88%, more than 89%, more than 90%, more than 91%, more than 92%, more than 93%, more than 94%, more than 95%, more than 96%, more than 97%, more than 98%, more than 99%, or 100% of the nucleotides disposed between the PAM sites associated with each gRNA binding site. In embodiments, the deletion further comprises of one or more nucleotides within one or more of the PAM sites associated with each gRNA binding site. In embodiments, the deletion also comprises one or more nucleotides outside of the region between the PAM sites associated with each gRNA binding site.

In one aspect, the two or more gRNA molecules comprise targeting domains targeting target sequences flanking a gene regulatory element, e.g., a promotor binding site, an enhancer region, or a

repressor region, such that excision of the intervening sequence (or a portion of the intervening sequence) causes up- or down-regulation of a gene of interest.

In an embodiment, the two or more gRNA molecules include targeting domains comprising, e.g., consisting of, a targeting domain sequence of Table 1 or Table 5. In aspects, the two or more gRNA molecules comprise targeting domains that are complementary with sequences in the same gene. In aspects, the two or more gRNA molecules comprise targeting domains that are complementary with sequences of different genes. In an embodiment, the two or more gRNA molecules include targeting domains comprising, e.g., consisting of, a targeting domain sequence of Table 6. In an embodiment, the two or more gRNA molecules include targeting domains comprising, e.g., consisting of, a targeting domain sequence of Table 2, Table 7, Table 8 and/or Table 9. In aspects, the two or more gRNA molecules comprise targeting domains that are complementary with sequences in the same gene. In aspects, the two or more gRNA molecules comprise targeting domains that are complementary with sequences of different genes. In an embodiment, the two or more gRNA molecules are selected from the gRNA molecules of Table 7, Table 8 and/or Table 9. In an embodiment, the first and second gRNA molecules comprise targeting domains comprising, e.g., consisting of, targeting domain sequences selected from Tables 1-9, and are selected from different tables, e.g., and comprise targeting domains that are complementary with sequences of different genes.

In one aspect, the two or more gRNA molecules comprise targeting domains targeting target sequences flanking a gene regulatory element, e.g., a promotor binding site, an enhancer region, or a repressor region, such that excision of the intervening sequence (or a portion of the intervening sequence) causes up- or down-regulation of a gene of interest. By way of example, the two or more gRNA molecules comprise targeting domains targeting target sequences flanking a GATA1 binding site (or portion thereof) or TAL1 binding site (or portion thereof) of the erythroid enhancer region of the BCL11a gene (e.g., within the +55, +58 or +62 region). In other embodiments, the gRNA molecule or molecules do not result in a disruption of the GATA1 binding site or TAL1 binding site within the BCL11a Enhancer.

In an embodiment, the two or more gRNA molecules comprise targeting domains that comprise, e.g., consist of, targeting domains selected from Table 1. In an embodiment, the two or more gRNA molecules comprise targeting domains that comprise, e.g., consist of, targeting domains selected from Table 2. In an embodiment, the two or more gRNA molecules comprise targeting domains that comprise, e.g., consist of, targeting domains selected from Table 3. In an embodiment, the two or more gRNA molecules comprise targeting domains that comprise, e.g., consist of, targeting domains selected from Table 4. In an embodiment, the two or more gRNA molecules comprise targeting domains that comprise, e.g., consist of, targeting domains selected from Table 5. In an embodiment,

the two or more gRNA molecules comprise targeting domains that comprise, e.g., consist of, targeting domains selected from Table 6. In an embodiment, the two or more gRNA molecules comprise targeting domains that comprise, e.g., consist of, targeting domains selected from Table 7. In an embodiment, the two or more gRNA molecules comprise targeting domains that comprise, e.g., consist of, targeting domains selected from Table 8. In an embodiment, the two or more gRNA molecules comprise targeting domains that comprise, e.g., consist of, targeting domains selected from Table 9.

In aspects, the two or more gRNA molecules comprise targeting domains comprising, e.g., consisting of the targeting domain sequence pairs listed in section II, above.

Without being bound by theory, it is believed that increasing the expression of fetal hemoglobin (e.g., gamma globin) while simultaneously reducing or eliminating expression of beta globin (e.g., beta globin comprising a sickling mutation), will result in increased efficacy in treating a hemoglobinopathy, e.g., sickle cell disease. Thus, in one aspect, the two or more gRNA molecules comprise a first gRNA molecule that causes an increase in gamma globin expression and a second gRNA molecule that reduces or eliminates expression of beta globin, e.g., beta globin carrying a sickle cell mutation. In embodiments, the two or more gRNA molecules comprise a first gRNA molecule that targets a sequence within a BCL11a enhancer region, e.g., as described herein, e.g., a gRNA molecule comprising a targeting domain comprising, e.g., consisting of, a targeting domain of Table 7, Table 8 or Table 9, and a second gRNA molecule that targets a sequence of a sickle globin gene (e.g., a beta globin gene comprising a sickling mutation).

IX. Properties of the gRNA

It has further been surprisingly shown herein that gRNA molecules and CRISPR systems comprising said gRNA molecules produce similar or identical indel patterns across multiple experiments using the same cell type, method of delivery and crRNA/tracr components. Without being bound by theory, it is believed that some indel patterns may be more advantageous than others. For example, indels which predominantly include insertions and/or deletions wich result in a "frameshift mutation" (e.g., 1- or 2- base pair insertion or deletions, or any insertion or deletion where n/3 is not a whole number (where n=the number of nucleotides in the insertion or deletion)) may be beneficial in reducing or eliminating expression of a functional protein. Likewise, indels which predominantly include "large deletions" (deletions of more than 10, 11, 12, 13, 14, 15, 20, 25, or 30 nucleotides) may also be beneficial in, for example, removing critical regulatory sequences such as promoter binding sites, which may similarly have an impoved effect on expression of functional protein. While the indel patterns induced by a given gRNA/CRISPR system have surprisingly been found to be consistently reproduced across cell types, as described herein, not any single indel structure will inevtiably be produced in a given cell upon introduction of a gRNA/CRISPR system.

The invention thus provides for gRNA molecules which create a beneficial indel pattern or structure, for example, which have indel patterns or structures predominantly composed of frameshif mutation(s) and/or large deletions. Such gRNA molecules may be selected by assessing the indel pattern or structure created by a candidate gRNA molecule in a test cell (for example, a HEK293 cell) or in the cell of interest, e.g., a HSPC cell by NGS, as described herein. As shown in the Examples, gRNA molecules have been discovered, which, when introduced into the desired cell population, result in a population of cells comprising a significant fraction of the cells having a frameshift mutation in the targeted gene. In some cases, the rate of frameshift mutation is as high as 75%, 80%, 85%, 90% or more. The invention thus provides for populations of cells which comprise at least about 40% of cells (e.g., at least about 45%, at least about 50%, at least about 55%, at least about 60%, at least about 65%, at least about 70%, at least about 75%, at least about 80%, at least about 85%, at least about 90%, at least about 95%, or at least about 99%) having a frameshift mutation, e.g., as described herein, at or near the target site of a gRNA moleucle described herein. The invention also provides for populations of cells which comprise at least about 50% of cells (e.g., at least about 55%, at least about 60%, at least about 65%, at least about 70%, at least about 75%, at least about 80%, at least about 85%, at least about 90%, at least about 95%, or at least about 99%) having a frameshift mutation, e.g., as described herein, at or near the target site of a gRNA moleucle described herein.

The invention thus provides methods of selecting gRNA molecules for use in the therapeutic methods of the invention comprising: 1) providing a plurality of gRNA molecules to a target of interest, 2) assessing the indel pattern or structure created by use of said gRNA molecules, 3) selecting a gRNA molecule that forms an indel pattern or structure composed predominantly of frameshift mutations, large deletions or a combination thereof, and 4) using said selected gRNA in a methods of the invention.

The invention further provides methods of altering cells, and altered cells, wherein a particular indel pattern is constently produced with a given gRNA/CRISPR system in that cell type. The indel patterns, including the top 5 most frequently occuring indels observed with the gRNA/CRISPR systems described herein are disclosed, for example, in the Examples. As shown in the examples, populations of cells are generated, wherein a signficant fraction of the cells comprises one of the top 5 indels (for example, populations of cells wherein one of the top 5 indels is present in more than 30%, more than 40%, more than 50%, more than 60% or more of the cells of the population. Thus, the invention provides cells, e.g., HSPCs (as described herein), which comprise an indel of any one of the top 5 indels observed with a given gRNA/CRISPR system. Further, the invention provides populations of cells, e.g., HSPCs (as described herein), which when assessed by, for example, NGS, comprise a high percentage of cells comprising one of the top 5 indels described herein for a given gRNA/CRISPR system. When used in connection with indel pattern analysis, a “high percentage”

refers to at least about 50% (e.g., at least about 55%, at least about 60%, at least about 65%, at least about 70%, at least about 75%, at least about 80%, at least about 85%, at least about 90%, at least about 95%, or at least about 99%) of the cells of the population comprising one of the top 5 indels described herein for a given gRNA/CRISPR system. In other embodiments, the population of cells comprises at least about 25% (e.g., from about 25% to about 60%, e.g., from about 25% to about 50%, e.g., from about 25% to about 40%, e.g., from about 25% to about 35%) of cells which have one of the top 5 indels described herein for a given gRNA/CRISPR system. In embodiments, the top indels, e.g., top 5 indels for a given gRNA/CRISPR system which targets a +58 region of the BCL11a enhancer are provided in Table 15, Figure 25, and Table 37. In embodiments, the top indels, e.g., top 5 indels for a given gRNA/CRISPR system which targets a HPFH region are provided in Table 26, Table 27 and Table 37.

It has also been discovered that certain gRNA molecules do not create indels at off-target sequences within the genome of the target cell type, or produce indels at off target sites at very low frequencies (e.g., <5% of cells within a population) relative to the frequency of indel creation at the target site. Thus, the invention provides for gRNA molecules and CRISPR systems which do not exhibit off-target indel formation in the target cell type, or which produce a frequency of off-target indel formation of <5%. In embodiments, the invention provides gRNA molecules and CRISPR systems which do not exhibit any off target indel formation in the target cell type. Thus, the invention further provides a cell, e.g., a population of cells, e.g., HSPCs, e.g., as described herein, which comprise an indel at or near a target site of a gRNA molecule described herein (e.g., a frameshift indel, or any one of the top 5 indels produced by a given gRNA/CRISPR system, e.g., as described herein), but does not comprise an indel at any off-target site of the gRNA molecule. In other embodiments, the invention further provides a a population of cells, e.g., HSPCs, e.g., as described herein, which comprises > 50% of cells which have an indel at or near a target site of a gRNA molecule described herein (e.g., a frameshift indel, or any one of the top 5 indels produced by a given gRNA/CRISPR system, e.g., as described herein), but which comprises less than 5%, e.g., less than 4%, less than 3%, less than 2% or less than 1%, of cells comprising an indel at any off-target site of the gRNA molecule.

In embodiments, the indel produced by a CRISPR system described herein (e.g., a CRISPR system comprising a gRNA molecule described herein), does not comprise a nucelotide of a GATA-1 binding site and/or does not comprise a nucelotide of a TAL-1 binding site (e.g., does not comprise a nucleotide of a GATA-1 binding site and/or TAL-1 binding site described in Figure 25).

X. Delivery/Constructs

The components, e.g., a Cas9 molecule or gRNA molecule, or both, can be delivered, formulated, or administered in a variety of forms. As a non-limiting example, the gRNA molecule and Cas9 molecule can be formulated (in one or more compositions), directly delivered or administered to a cell

in which a genome editing event is desired. Alternatively, nucleic acid encoding one or more components, e.g., a Cas9 molecule or gRNA molecule, or both, can be formulated (in one or more compositions), delivered or administered. In one aspect, the gRNA molecule is provided as DNA encoding the gRNA molecule and the Cas9 molecule is provided as DNA encoding the Cas9 molecule. In one embodiment, the gRNA molecule and Cas9 molecule are encoded on separate nucleic acid molecules. In one embodiment, the gRNA molecule and Cas9 molecule are encoded on the same nucleic acid molecule. In one aspect, the gRNA molecule is provided as RNA and the Cas9 molecule is provided as DNA encoding the Cas9 molecule. In one embodiment, the gRNA molecule is provided with one or more modifications, e.g., as described herein. In one aspect, the gRNA molecule is provided as RNA and the Cas9 molecule is provided as mRNA encoding the Cas9 molecule. In one aspect, the gRNA molecule is provided as RNA and the Cas9 molecule is provided as a protein. In one embodiment, the gRNA and Cas9 molecule are provided as a ribonuclear protein complex (RNP). In one aspect, the gRNA molecule is provided as DNA encoding the gRNA molecule and the Cas9 molecule is provided as a protein.

Delivery, e.g., delivery of the RNP, (e.g., to HSPC cells as described herein) may be accomplished by, for example, electroporation (e.g., as known in the art) or other method that renders the cell membrane permeable to nucleic acid and/or polypeptide molecules. In embodiments, the CRISPR system, e.g., the RNP as described herein, is delivered by electroporation using a 4D-Nucleofector (Lonza), for example, using program CM-137 on the 4D-Nucleofector (Lonza). In embodiments, the CRISPR system, e.g., the RNP as described herein, is delivered by electroporation using a voltage from about 800 volts to about 2000 volts, e.g., from about 1000 volts to about 1800 volts, e.g., from about 1200 volts to about 1800 volts, e.g., from about 1400 volts to about 1800 volts, e.g., from about 1600 volts to about 1800 volts, e.g., about 1700 volts, e.g., at a voltage of 1700 volts. In embodiments, the pulse width/lenth is from about 10 ms to about 50 ms, e.g., from about 10 ms to about 40 ms, e.g., from about 10 ms to about 30 ms, e.g., from about 15 ms to about 25 ms, e.g., about 20 ms, e.g., 20 ms. In embodiments, 1, 2, 3, 4, 5, or more, e.g., 2, e.g., 1 pulses are used. In an embodiment, the CRISPR system, e.g., the RNP as described herein, is delivered by electroporation using a voltage of about 1700 volts (e.g., 1700 volts), a pulse width of about 20 ms (e.g., 20 ms), using a single (1) pulse. In embodiments, electroporation is accomplished using a Neon electroporator. Additional techniques for rendering the membrane permeable are known in the art and include, for example, cell squeezing (e.g., as described in WO2015/023982 and WO2013/059343, the contents of which are hereby incorporated by reference in their entirety), nanoneedles (e.g., as described in Chiappini et al., Nat. Mat., 14; 532-39, or US2014/0295558, the contents of which are hereby incorporated by reference in their entirety) and nanostraws (e.g., as described in Xie, ACS Nano, 7(5); 4351-58, the contents of which are hereby incorporated by reference in their entirety).

When a component is delivered encoded in DNA the DNA will typically include a control region, e.g., comprising a promoter, to effect expression. Useful promoters for Cas9 molecule sequences include CMV, EF- lalpha, MSCV, PGK, CAG control promoters. Useful promoters for gRNAs include H1, EF- 1a and U6 promoters. Promoters with similar or dissimilar strengths can be selected to tune the expression of components. Sequences encoding a Cas9 molecule can comprise a nuclear localization signal (NLS), e.g., an SV40 NLS. In an embodiment, a promoter for a Cas9 molecule or a gRNA molecule can be, independently, inducible, tissue specific, or cell specific.

DNA-based Delivery of a Cas9 molecule and or a gRNA molecule

DNA encoding Cas9 molecules and/or gRNA molecules, can be administered to subjects or delivered into cells by art-known methods or as described herein. For example, Cas9-encoding and/or gRNA-encoding DNA can be delivered, e.g., by vectors (e.g., viral or non-viral vectors), non-vector based methods (e.g., using naked DNA or DNA complexes), or a combination thereof.

In some embodiments, the Cas9- and/or gRNA-encoding DNA is delivered by a vector (e.g., viral vector/virus, plasmid, minicircle or nanoplasmid).

A vector can comprise a sequence that encodes a Cas9 molecule and/or a gRNA molecule. A vector can also comprise a sequence encoding a signal peptide (e.g., for nuclear localization, nucleolar localization, mitochondrial localization), fused, e.g., to a Cas9 molecule sequence. For example, a vector can comprise one or more nuclear localization sequence (e.g., from SV40) fused to the sequence encoding the Cas9 molecule.

One or more regulatory/control elements, e.g., a promoter, an enhancer, an intron, a polyadenylation signal, a Kozak consensus sequence, internal ribosome entry sites (IRES), a 2A sequence, and a splice acceptor or donor can be included in the vectors. In some embodiments, the promoter is recognized by RNA polymerase II (e.g., a CMV promoter). In other embodiments, the promoter is recognized by RNA polymerase III (e.g., a U6 promoter). In some embodiments, the promoter is a regulated promoter (e.g., inducible promoter). In other embodiments, the promoter is a constitutive promoter. In some embodiments, the promoter is a tissue specific promoter. In some embodiments, the promoter is a viral promoter. In other embodiments, the promoter is a non-viral promoter.

In some embodiments, the vector or delivery vehicle is a minicircle. In some embodiments, the vector or delivery vehicle is a nanoplasmid.

In some embodiments, the vector or delivery vehicle is a viral vector (e.g., for generation of recombinant viruses). In some embodiments, the virus is a DNA virus (e.g., dsDNA or ssDNA virus). In other embodiments, the virus is an RNA virus (e.g., an ssRNA virus).

Exemplary viral vectors/viruses include, e.g., retroviruses, lentiviruses, adenovirus, adeno- associated virus (AAV), vaccinia viruses, poxviruses, and herpes simplex viruses. Viral vector technology is well known in the art and is described, for example, in Sambrook et al., 2012, MOLECULAR CLONING: A LABORATORY MANUAL, volumes 1 -4, Cold Spring Harbor Press, NY), and in other virology and molecular biology manuals.

In some embodiments, the virus infects dividing cells. In other embodiments, the virus infects non-dividing cells. In some embodiments, the virus infects both dividing and non-dividing cells. In some embodiments, the virus can integrate into the host genome. In some embodiments, the virus is engineered to have reduced immunity, e.g., in human. In some embodiments, the virus is replication-competent. In other embodiments, the virus is replication- defective, e.g., having one or more coding regions for the genes necessary for additional rounds of virion replication and/or packaging replaced with other genes or deleted. In some embodiments, the virus causes transient expression of the Cas9 molecule and/or the gRNA molecule. In other embodiments, the viurs causes long-lasting, e.g., at least 1 week, 2 weeks, 1 month, 2 months, 3 months, 6 months, 9 months, 1 year, 2 years, or permanent expression, of the Cas9 molecule and/or the gRNA molecule. The packaging capacity of the viruses may vary, e.g., from at least about 4 kb to at least about 30 kb, e.g., at least about 5 kb, 10 kb, 15 kb, 20 kb, 25 kb, 30 kb, 35 kb, 40 kb, 45 kb, or 50 kb.

In some embodiments, the Cas9- and/or gRNA-encoding DNA is delivered by a recombinant retrovirus. In some embodiments, the retrovirus (e.g., Moloney murine leukemia vims) comprises a reverse transcriptase, e.g., that allows integration into the host genome. In some embodiments, the retrovirus is replication-competent. In other embodiments, the retrovirus is replication-defective, e.g., having one of more coding regions for the genes necessary for additional rounds of virion replication and packaging replaced with other genes, or deleted.

In some embodiments, the Cas9- and/or gRNA-encoding DNA is delivered by a recombinant lentivirus. For example, the lentivirus is replication-defective, e.g., does not comprise one or more genes required for viral replication.

In some embodiments, the Cas9- and/or gRNA-encoding DNA is delivered by a recombinant adenovirus. In some embodiments, the adenovirus is engineered to have reduced immunity in human.

In some embodiments, the Cas9- and/or gRNA-encoding DNA is delivered by a recombinant AAV. In some embodiments, the AAV can incorporate its genome into that of a host cell, e.g., a target cell as described herein. In some embodiments, the AAV is a self- complementary adeno-associated virus (scAAV), e.g., a scAAV that packages both strands which anneal together to form double stranded DNA. AAV serotypes that may be used in the disclosed methods include, e.g., AAV 1 , AAV2, modified AAV2 (e.g., modifications at Y444F, Y500F, Y730F and/or S662V), AAV3, modified AAV3 (e.g., modifications at Y705F, Y73 1 F and/or. T492V), AAV4, AAV5, AAV6, modified

AAV6 (e.g., modifications at S663V and/or T492V), AAV8. AAV 8.2, AAV9, AAV rh 10, and pseudotyped AAV, such as AAV2/8, AAV2/5 and AAV2/6 can also be used in the disclosed methods.

In some embodiments, the Cas9- and/or gRNA-encoding DNA is delivered by a hybrid virus, e.g., a hybrid of one or more of the viruses described herein.

A Packaging cell is used to form a virus particle that is capable of infecting a host or target cell. Such a cell includes a 293 cell, which can package adenovirus, and a ψ2 cell or a PA317 cell, which can package retrovirus. A viral vector used in gene therapy is usually generated by a producer cell line that packages a nucleic acid vector into a viral particle. The vector typically contains the minimal viral sequences required for packaging and subsequent integration into a host or target cell (if applicable), with other viral sequences being replaced by an expression cassette encoding the protein to be expressed. For example, an AAV vector used in gene therapy typically only possesses inverted terminal repeat (ITR) sequences from the AAV genome which are required for packaging and gene expression in the host or target cell. The missing viral functions are supplied in trans by the packaging cell line. Henceforth, the viral DNA is packaged in a cell line, which contains a helper plasmid encoding the other AAV genes, namely rep and cap, but lacking ITR sequences. The cell line is also infected with adenovirus as a helper. The helper virus promotes replication of the AAV vector and expression of AAV genes from the helper plasmid. The helper plasmid is not packaged in significant amounts due to a lack of ITR sequences. Contamination with adenovirus can be reduced by, e.g., heat treatment to which adenovirus is more sensitive than AAV.

In an embodiment, the viral vector has the ability of cell type and/or tissue type recognition. For example, the viral vector can be pseudotyped with a different/alternative viral envelope glycoprotein; engineered with a cell type-specific receptor (e.g., genetic modification of the viral envelope glycoproteins to incorporate targeting ligands such as a peptide ligand, a single chain antibodie, a growth factor); and/or engineered to have a molecular bridge with dual specificities with one end recognizing a viral glycoprotein and the other end recognizing a moiety of the target cell surface (e.g., ligand-receptor, monoclonal antibody, avidin-biotin and chemical conjugation).

In an embodiment, the viral vector achieves cell type specific expression. For example, a tissue-specific promoter can be constructed to restrict expression of the transgene (Cas 9 and gRNA) in only the target cell. The specificity of the vector can also be mediated by microRNA- dependent control of transgene expression. In an embodiment, the viral vector has increased efficiency of fusion of the viral vector and a target cell membrane. For example, a fusion protein such as fusion-competent hemagglutin (HA) can be incorporated to increase viral uptake into cells. In an embodiment, the viral vector has the ability of nuclear localization. For example, aviruse that requires the breakdown of the cell wall (during cell division) and therefore will not infect a non-diving cell can be altered to

incorporate a nuclear localization peptide in the matrix protein of the virus thereby enabling the transduction of non-proliferating cells.

In some embodiments, the Cas9- and/or gRNA-encoding DNA is delivered by a non- vector based method (e.g., using naked DNA or DNA complexes). For example, the DNA can be delivered, e.g., by organically modified silica or silicate (Ormosil), electroporation, gene gun, sonoporation, magnetofection, lipid-mediated transfection, dendrimers, inorganic nanoparticles, calcium phosphates, or a combination thereof.

In some embodiments, the Cas9- and/or gRNA-encoding DNA is delivered by a combination of a vector and a non-vector based method. For example, a virosome comprises a liposome combined with an inactivated virus (e.g., HIV or influenza virus), which can result in more efficient gene transfer, e.g., in a respiratory epithelial cell than either a viral or a liposomal method alone.

In an embodiment, the delivery vehicle is a non-viral vector. In an embodiment, the non- viral vector is an inorganic nanoparticle (e.g., attached to the payload to the surface of the nanoparticle). Exemplary inorganic nanoparticles include, e.g., magnetic nanoparticles (e.g., Fe lvln0_2), or silica. The outer surface of the nanoparticle can be conjugated with a positively charged polymer (e.g., polyethylenimine, polylysine, polyserine) which allows for attachment (e.g., conjugation or entrapment) of payload. In an embodiment, the non-viral vector is an organic nanoparticle (e.g., entrapment of the payload inside the nanoparticle). Exemplary organic nanoparticles include, e.g., SNALP liposomes that contain cationic lipids together with neutral helper lipids which are coated with polyethylene glycol (PEG) and protamine and nucleic acid complex coated with lipid coating.

Exemplary lipids and/or polymers for for transfer of CRISPR systems or nucleic acid, e.g., vectors, encoding CRISPR systems or components thereof include, for example, those described in WO2011/076807, WO2014/136086, WO2005/060697, WO2014/140211, WO2012/031046, WO2013/103467, WO2013/006825, WO2012/006378, WO2015/095340, and WO2015/095346, the contents of each of the foregoing are hereby incorported by reference in their entirety. In an embodiment, the vehicle has targeting modifications to increase target cell update of nanoparticles and liposomes, e.g., cell specific antigens, monoclonal antibodies, single chain antibodies, aptamers, polymers, sugars, and cell penetrating peptides. In an embodiment, the vehicle uses fusogenic and endosome-destabilizing peptides/polymers. In an embodiment, the vehicle undergoes acid-triggered conformational changes (e.g., to accelerate endosomal escape of the cargo). In an embodiment, a stimuli-cleavable polymer is used, e.g., for release in a cellular compartment. For example, disulfide-based cationic polymers that are cleaved in the reducing cellular environment can be used.

In an embodiment, the delivery vehicle is a biological non-viral delivery vehicle. In an embodiment, the vehicle is an attenuated bacterium (e.g., naturally or artificially engineered to be invasive but attenuated to prevent pathogenesis and expressing the transgene (e.g., Listeria monocytogenes, certain

Salmonella strains, Bifidobacterium longum, and modified Escherichia coli), bacteria having nutritional and tissue-specific tropism to target specific tissues, bacteria having modified surface proteins to alter target tissue specificity). In an embodiment, the vehicle is a genetically modified bacteriophage (e.g., engineered phages having large packaging capacity, less immunogenic, containing mammalian plasmid maintenance sequences and having incorporated targeting ligands). In an embodiment, the vehicle is a mammalian virus-like particle. For example, modified viral particles can be generated (e.g., by purification of the "empty" particles followed by ex vivo assembly of the virus with the desired cargo). The vehicle can also be engineered to incorporate targeting ligands to alter target tissue specificity. In an embodiment, the vehicle is a biological liposome. For example, the biological liposome is a phospholipid-based particle derived from human cells (e.g., erythrocyte ghosts, which are red blood cells broken down into spherical structures derived from the subject (e.g., tissue targeting can be achieved by attachment of various tissue or cell-specific ligands), or secretory exosomes - subject (i.e., patient) derived membrane-bound nanovescicle (30 - 100 nm) of endocytic origin (e.g., can be produced from various cell types and can therefore be taken up by cells without the need of for targeting ligands).

In an embodiment, one or more nucleic acid molecules (e.g., DNA molecules) other than the components of a Cas system, e.g., the Cas9 molecule component and/or the gRNA molecule component described herein, are delivered. In an embodiment, the nucleic acid molecule is delivered at the same time as one or more of the components of the Cas system are delivered. In an embodiment, the nucleic acid molecule is delivered before or after (e.g., less than about 30 minutes, 1 hour, 2 hours, 3 hours, 6 hours, 9 hours, 12 hours, 1 day, 2 days, 3 days, 1 week, 2 weeks, or 4 weeks) one or more of the components of the Cas9 system are delivered. In an embodiment, the nucleic acid molecule is delivered by a different means than one or more of the components of the Cas9 system, e.g., the Cas9 molecule component and/or the gRNA molecule component, are delivered. The nucleic acid molecule can be delivered by any of the delivery methods described herein. For example, the nucleic acid molecule can be delivered by a viral vector, e.g., an integration-deficient lentivirus, and the Cas9 molecule component and/or the gRNA molecule component can be delivered by electroporation, e.g., such that the toxicity caused by nucleic acids (e.g., DNAs) can be reduced. In an embodiment, the nucleic acid molecule encodes a therapeutic protein, e.g., a protein described herein. In an embodiment, the nucleic acid molecule encodes an RNA molecule, e.g., an RNA molecule described herein. Delivery of RNA encoding a Cas9 molecule

RNA encoding Cas9 molecules (e.g., active Cas9 molecules, inactive Cas9 molecules or inactive Cas9 fusion proteins) and/or gRNA molecules, can be delivered into cells, e.g., target cells described herein, by art-known methods or as described herein. For example, Cas9-encoding and/or gRNA-encoding RNA can be delivered, e.g., by microinjection, electroporation, lipid-mediated transfection, peptide-mediated delivery, or a combination thereof.

Delivery of Cas9 molecule as protein

Cas9 molecules (e.g., active Cas9 molecules, inactive Cas9 molecules or inactive Cas9 fusion proteins) can be delivered into cells by art-known methods or as described herein. For example, Cas9 protein molecules can be delivered, e.g., by microinjection, electroporation, lipid-mediated transfection, peptide-mediated delivery, cell squeezing or abrasion (e.g., by nanoneedles) or a combination thereof. Delivery can be accompanied by DNA encoding a gRNA or by a gRNA, e.g., by precomplexing the gRNA and the Cas9 protein in a ribonuclear protein complex (RNP).

In an aspect the Cas9 molecule, e.g., as described herein, is delivered as a protein and the gRNA molecule is delivered as one or more RNAs (e.g., as a dgRNA or sgRNA, as described herein). In embodiments, the Cas9 protein is complexed with the gRNA molecule prior to delivery to a cell, e.g., as described herein, as a ribonuclear protein complex ("RNP"). In embodiments, the RNP can be delivered into cells, e.g., described herein, by any art-known method, e.g., electroporation. As described herein, and without being bound by theory, it can be preferrable to use a gRNA moleucle and Cas9 molecule which result in high % editing at the target sequence (e.g., >85%, >90%, >95%, >98%, or >99%) in the target cell, e.g., described herein, even when the concentration of RNP delivered to the cell is reduced. Again, without being bound by theory, delivering a reduced or low concentration of RNP comprising a gRNA moleucle that produces a high % editing at the target sequence in the target cell (including at the low RNP concentration), can be beneficial because it may reduce the frequency and number of off-target editing events. In one aspect, where a low or reduced concentration of RNP is to be used, the following exemplary procedure can be used to generate the RNP with a dgRNA molecule:

1. Provide the Cas9 molecule and the tracr in solution at a high concentration (e.g., a concentration higher than the final RNP concentration to be delivered to the cell), and allow the two components to equilibrate;
2. Provide the crRNA molecule, and allow the components to equilibrate (thereby forming a high-concentration solution of the RNP);
3. Dilute the RNP solution to the desired concentration;
4. Deliver said RNP at said desired concentration to the target cells, e.g., by electroporation.

The above procedure may be modified for use with sgRNA molecules by omitting step 2, above, and in step 1, providing the Cas9 molecule and the sgRNA molecule in solution at high concentraiton, and allowing the components to equilibrate. In embodiments, the Cas9 moleucle and each gRNA component are provided in solution at a 1:2 ratio (Cas9:gRNA), e.g., a 1:2 molar ratio of Cas9:gRNA molecule. Where dgRNA molecules are used, the ratio, e.g., molar rato, is 1:2:2 (Cas9:tracr:crRNA). In embodiments, the RNP is formed at a concentration of 20uM or higher, e.g., a concentration from about 20uM to about 50 uM. In embodiments, the RNP is formed at a concentration of 10 uM or

higher, e.g., a concentration from about 10 uM to about 30 uM. In embodiments, the RNP is diluted to a final concentration of 10uM or less (e.g., a concentration from about 0.01 uM to about 10uM) in a solution comprising the target cell (e.g., described herein) for delivery to said target cell. In embodiments, the RNP is diluted to a final concentration of 3uM or less (e.g., a concentration from about 0.01 uM to about 3uM) in a solution comprising the target cell (e.g., described herein) for delivery to said target cell. In embodiments, the RNP is diluted to a final concentration of 1uM or less (e.g., a concentration from about 0.01 uM to about 1uM) in a solution comprising the target cell (e.g., described herein) for delivery to said target cell. In embodiments, the RNP is diluted to a final concentration of 0.3uM or less (e.g., a concentration from about 0.01 uM to about 0.3uM) in a solution comprising the target cell (e.g., described herein) for delivery to said target cell. In embodiments, the RNP is provided at a final concentration of about 3uM in a solution comprising the target cell (e.g., described herein) for delivery to said target cell. In embodiments, the RNP is provided at a final concentration of about 1uM in a solution comprising the target cell (e.g., described herein) for delivery to said target cell. In embodiments, the RNP is provided at a final concentration of about 0.3uM in a solution comprising the target cell (e.g., described herein) for delivery to said target cell. In embodiments, the RNP is provided at a final concentration of about 0.1uM in a solution comprising the target cell (e.g., described herein) for delivery to said target cell. In embodiments, the RNP is provided at a final concentration of about 0.05uM in a solution comprising the target cell (e.g., described herein) for delivery to said target cell. In embodiments, the RNP is provided at a final concentration of about 0.03uM in a solution comprising the target cell (e.g., described herein) for delivery to said target cell. In embodiments, the RNP is provided at a final concentration of about 0.01uM in a solution comprising the target cell (e.g., described herein) for delivery to said target cell. In embodiments, the RNP is formulated in a medium suitable for electroporation. In embodiments, the RNP is delivered to cells, e.g., HSPC cells, e.g., as described herein, by electroporation, e.g., using electroporation conditions described herein.

Bi-Modal or Differential Delivery of Components

Separate delivery of the components of a Cas system, e.g., the Cas9 molecule component and the gRNA molecule component, and more particularly, delivery of the components by differing modes, can enhance performance, e.g., by improving tissue specificity and safety.

In an embodiment, the Cas9 molecule and the gRNA molecule are delivered by different modes, or as sometimes referred to herein as differential modes. Different or differential modes, as used herein, refer modes of delivery that confer different pharmacodynamic or pharmacokinetic properties on the subject component molecule, e.g., a Cas9 molecule, gRNA molecule, or template nucleic acid. For example, the modes of delivery can result in different tissue distribution, different half-life, or different temporal distribution, e.g., in a selected compartment, tissue, or organ.

Some modes of delivery, e.g., delivery by a nucleic acid vector that persists in a cell, or in progeny of a cell, e.g., by autonomous replication or insertion into cellular nucleic acid, result- in more persistent expression of and presence of a component.

XI. Methods of Treatment

The Cas9 systems, e.g., one or more gRNA molecules and one or more Cas9 molecules, described herein are useful for the treatment of disease in a mammal, e.g., in a human. The terms "treat," "treated," "treating," and "treatment," include the administration of cas9 systems, e.g., one or more gRNA molecules and one or more cas9 molecules, to cells to prevent or delay the onset of the symptoms, complications, or biochemical indicia of a disease, alleviating the symptoms or arresting or inhibiting further development of the disease, condition, or disorder. Treatment may also include the administration of one or more (e.g., a population of) cells, e.g., HSPCs, that have been modified by the introduction of a gRNA molecule (or more than one gRNA molecule) of the present invention, or by the introduction of a CRISPR system as described herein, or by any of the methods of preparing said cells described herein, to prevent or delay the onset of the symptoms, complications, or biochemical indicia of a disease, alleviating the symptoms or arresting or inhibiting further development of the disease, condition, or disorder. Treatment may be prophylactic (to prevent or delay the onset of the disease, or to prevent the manifestation of clinical or subclinical symptoms thereof) or therapeutic suppression or alleviation of symptoms after the manifestation of the disease. Treatment can be measured by the therapeutic measures described hererin. Thus, the methods of "treatment" of the present invention also include administration of cells altered by the introduction of a cas9 system (e.g., one or more gRNA molecules and one or more Cas9 molecules) into said cells to a subject in order to cure, reduce the severity of, or ameliorate one or more symptoms of a disease or condition, in order to prolong the health or survival of a subject beyond that expected in the absence of such treatment. For example, "treatment" includes the alleviation of a disease symptom in a subject by at least 5%, 6%, 7%, 8%, 9%, 10%, 11%, 12%, 13%, 14%, 15%, 16%, 17%, 18%, 19%, 20%, 25%, 30%, 35%, 40%, 45%, 50%, 55%, 60%, 65%, 70%, 75%, 80%, 85%, 90%, 95% or more.

Cas9 systems comprising gRNA molecules comprising the targeting domains described herein, e.g., in Tables 1, 2, 3, 4, 5, 6, 7, 8, and/or 9, are useful for the treatment of hemoglobinopathies.

Hemoglobinopathies

Hemoglobinopathies encompass a number of anemias of genetic origin in which there is a decreased production and/or increased destruction (hemolysis) of red blood cells (RBCs). These also include genetic defects that result in the production of abnormal hemoglobins with a concomitant impaired ability to maintain oxygen concentration. Some such disorders involve the failure to produce normal β -globin in sufficient amounts, while others involve the failure to produce normal β -globin entirely. These disorders associated with the β -globin protein are referred to generally as β-

hemoglobinopathies. For example, β -thalassemias result from a partial or complete defect in the expression of the β -globin gene, leading to deficient or absent HbA. Sickle cell anemia results from a point mutation in the β -globin structural gene, leading to the production of an abnormal (sickle) hemoglobin (HbS). HbS is prone to polymerization, particularly under deoxygenated conditions. HbS RBCs are more fragile than normal RBCs and undergo hemolysis more readily, leading eventually to anemia.

In an embodiment, a genetic defect in alpha globin or beta globin is corrected, e.g., by homologous recombination, using the Cas9 molecules and gRNA molecules, e.g., CRISPR systems, described herein.

In an embodiment, a gene encoding a wild type (e.g., non-mutated) copy of alpha globin or beta globin is inserted into the genome of the cell, e.g., at a safe harbor site, e.g., at an AAVS1 safe harbor site, by homologous recombination, using a CRISPR system and methods described herein.

In an embodiment, a hemoglobinopathies-associated gene is targeted, using the Cas9 molecule and gRNA molecule described herein. Exemplary targets include, e.g., genes associated with control of the gamma-globin genes. In an embodiment, the target is BCL11A. In an embodiment, the target is a BCL11a enhancer. In an embodiment, the target is a HPFH region.

Fetal hemoglobin (also hemoglobin F or HbF or $\alpha 2\gamma 2$) is a tetramer of two adult alpha- globin polypeptides and two fetal beta-like gamma-globin polypeptides. HbF is the main oxygen transport protein in the human fetus during the last seven months of development in the uterus and in the newborn until roughly 6 months old. Functionally, fetal hemoglobin differs most from adult hemoglobin in that it is able to bind oxygen with greater affinity than the adult form, giving the developing fetus better access to oxygen from the mother's bloodstream.

In newborns, fetal hemoglobin is nearly completely replaced by adult hemoglobin by approximately 6 months postnatally. In adults, fetal hemoglobin production can be reactivated pharmacologically, which is useful in the treatment of diseases such as hemoglobinopathies. For example, in certain patients with hemoglobinopathies, higher levels of gamma-globin expression can partially compensate for defective or impaired beta-globin gene production, which can ameliorate the clinical severity in these diseases. Increased HbF levels or F-cell (HbF containing erythrocyte) numbers can ameliorate the disease severity of hemoglobinopathies, e.g., beta- thalassemia major and sickle cell anemia.

Increased HbF levels or F-cell can be associated reduced BCL11A expression in cells. The BCL11A gene encodes a multi-zinc finger transcription factor. In an embodiment, the expression of BCL11A is modulated, e.g., down-regulated. In an embodiment, the BCL11A gene is edited. In an embodiment, the function of BCL11a, e.g., in an enrythroid lineage cell, is impaired or down-regulated. In an embodiment, the cell is a hemopoietic stem cell or progenitor cell.

Sickle cell diseases

Sickle cell disease is a group of disorders that affects hemoglobin. People with this disorder have atypical hemoglobin molecules (hemoglobin S), which can distort red blood cells into a sickle, or crescent, shape. Characteristic features of this disorder include a low number of red blood cells (anemia), repeated infections, and periodic episodes of pain.

Mutations in the HBB gene cause sickle cell disease. T e HBB gene provides instructions for making beta-globin. Various versions of beta-globin result from different mutations in the HBB gene. One particular HBB gene mutation produces an abnormal version of beta-globin known as hemoglobin S (HbS). Other mutations in the HBB gene lead to additional abnormal versions of beta-globin such as hemoglobin C (HbC) and hemoglobin E (HbE). HBB gene mutations can also result in an unusually low level of beta-globin, i.e., beta thalassemia.

In people with sickle cell disease, at least one of the beta-globin subunits in hemoglobin is replaced with hemoglobin S. In sickle cell anemia, which is a common form of sickle cell disease, hemoglobin S replaces both beta-globin subunits in hemoglobin. In other types of sickle cell disease, just one beta-globin subunit in hemoglobin is replaced with hemoglobin S. The other beta-globin subunit is replaced with a different abnormal variant, such as hemoglobin C. For example, people with sickle-hemoglobin C (HbSC) disease have hemoglobin molecules with hemoglobin S and hemoglobin C instead of beta-globin. If mutations that produce hemoglobin S and beta thalassemia occur together, individuals have hemoglobin S-beta thalassemia (HbSBetaThal) disease.

Beta thalassemia

Beta thalassemia is a blood disorder that reduces the production of hemoglobin. In people with beta thalassemia, low levels of hemoglobin lead to a lack of oxygen in many parts of the body. Affected individuals also have a shortage of red blood cells (anemia), which can cause pale skin, weakness, fatigue, and more serious complications. People with beta thalassemia are at an increased risk of developing abnormal blood clots.

Beta thalassemia is classified into two types depending on the severity of symptoms: thalassemia major (also known as Cooley's anemia) and thalassemia intermedia. Of the two types, thalassemia major is more severe.

Mutations in the HBB gene cause beta thalassemia. The HBB gene provides instructions for making beta-globin. Some mutations in the HBB gene prevent the production of any beta- globin. The absence of beta-globin is referred to as beta-zero (B°) thalassemia. Other HBB gene mutations allow some beta-globin to be produced but in reduced amounts, i.e., beta-plus (B^{+}) thalassemia. People with both types have been diagnosed with thalassemia major and thalassemia intermedia.

In an embodiment, a Cas9 molecule/gRNA molecule complex targeting a first gene is used to treat a disorder characterized by second gene, e.g., a mutation in a second gene. By way of example, targeting of the first gene, e.g., by editing or payload delivery, can compensate for, or inhibit further damage from, the affect of a second gene, e.g., a mutant second gene. In an embodiment the allele(s) of the first gene carried by the subject is not causative of the disorder.

In one aspect, the invention relates to the treatment of a mammal, e.g., a human, in need of increased fetal hemoglobin (HbF).

In one aspect, the invention relates to the treatment of a mammal, e.g., a human, that has been diagnosed with, or is at risk of developing, a hemoglobinopathy.

In one aspect, the hemoglobinopathy is a β -hemoglobinopathy. In one aspect, the hemoglobinopathy is sickle cell disease. In one aspect, the hemoglobinopathy is beta thalassemia.

Methods of Treatment of Hemoglobinopathies

In another aspect the invention provides methdos of treatment. In aspects, the gRNA molecules, CRISPR systems and/or cells of the invention are used to treat a patient in need thereof. In aspects, the patient is a mammal, e.g., a human. In aspects, the patient has a hemoglobinopathy. In embodiments, the patient has sickle cell disease. In embodiments, the patient has beta thalassemia.

In one aspect, the method of treatment comprises administering to a mammal, e.g., a human, one or more gRNA molecules, e.g., one or more gRNA molecules comprising a targeting domain described in Table 1, 2, 3, 4, 5, 6, 7, 8, or 9, and one or more cas9 molecules described herein.

In one aspect, the method of treatment comprises administering to a mammal a cell population, wherein the cell population is a cell population from a mammal, e.g., a human, that has been administered one or more gRNA molecules, e.g., one or more gRNA molecules comprising a targeting domain described in Table 1, 2, 3, 4, 5, 6, 7, 8, or 9, and one or more cas9 molecules described herein, e.g., a CRISPR system as described herein. In one embodiment, the administration of the one or more gRNA molecules or CRISPR systems to the cell is accomplished in vivo. In one embodiment the administration of the one or more gRNA molecules or CRISPR systems to the cell is accomplished ex vivo.

In one aspect, the method of treatment comprises administering to the mammal, e.g., the human, an effective amount of a cell population comprising cells which comprise or at one time comprised one or more gRNA molecules, e.g., one or more gRNA molecules comprising a targeting domain described in Table 1, 2, 3, 4, 5, 6, 7, 8, or 9, and one or more cas9 molecules described herein, or the progeny of said cells. In one embodiment, the cells are allogeneic to the mammal. In one

embodiment, the cells are autologous to the mammal. In one embodiment the cells are harvested from the mammal, manipulated ex vivo, and returned to the mammal.

In aspects, the cells comprising or which at one time comprised one or more gRNA molecules, e.g., one or more gRNA molecules comprising a targeting domain described in Table 1, 2, 3, 4, 5, 6, 7, 8, or 9, and one or more cas9 molecules described herein, or the progeny of said cells, comprise stem cells or progenitor cells. In one aspect, the stem cells are hematopoietic stem cells. In one aspect, the progenitor cells are hematopoietic progenitor cells. In one aspect, the cells comprise both hematopoietic stem cells and hematopoietic progenitor cells, e.g., are HSPCs. In one aspect, the cells comprise, e.g., consist of, CD34+ cells. In one aspect the cells are substantially free of CD34- cells. In one aspect, the cells comprise, e.g., consist of, CD34+/CD90+ stem cells. In one aspect, the cells comprise, e.g., consist of, CD34+/CD90- cells. In an aspect, the cells are a population comprising one or more of the cell types described above or described herein.

In one embodiment, the disclosure provides a method for treating a hemoglobinopathy, e.g., sickle cell disease or beta-thalassemia, or a method for increasing fetal hemoglobin expression in a mammal, e.g., a human, in need thereof, the method comprising:

a) providing, e.g., harvesting or isolating, a population of HSPCs (e.g., CD34+ cells) from a mammal;

b) providing said cells ex vivo, e.g., in a cell culture medium, optionally in the presence of an effective amount of a composition comprising at least one stem cell expander, whereby said population of HSPCs (e.g., CD34+ cells) expands to a greater degree than an untreated population;

c) contacting the population of HSPCs (e.g., CD34+ cells) with an effective amount of: a composition comprising at least one gRNA molecule comprising a targeting domain described herein, e.g., a targeting domain described in Tables 1, 2, 3, 4, 5, 6, 7, 8, or 9, or a nucleic acid encoding said gRNA molecule, and at least one cas9 molecule, e.g., described herein, or a nucleic acid encoding said cas9 molecule, e.g., one or more RNPs as described herein, e.g., with a CRISPR system described herein;

d) causing at least one modification in at least a portion of the cells of the population (e.g., at least a portion of the HSPCs, e.g., CD34+ cells, of the population), whereby, e.g., when said HSPCs are differentiated into cells of an erythroid lineage, e.g., red blood cells, fetal hemoglobin expression is increased, e.g., relative to cells not contacted according to step c); and

f) returning a population of cells comprising said modified HSPCs (e.g., CD34+ cells) to the mammal.

In an aspect, the HSPCs are allogeneic to the mammal to which they are returned. In an aspect, the HSPCs are autologous to the mammal to which they are returned. In aspects, the HSPCs are isolated from bone marrow. In aspects, the HSPCs are isolated from peripheral blood, e.g., mobilized peripheral blood. In aspects, the moblized peripheral blood is isolated from a subject who has been

administered a G-CSF. In aspects, the moblized peripheral blood is isolated from a subject who has been administered a moblization agent other than G-CSF, for example, Plerixafor® (AMD3100). In aspects, the HSPCs are isolated from umbilical cord blood.

In further embodiments of the method, the method furhter comprises, after providing a population of HSPCs (e.g., CD34+ cells), e.g., from a source described above, the step of enriching the population of cells for HSPCs (e.g., CD34+ cells). In embodiments of the method, after said enriching, the population of cells, e.g., HSPCs, is substantially free of CD34- cells.

In embodiments, the population of cells which is returned to the mammal includes at least 70% viable cells. In embodiments, the population of cells which is returned to the mammal includes at least 75% viable cells. In embodiments, the population of cells which is returned to the mammal includes at least 80% viable cells. In embodiments, the population of cells which is returned to the mammal includes at least 85% viable cells. In embodiments, the population of cells which is returned to the mammal includes at least 90% viable cells. In embodiments, the population of cells which is returned to the mammal includes at least 95% viable cells. In embodiments, the population of cells which is returned to the mammal includes at least 99% viable cells. Viability can be determined by staining a representative portion of the population of cells for a cell viability marker, e.g., as known in the art.

In another embodiment, the disclosure provides a method for treating a hemoglobinopathy, e.g., sickle cell disease or beta-thalassemia, or a method for increasing fetal hemoglobin expression in a mammal, e.g., a human, in need thereof, the method comprising the steps of:

a) providing, e.g., harvesting or isolating, a population of HSPCs (e.g., CD34+ cells) of a mammal, e.g., from the bone marrow of a mammal;

b) isolating the CD34+ cells from the population of cells of step a);

c) providing said CD34+ cells ex vivo, and culturing said cells, e.g., in a cell culture medium, in the presence of an effective amount of a composition comprising at least one stem cell expander, e.g., Compound 4, e.g., Compound 4 at a concentration of about 0.5 to about 0.75 micromolar, whereby said population of CD34+ cells expands to a greater degree than an untreated population;

d) introducing into the cells of the population CD34+ cells an effective amount of: a composition comprising a Cas9 molecule, e.g., as described herein, and a gRNA molecule, e.g., as described herein, e.g., optionally where the Cas9 molecule and the gRNA molecule are in the form of an RNP, e.g., as dsecribed herein, and optionally where said introduction is by electroporation, e.g., as desecribed herein, of said RNP into said cells;

e) causing at least one genetic modification in at least a portion of the cells of the population (e.g., at least a portion of the HSPCs, e.g., CD34+ cells, of the population), whereby an indel, e.g., as

described herein, is created at or near the genomic site complementary to the targeting domain of the gRNA introduced in step d);

f) optionally, additionallly culturing said cells after said introducing, e.g., in a cell culture medium, in the presence of an effective amount of a composition comprising at least one stem cell expander, e.g., Compound 4, e.g., Compound 4 at a concentration of about 0.5 to about 0.75 micromolar, such that the cells expand at least 2-fold, e.g., at least 4-fold, e.g., at least 5-fold;

g) cryopreserving said cells; and

h) returning the cells to the mammal, wherein,

the cells returned to the mammal comprise cells that 1) maintain the abilitiy to differentiate into cells of the erythroid lineage, e.g., red blood cells; 2) when differentiated into red blood cells, produce an increased level of fetal hemoglobin, e.g., relative to cells unmodified by the gRNA of step e), e.g., produce at least 6 picograms fetal hemoglobin per cell.

In an aspect, the HSPCs are allogeneic to the mammal to which they are returned. In an aspect, the HSPCs are autologous to the mammal to which they are returned. In aspects, the HSPCs are isolated from bone marrow. In aspects, the HSPCs are isolated from peripheral blood, e.g., mobilized peripheral blood. In aspects, the moblized peripheral blood is isolated from a subject who has been administered a G-CSF. In aspects, the moblized peripheral blood is isolated from a subject who has been administered a moblization agent other than G-CSF, for example, Plerixafor® (AMD3100). In aspects, the HSPCs are isolated from umbilical cord blood.

In embodiments of the method above, the recited step b) results in a population of cells which is substantially free of CD34- cells.

In further embodiments of the method, the method furhter comprises, after providing a population of HSPCs (e.g., CD34+ cells), e.g., from a source described above, the population of cells is enriched for HSPCs (e.g., CD34+ cells).

In a further embodiments of these methods, the population of modified HSPCs (e.g., CD34+ stem cells) having the ability to differentiate increased fetal hemoglobin expression is cryopreserved and stored prior to being reintroduced into the mammal. In embodiments, the cryopreserved population of HSPCs having the ability to differentiate into cells of the erythroid lineage, e.g., red blood cells, and/or when differentiated into cells of the erythroid lineage, e.g., red blood cells, produce an increased level of fetal hemoglobin is thawed and then reintroduced into the mammal. In a further embodiment of these methods, the method comprises chemotherapy and/or radiation therapy to remove or reduce the endogenous hematopoietic progenitor or stem cells in the mammal. In a further embodiment of these methods, the method does not comprise a step of chemotherapy and/or radiation

therapy to remove or reduce the endogenous hematopoietic progenitor or stem cells in the mammal. In a further embodiment of these methods, the method comprises a chemotherapy and/or radiation therapy to reduce partially (e.g., partial lymphodepletion) the endogenous hematopoietic progenitor or stem cells in the mammal. In embodiments the patient is treated with a fully lymphodepleting dose of busulfan prior to reintroduction of the modifiedHSPCs to the mammal. In embodiments, the patient is treated with a partially lymphodepleting dose of busulfan prior to reintroduction of the modified HSPCs to the mammal.

In embodiments, the cells are contacted with RNP comprising a Cas9 molecule, e.g., as described herein, complexed with a gRNA to the +58 BCL11a enhancer region. In embodiments, the gRNA comprises the targeting domain of CR000312. In embodiments, the gRNA comprises the targeting domain of CR000311. In embodiments, the gRNA comprises the targeting domain of CR001128. In embodiments, the gRNA comprises the targeting domain of CR001125. In embodiments, the gRNA comprises the targeting domain of CR001126. In embodiments, the gRNA comprises the targeting domain of CR001127. In embodiments the gRNA is a dual guide RNA comprising a crRNA comprising, e.g., consisting of, [SEQ ID NO: 248]-[SEQ ID NO: 6607], and a tracr comprising, e.g., consisting of, [SEQ ID NO: 7812], optionally with 1, 2, 3, 4, 5, 6, or 7 additional 3' uracil nucleotides, e.g., SEQ ID NO: 6660. In embodiments, the gRNA is a sgRNA comprising, e.g., consisting of, [SEQ ID NO: 248]-[SEQ ID NO: 6601, optionally with 1, 2, 3, 4, 5, 6, or 7 additional 3' uracil nucleotides, e.g., [SEQ ID NO: 248]-[SEQ ID NO: 7811]. In embodiments the gRNA is a dual guide RNA comprising a crRNA comprising, e.g., consisting of, [SEQ ID NO: 247]-[SEQ ID NO: 6607], and a tracr comprising, e.g., consisting of, SEQ ID NO: 7812, optionally with 1, 2, 3, 4, 5, 6, or 7 additional 3' uracil nucleotides, e.g., SEQ ID NO: 6660. In embodiments, the gRNA is a sgRNA comprising, e.g., consisting of, [SEQ ID NO: 247]-[SEQ ID NO: 6601, optionally with 1, 2, 3, 4, 5, 6, or 7 additional 3' uracil nucleotides, e.g., [SEQ ID NO: 247]-[SEQ ID NO: 7811]. In embodiments the gRNA is a dual guide RNA comprising a crRNA comprising, e.g., consisting of, [SEQ ID NO: 338]-[SEQ ID NO: 6607], and a tracr comprising, e.g., consisting of, SEQ ID NO: 7812, optionally with 1, 2, 3, 4, 5, 6, or 7 additional 3' uracil nucleotides, e.g., SEQ ID NO: 6660. In embodiments, the gRNA is a sgRNA comprising, e.g., consisting of, [SEQ ID NO: 338]-[SEQ ID NO: 6601], optionally with 1, 2, 3, 4, 5, 6, or 7 additional 3' uracil nucleotides, e.g., [SEQ ID NO: 338]-[SEQ ID NO: 7811]. In embodiments the gRNA is a dual guide RNA comprising a crRNA comprising, e.g., consisting of, [SEQ ID NO: 335]-[SEQ ID NO: 6607], and a tracr comprising, e.g., consisting of, SEQ ID NO: 7812, optionally with 1, 2, 3, 4, 5, 6, or 7 additional 3' uracil nucleotides, e.g., SEQ ID NO: 6660. In embodiments, the gRNA is a sgRNA comprising, e.g., consisting of, [SEQ ID NO: 335]-[SEQ ID NO: 6601], optionally with 1, 2, 3, 4, 5, 6, or 7 additional 3' uracil nucleotides, e.g., [SEQ ID NO: 335]-[SEQ ID NO: 7811]. In embodiments the gRNA is a dual guide RNA comprising a crRNA comprising, e.g., consisting of, [SEQ ID NO: 336]-[SEQ ID NO: 6607],

and a tracr comprising, e.g., consisting of, SEQ ID NO: 7812, optionally with 1, 2, 3, 4, 5, 6, or 7 additional 3' uracil nucleotides, e.g., SEQ ID NO: 6660. In embodiments, the gRNA is a sgRNA comprising, e.g., consisting of, [SEQ ID NO: 336]-[SEQ ID NO: 6601], optionally with 1, 2, 3, 4, 5, 6, or 7 additional 3' uracil nucleotides, e.g., [SEQ ID NO: 336]-[SEQ ID NO: 7811]. In embodiments the gRNA is a dual guide RNA comprising a crRNA comprising, e.g., consisting of, [SEQ ID NO: 337]-[SEQ ID NO: 6607], and a tracr comprising, e.g., consisting of, SEQ ID NO: 7812, optionally with 1, 2, 3, 4, 5, 6, or 7 additional 3' uracil nucleotides, e.g., SEQ ID NO: 6660. In embodiments, the gRNA is a sgRNA comprising, e.g., consisting of, [SEQ ID NO: 337]-[SEQ ID NO: 6601], optionally with 1, 2, 3, 4, 5, 6, or 7 additional 3' uracil nucleotides, e.g., [SEQ ID NO: 337]-[SEQ ID NO: 7811]. In any of the aforementioned embodiments, any or all of the RNA componments of the gRNA may be modified at one or more nucleotides, e.g., as described herein. In embodiments, the gRNA molecule is SEQ ID NO: 342. In embodiments, the gRNA molecule is SEQ ID NO: 343. In embodiments, the gRNA molecule is SEQ ID NO: 1762. In embodiments the gRNA molecule is a dgRNA molecule that consists of SEQ ID NO: 344 and SEQ ID NO: 6660. In embodiments the gRNA molecule is a dgRNA molecule that consists of SEQ ID NO: 344 and SEQ ID NO: 346. In embodiments the gRNA molecule is a dgRNA molecule that consists of SEQ ID NO: 345 and SEQ ID NO: 6660. In embodiments the gRNA molecule is a dgRNA molecule that consists of SEQ ID NO: 345 and SEQ ID NO: 346. In embodiments, the gRNA molecule is SEQ ID NO: 347. In embodiments, the gRNA molecule is SEQ ID NO: 348. In embodiments, the gRNA molecule is SEQ ID NO: 1763. In embodiments the gRNA molecule is a dgRNA molecule that consists of SEQ ID NO: 349 and SEQ ID NO: 6660. In embodiments the gRNA molecule is a dgRNA molecule that consists of SEQ ID NO: 349 and SEQ ID NO: 346. In embodiments the gRNA molecule is a dgRNA molecule that consists of SEQ ID NO: 350 and SEQ ID NO: 6660. In embodiments the gRNA molecule is a dgRNA molecule that consists of SEQ ID NO: 350 and SEQ ID NO: 346. In embodiments, the gRNA molecule is SEQ ID NO: 351. In embodiments, the gRNA molecule is SEQ ID NO: 352. In embodiments, the gRNA molecule is SEQ ID NO: 1764. In embodiments the gRNA molecule is a dgRNA molecule that consists of SEQ ID NO: 353 and SEQ ID NO: 6660. In embodiments the gRNA molecule is a dgRNA molecule that consists of SEQ ID NO: 353 and SEQ ID NO: 346. In embodiments the gRNA molecule is a dgRNA molecule that consists of SEQ ID NO: 354 and SEQ ID NO: 6660. In embodiments the gRNA molecule is a dgRNA molecule that consists of SEQ ID NO: 354 and SEQ ID NO: 346. In embodiments, the gRNA molecule is SEQ ID NO: 355. In embodiments, the gRNA molecule is SEQ ID NO: 356. In embodiments, the gRNA molecule is SEQ ID NO: 1765. In embodiments the gRNA molecule is a dgRNA molecule that consists of SEQ ID NO: 357 and SEQ ID NO: 6660. In embodiments the gRNA molecule is a dgRNA molecule that consists of SEQ ID NO: 357 and SEQ ID NO: 346. In embodiments the gRNA molecule is a dgRNA molecule that consists of SEQ ID NO: 358 and SEQ ID NO: 6660. In embodiments the gRNA molecule is a dgRNA molecule that consists of SEQ ID NO: 358 and SEQ ID NO: 346. In

embodiments, the gRNA molecule is SEQ ID NO: 359. In embodiments, the gRNA molecule is SEQ ID NO: 360. In embodiments, the gRNA molecule is SEQ ID NO: 1766. In embodiments the gRNA molecule is a dgRNA molecule that consists of SEQ ID NO: 361 and SEQ ID NO: 6660. In embodiments the gRNA molecule is a dgRNA molecule that consists of SEQ ID NO: 361 and SEQ ID NO: 346. In embodiments the gRNA molecule is a dgRNA molecule that consists of SEQ ID NO: 362 and SEQ ID NO: 6660. In embodiments the gRNA molecule is a dgRNA molecule that consists of SEQ ID NO: 362 and SEQ ID NO: 346. In embodiments, the gRNA molecule is SEQ ID NO: 363. In embodiments, the gRNA molecule is SEQ ID NO: 364. In embodiments, the gRNA molecule is SEQ ID NO: 1767. In embodiments the gRNA molecule is a dgRNA molecule that consists of SEQ ID NO: 365 and SEQ ID NO: 6660. In embodiments the gRNA molecule is a dgRNA molecule that consists of SEQ ID NO: 365 and SEQ ID NO: 346. In embodiments the gRNA molecule is a dgRNA molecule that consists of SEQ ID NO: 366 and SEQ ID NO: 6660. In embodiments the gRNA molecule is a dgRNA molecule that consists of SEQ ID NO: 366 and SEQ ID NO: 346. In embodiments, the gRNA molecule is SEQ ID NO: 367. In embodiments, the gRNA molecule is SEQ ID NO: 368. In embodiments, the gRNA molecule is SEQ ID NO: 1768. In embodiments the gRNA molecule is a dgRNA molecule that consists of SEQ ID NO: 369 and SEQ ID NO: 6660. In embodiments the gRNA molecule is a dgRNA molecule that consists of SEQ ID NO: 369 and SEQ ID NO: 346. In embodiments the gRNA molecule is a dgRNA molecule that consists of SEQ ID NO: 370 and SEQ ID NO: 6660. In embodiments the gRNA molecule is a dgRNA molecule that consists of SEQ ID NO: 370 and SEQ ID NO: 346. In embodiments, the gRNA molecule is SEQ ID NO: 371. In embodiments, the gRNA molecule is SEQ ID NO: 372. In embodiments, the gRNA molecule is SEQ ID NO: 1769. In embodiments the gRNA molecule is a dgRNA molecule that consists of SEQ ID NO: 373 and SEQ ID NO: 6660. In embodiments the gRNA molecule is a dgRNA molecule that consists of SEQ ID NO: 373 and SEQ ID NO: 346. In embodiments the gRNA molecule is a dgRNA molecule that consists of SEQ ID NO: 374 and SEQ ID NO: 6660. In embodiments the gRNA molecule is a dgRNA molecule that consists of SEQ ID NO: 374 and SEQ ID NO: 346.

In embodiments, the cells are contacted with RNP comprising a Cas9 molecule, e.g., as described herein, complexed with a gRNA to the HPFH region. In embodiments, the gRNA comprises the targeting domain of CR001030. In embodiments, the gRNA comprises the targeting domain of CR001028. In embodiments, the gRNA comprises the targeting domain of CR001221. In embodiments, the gRNA comprises the targeting domain of CR001137. In embodiments, the gRNA comprises the targeting domain of CR003035. In embodiments, the gRNA comprises the targeting domain of CR003085. In embodiments the gRNA is a dual guide RNA comprising a crRNA comprising, e.g., consisting of, [SEQ ID NO: 98]-[SEQ ID NO: 6607], and a tracr comprising, e.g., consisting of, SEQ ID NO: 7812, optionally with 1, 2, 3, 4, 5, 6, or 7 additional 3' uracil nucleotides, e.g., SEQ ID NO: 6660. In embodiments, the gRNA is a sgRNA comprising, e.g., consisting of,

[SEQ ID NO: 98]-[SEQ ID NO: 6601], optionally with 1, 2, 3, 4, 5, 6, or 7 additional 3' uracil nucleotides, e.g., [SEQ ID NO: 98]-[SEQ ID NO: 7811]. In embodiments the gRNA is a dual guide RNA comprising a crRNA comprising, e.g., consisting of, [SEQ ID NO: 100]-[SEQ ID NO: 6607], and a tracr comprising, e.g., consisting of, SEQ ID NO: 7812, optionally with 1, 2, 3, 4, 5, 6, or 7 additional 3' uracil nucleotides, e.g., SEQ ID NO: 6660. In embodiments, the gRNA is a sgRNA comprising, e.g., consisting of, [SEQ ID NO: 100]-[SEQ ID NO: 6601], optionally with 1, 2, 3, 4, 5, 6, or 7 additional 3' uracil nucleotides, e.g., [SEQ ID NO: 100]-[SEQ ID NO: 7811]. In embodiments the gRNA is a dual guide RNA comprising a crRNA comprising, e.g., consisting of, [SEQ ID NO: 1589]-[SEQ ID NO: 6607], and a tracr comprising, e.g., consisting of, SEQ ID NO: 7812, optionally with 1, 2, 3, 4, 5, 6, or 7 additional 3' uracil nucleotides, e.g., SEQ ID NO: 6660. In embodiments, the gRNA is a sgRNA comprising, e.g., consisting of, [SEQ ID NO: 1589]-[SEQ ID NO: 6601], optionally with 1, 2, 3, 4, 5, 6, or 7 additional 3' uracil nucleotides, e.g., [SEQ ID NO: 1589]-[SEQ ID NO: 7811]. In embodiments the gRNA is a dual guide RNA comprising a crRNA comprising, e.g., consisting of, [SEQ ID NO: 1505]-[SEQ ID NO: 6607], and a tracr comprising, e.g., consisting of, SEQ ID NO: 7812, optionally with 1, 2, 3, 4, 5, 6, or 7 additional 3' uracil nucleotides, e.g., SEQ ID NO: 6660. In embodiments, the gRNA is a sgRNA comprising, e.g., consisting of, [SEQ ID NO: 1505]-[SEQ ID NO: 6601], optionally with 1, 2, 3, 4, 5, 6, or 7 additional 3' uracil nucleotides, e.g., [SEQ ID NO: 1505]-[SEQ ID NO: 7811]. In embodiments the gRNA is a dual guide RNA comprising a crRNA comprising, e.g., consisting of, [SEQ ID NO: 1700]-[SEQ ID NO: 6607], and a tracr comprising, e.g., consisting of, SEQ ID NO: 7812, optionally with 1, 2, 3, 4, 5, 6, or 7 additional 3' uracil nucleotides, e.g., SEQ ID NO: 6660. In embodiments, the gRNA is a sgRNA comprising, e.g., consisting of, [SEQ ID NO: 1700]-[SEQ ID NO: 6601], optionally with 1, 2, 3, 4, 5, 6, or 7 additional 3' uracil nucleotides, e.g., [SEQ ID NO: 1700]-[SEQ ID NO: 7811]. In embodiments the gRNA is a dual guide RNA comprising a crRNA comprising, e.g., consisting of, [SEQ ID NO: 1750]-[SEQ ID NO: 6607], and a tracr comprising, e.g., consisting of, SEQ ID NO: 7812, optionally with 1, 2, 3, 4, 5, 6, or 7 additional 3' uracil nucleotides, e.g., SEQ ID NO: 6660. In embodiments, the gRNA is a sgRNA comprising, e.g., consisting of, [SEQ ID NO: 1750]-[SEQ ID NO: 6601], optionally with 1, 2, 3, 4, 5, 6, or 7 additional 3' uracil nucleotides, e.g., [SEQ ID NO: 1750]-[SEQ ID NO: 7811]. In embodiments, the gRNA molecule is SEQ ID NO: 375. In embodiments, the gRNA molecule is SEQ ID NO: 376. In embodiments, the gRNA molecule is SEQ ID NO: 1770. In embodiments the gRNA molecule is a dgRNA molecule that consists of SEQ ID NO: 377 and SEQ ID NO: 6660. In embodiments the gRNA molecule is a dgRNA molecule that consists of SEQ ID NO: 377 and SEQ ID NO: 346. In embodiments the gRNA molecule is a dgRNA molecule that consists of SEQ ID NO: 378 and SEQ ID NO: 6660. In embodiments the gRNA molecule is a dgRNA molecule that consists of SEQ ID NO: 378 and SEQ ID NO: 346. In embodiments, the gRNA molecule is SEQ ID NO: 379. In embodiments, the gRNA molecule is SEQ ID NO: 380. In embodiments, the gRNA molecule is SEQ ID NO: 1771. In embodiments the gRNA molecule is a dgRNA molecule that consists of SEQ

ID NO: 381 and SEQ ID NO: 6660. In embodiments the gRNA molecule is a dgRNA molecule that consists of SEQ ID NO: 381 and SEQ ID NO: 346. In embodiments the gRNA molecule is a dgRNA molecule that consists of SEQ ID NO: 382 and SEQ ID NO: 6660. In embodiments the gRNA molecule is a dgRNA molecule that consists of SEQ ID NO: 382 and SEQ ID NO: 346. In embodiments, the gRNA molecule is SEQ ID NO: 383. In embodiments, the gRNA molecule is SEQ ID NO: 384. In embodiments, the gRNA molecule is SEQ ID NO: 1772. In embodiments the gRNA molecule is a dgRNA molecule that consists of SEQ ID NO: 385 and SEQ ID NO: 6660. In embodiments the gRNA molecule is a dgRNA molecule that consists of SEQ ID NO: 385 and SEQ ID NO: 346. In embodiments the gRNA molecule is a dgRNA molecule that consists of SEQ ID NO: 386 and SEQ ID NO: 6660. In embodiments the gRNA molecule is a dgRNA molecule that consists of SEQ ID NO: 386 and SEQ ID NO: 346. In embodiments, the gRNA molecule is SEQ ID NO: 387. In embodiments, the gRNA molecule is SEQ ID NO: 388. In embodiments, the gRNA molecule is SEQ ID NO: 1773. In embodiments the gRNA molecule is a dgRNA molecule that consists of SEQ ID NO: 389 and SEQ ID NO: 6660. In embodiments the gRNA molecule is a dgRNA molecule that consists of SEQ ID NO: 389 and SEQ ID NO: 346. In embodiments the gRNA molecule is a dgRNA molecule that consists of SEQ ID NO: 390 and SEQ ID NO: 6660. In embodiments the gRNA molecule is a dgRNA molecule that consists of SEQ ID NO: 390 and SEQ ID NO: 346. In embodiments, the gRNA molecule is SEQ ID NO: 391. In embodiments, the gRNA molecule is SEQ ID NO: 392. In embodiments, the gRNA molecule is SEQ ID NO: 1774. In embodiments the gRNA molecule is a dgRNA molecule that consists of SEQ ID NO: 393 and SEQ ID NO: 6660. In embodiments the gRNA molecule is a dgRNA molecule that consists of SEQ ID NO: 393 and SEQ ID NO: 346. In embodiments the gRNA molecule is a dgRNA molecule that consists of SEQ ID NO: 394 and SEQ ID NO: 6660. In embodiments the gRNA molecule is a dgRNA molecule that consists of SEQ ID NO: 394 and SEQ ID NO: 346. In embodiments, the gRNA molecule is SEQ ID NO: 395. In embodiments, the gRNA molecule is SEQ ID NO: 396. In embodiments, the gRNA molecule is SEQ ID NO: 1775. In embodiments the gRNA molecule is a dgRNA molecule that consists of SEQ ID NO: 397 and SEQ ID NO: 6660. In embodiments the gRNA molecule is a dgRNA molecule that consists of SEQ ID NO: 397 and SEQ ID NO: 346. In embodiments the gRNA molecule is a dgRNA molecule that consists of SEQ ID NO: 398 and SEQ ID NO: 6660. In embodiments the gRNA molecule is a dgRNA molecule that consists of SEQ ID NO: 398 and SEQ ID NO: 346.

In embodiments, the stem cell expander is Compound 1. In embodiments, the stem cell expander is Compound 2. In embodiments, the stem cell expander is Compound 3. In embodiments, the stem cell expander is Compound 4. In embodiments, the stem cell expander is Compound 4 and is present at a concentration of 2-0.1 micromolar, e.g., 1-0.25 micromolar, e.g., 0.75-0.5 micromolar. In embodiments, the stem cell expander is a molecule described in WO2010/059401 (e.g., the molecule described in Example 1 of WO2010/059401).

In embodiments, the cells, e.g., HSPCs, e.g., as described herein, are cultured ex vivo for a period of about 1 hour to about 15 days, e.g., a period of about 12 hours to about 12 days, e.g., a period of about 12 hours to 4 days, e.g., a period of about 1 day to about 4 days, e.g., a period of about 1 day to about 2 days, e.g., a period of about 1 day or a period of about 2 days, prior to the step of contacting the cells with a CRISPR system, e.g., described herein. In embodiments, said culturing prior to said contacting step is in a composition (e.g., a cell culture medium) comprising a stem cell expander, e.g., described herein, e.g., compound 4, e.g., compound 4 at a concentration of about 0.25 uM to about 1 uM, e.g., compound 4 at a concentration of about 0.75-0.5 micromolar. In embodiments, the cells are cultured ex vivo for a period of no more than about about 1 day, e.g., no more than about 18, 17, 16, 15, 14, 13, 12, 11, 10, 9, 8, 7, 6, 5, 4, 3, 2, or 1 hour(s) after the step of contacting the cells with a CRISPR system, e.g., described herein, e.g., in a cell culture medium which comprises a stem cell expander, e.g., described herein, e.g., compound 4, e.g., compound 4 at a concentration of about 0.25 uM to about 1 uM, e.g., compound 4 at a concentration of about 0.75-0.5 micromolar. In other embodiments, the cells are cultured ex vivo for a period of about 1 hour to about 15 days, e.g., a period of about 12 hours to about 10 days, e.g., a period of about 1 day to about 10 days, e.g., a period of about 1 day to about 5 days, e.g., a period of about 1 day to about 4 days, e.g., a period of about 2 days to about 4 days, e.g., a period of about 2 days, about 3 days or about 4 days, after the step of contacting the cells with a CRISPR system, e.g., described herein, in a cell culture medium, e.g., which comprises a stem cell expander, e.g., described herein, e.g., compound 4, e.g., compound 4 at a concentration of about 0.25 uM to about 1 uM, e.g., compound 4 at a concentration of about 0.75-0.5 micromolar. In embodiments, the cells are cultured ex vivo (e.g., cultured prior to said contacting step and/or cultured after said contacting step) for a period of about 1 hour to about 20 days, e.g., a period of about 6-12 days, e.g., a period of about 6, about 7, about 8, about 9, about 10, about 11, or about 12 days.

In embodiments, the population of cells comprising the modified HSPCs returned to the mammal comprises at least about 1 million cells (e.g., at least about 1 million CD34+ cells) per kg. In embodiments, the population of cells comprising the modified HSPCs returned to the mammal comprises at least about 2 million cells (e.g., at least about 2 million CD34+ cells) per kg. In embodiments, the population of cells comprising the modified HSPCs returned to the mammal comprises at least about 3 million cells (e.g., at least about 3 million CD34+ cells) per kg. In embodiments, the population of cells comprising the modified HSPCs returned to the mammal comprises at least about 4 million cells (e.g., at least about 4 million CD34+ cells) per kg. In embodiments, the population of cells comprising the modified HSPCs returned to the mammal comprises at least about 5 million cells (e.g., at least about 5 million CD34+ cells) per kg. In embodiments, the population of cells comprising the modified HSPCs returned to the mammal comprises at least about 6 million cells (e.g., at least about 6 million CD34+ cells) per kg. In

embodiments, the population of cells comprising the modified HSPCs returned to the mammal comprises at least 1 million cells (e.g., at least 1 million CD34+ cells) per kg. In embodiments, the population of cells comprising the modified HSPCs returned to the mammal comprises at least 2 million cells (e.g., at least 2 million CD34+ cells) per kg. In embodiments, the population of cells comprising the modified HSPCs returned to the mammal comprises at least 3 million cells (e.g., at least 3 million CD34+ cells) per kg. In embodiments, the population of cells comprising the modified HSPCs returned to the mammal comprises at least 4 million cells (e.g., at least 4 million CD34+ cells) per kg. In embodiments, the population of cells comprising the modified HSPCs returned to the mammal comprises at least 5 million cells (e.g., at least 5 million CD34+ cells) per kg. In embodiments, the population of cells comprising the modified HSPCs returned to the mammal comprises at least 6 million cells (e.g., at least 6 million CD34+ cells) per kg. In embodiments, the population of cells comprising the modified HSPCs returned to the mammal comprises about 1 million cells (e.g., about 1 million CD34+ cells) per kg. In embodiments, the population of cells comprising the modified HSPCs returned to the mammal comprises about 2 million cells (e.g., about 2 million CD34+ cells) per kg. In embodiments, the population of cells comprising the modified HSPCs returned to the mammal comprises about 3 million cells (e.g., about 3 million CD34+ cells) per kg. In embodiments, the population of cells comprising the modified HSPCs returned to the mammal comprises about 4 million cells (e.g., about 4 million CD34+ cells) per kg. In embodiments, the population of cells comprising the modified HSPCs returned to the mammal comprises about 5 million cells (e.g., about 5 million CD34+ cells) per kg. In embodiments, the population of cells comprising the modified HSPCs returned to the mammal comprises about 6 million cells (e.g., about 6 million CD34+ cells) per kg. In embodiments, the population of cells comprising the modified HSPCs returned to the mammal comprises about 2×10^6 cells per kg body weight of the patient. In embodiments, the population of cells comprising the modified HSPCs returned to the mammal comprises at least 2×10^6 cells per kg body weight of the patient.

In embodiments, any of the methods described above results in the patient having at least 80% of its circulating CD34+ cells comprising an indel at or near the genomic site complementary to the targeting domain of the gRNA molecule used in the method, e.g., as measured at least 15 days, e.g., at least 20, at least 30, at least 40 at least 50 or at least 60 days after reintroduction of the cells into the mammal.

In embodiments, any of the methods described above results in the patient having at least 20% of its bone marrow CD34+ cells comprising an indel at or near the genomic site complementary to the targeting domain of the gRNA molecule used in the method, e.g., as measured at least 15 days, e.g., at least 20, at least 30, at least 40 at least 50 or at least 60 days after reintroduction of the cells into the mammal.

In embodiments, the HSPCs that are reintroduced into the mammal are able to differentiate in vivo into cells of the erythroid lineage, e.g., red blood cells, and said differentiated cells exhibit increased fetal hemoglobin levels, e.g., produce at least 6 picograms fetal hemoglobin per cell, e.g., at least 7 picograms fetal hemoglobin per cell, at least 8 picograms fetal hemoglobin per cell, at least 9 picograms fetal hemoglobin per cell, at least 10 picograms fetal hemoglobin per cell, e.g., between about 9 and about 10 picograms fetal hemoglobin per cell, e.g., such that the hemoglobinopathy is treated the mammal.

It will be understood that when a cell is characterized as having increased fetal hemoglobin, that includes embodiments in which a progeny, e.g., a differentiated progeny, of that cell exhibits increased fetal hemoglobin. For example, in the methods described herein, the altered or modified CD34+ cell (or cell population) may not express increased fetal hemoglobin, but when differentiated into cells of erythroid lineage, e.g., red blood cells, the cells express increased fetal hemoglobin, e.g., increased fetal hemoglobin relative to an unmodified or unaltered cell under similar conditions.

XII. Culture Methods and Methods of Manufacturing Cells

The disclosure provides methods of culturing cells, e.g., HSPCs, e.g., hematopoietic stem cells, e.g., CD34+ cells modified, or to be modified, with the gRNA molecules described herein.

DNA Repair Pathway Inhibitors

Without being bound by theory, it is believed that the pattern of indels produced by a given gRNA molecule at a particular target sequence is a product of each of the active DNA repair mechamisms within the cell (e.g., non-homologous end joining, microhomology-mediated end joining, etc.). Wihtout being bound by theory, it is believed that a particularlyfavorable indel may be selected for or enriched for by contacting the cells to be edited with an inhibitor of a DNA repair pathway that does not produce the desired indel. Thus, the gRNA molecules, CRISPR systems, methods and other aspects of the invention may be perfomred in combination with such inhibitors. Examples of such inhibitors include those described in, e.g., WO2014/130955, the contents of which are hereby incorproated by reference in their entirety. In embodiment, the inhibitor is a DNAPKc inhibitor, e.g., NU7441.

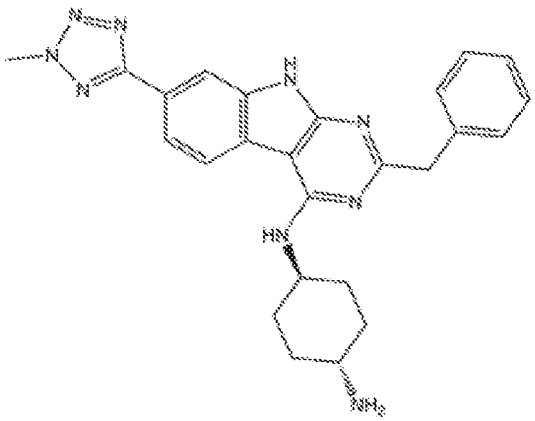
Stem Cell Expanders

In one aspect the invention relates to culturing the cells, e.g., HSPCs, e.g., CD34+ cells modified, or to be modified, with the gRNA molecules described herein, with one or more agents that result in an increased expansion rate, increased expansion level, or increased engraftment relative to cells not treated with the agent. Such agents are referred to herein as stem cell expanders.

In an aspect, the one or more agents that result in an increased expansion rate or increased expansion level, relative to cells not treated with the agent, e.g., the stem cell expander, comprises an agent that is an inhibitor of the aryl hydrocarbon receptor (AHR) pathway. In aspects, the stem cell expander is a compound disclosed in WO2013/110198 or a compound disclosed in WO2010/059401, the contents of which are incorporated by reference in their entirety.

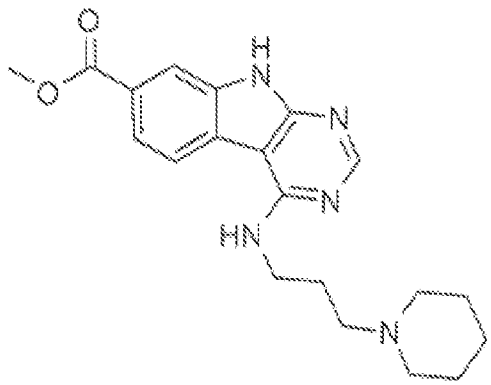
In one aspect, the one or more agents that result in an increased expansion rate or increased expansion level, relative to cells not treated with the agent, is a pyrimido[4,5-b]indole derivative, e.g., as disclosed in WO2013/110198, the contents of which are hereby incorporated by reference in their entirety. In one embodiment the agent is compound 1 ((1r,4r)-N^1-(2-benzyl-7-(2-methyl-2H-tetrazol-5-yl)-9H-pyrimido[4,5-b]indol-4-yl)cyclohexane-1,4-diamine):

Compound 1



In another aspect, the agent is Compound 2 (methyl 4-(3-piperidin-1-ylpropylamino)-9H-pyrimido[4,5-b]indole-7-carboxylate):

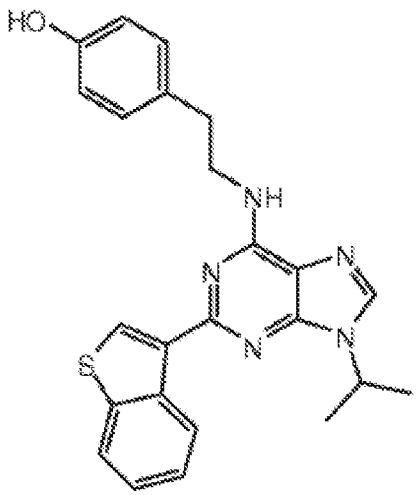
Compound 2:



In another aspect, the one or more agents that result in an increased expansion rate or increased expansion level, relative to cells not treated with the agent, is an agent disclosed in WO2010/059401, the contents of which are hereby incorporated by reference in their entirety.

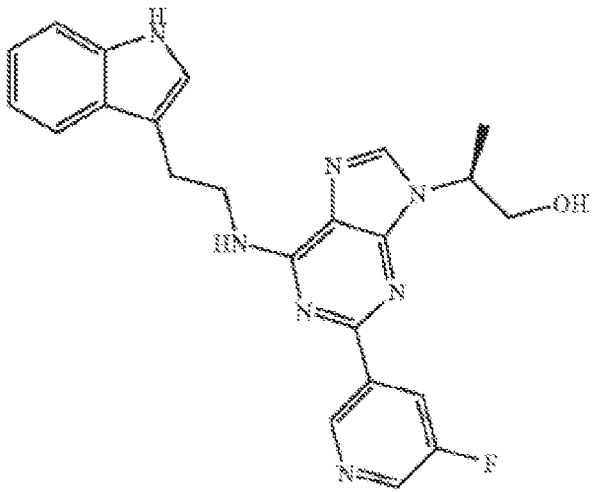
In one embodiment, the stem cell expander is 4-(2-(2-(benzo[b]thiophen-3-yl)-9-isopropyl-9H-purin-6-ylamino)ethyl)phenol, i.e., is the compound from example 1 of WO2010/059401, having the following structure:

Compound 3:



In another aspect, the stem cell expander is compound 4 ((S)-2-(6-(2-(lH-indol-3-yl)ethylamino)-2-(5-fluoropyridin-3-yl)-9H-purin-9-yl)propan-l-ol, i.e., is the compound 157S according to WO2010/059401), having the following structure:

Compound 4:



In embodiments the population of HSPCs is contacted with the stem cell expander, e.g., compound 1, compound 2, compound 3, compound 4, or combinations thereof (e.g., a combination of compound 1 and compound 4) before introduction of the CRISPR system (e.g., gRNA molecule and/or Cas9 molecule of the invention) to said HSPCs. In embodiements, the population of HSPCs is contacted with the stem cell expander, e.g., compound 1, compound 2, compound 3, compound 4, or combinations thereof (e.g., a combination of compound 1 and compound 4), after introduction of the CRISPR system (e.g., gRNA molecule and/or Cas9 molecule of the invention) to said HSPCs. In embodiments, the population of HSPCs is contacted with the stem cell expander, e.g., compound 1, compound 2, compound 3, compound 4, or combinations thereof (e.g., a combination of compound 1 and compound 4), both before and after introduction of the CRISPR system (e.g., gRNA molecule and/or Cas9 molecule of the invention) to said HSPCs.

In embodiments, the stem cell expander is present in an effective amount to increase the expansion level of the HSPCs, relative to HSPCs in the same media but for the absence of the stem cell expander. In embodimetns, the stem cell expander is present at a concentration ranging from about 0.01 to about 10 uM, e.g., from about 0.1 uM to about 1 uM. In embodiments, the stem cell expander is present in the cell culture medium at a concentration of about 1 uM, about 950 nM, about 900 nM, about 850 nM, about 800 nM, about 750 nM, about 700nM, about 650 nM, about 600 nM, about 550 nM, about 500 nM, about 450 nM, about 400 nM, about 350 nM, about 300 nM, about 250 nM, about 200 nM, about 150 nM, about 100 nM, about 50 nM, about 25 nM, or about 10 nM. In embodiments, the stem cell expander is present at a concentration ranging from about 500 nM to about 750 nM.

In embodiments, the stem cell expander is compound 4, which is present in the cell culture medium at a concentration ranging from about 0.01 to about 10 micromolar (uM). In embodiments, the stem cell expander is compound 4, which is present in the cell culture medium at a concentration ranging from

about 0.1 to about 1 micromolar (uM). In embodiments, the stem cell expander is compound 4, which is present in the cell culture medium at a concentration of about 0.75 micromolar (uM). In embodiments, the stem cell expander is compound 4, which is present in the cell culture medium at a concentration of about 0. 5 micromolar (uM). In embodiments of any of the foregoing, the cell culture medium additionally comprises compound 1.

In embodiments, the stem cell expander is a mixture of compound 1 and compound 4.

In embodiments, the cells of the invention are contacted with one or more stem cell expander molecules for a sufficient time and in a sufficient amount to cause a 2 to 10,000-fold expansion of CD34+ cells, e.g., a 2-1000-fold expansion of CD34+ cells, e.g., a 2-100-fold expansion of CD34+ cells, e.g., a 20-200-fold expansion of CD34+ cells. As described herein, the contacting with the one or more stem cell expanders may be before the cells are contacted with a CRISPR system, e.g., as described herein, after the cells are contacted with a CRISPR system, e.g., as described herein, or a combination thereof. In an embodiment, the cells are contacted with one or more stem cell expander molecules, e.g., Compound 4, for a sufficient time and in a sufficient amount to cause at least a 2-fold expansion of CD34+ cells, e.g., CD34+ cells comprising an indel at or near the target site having complementarity to the targeting domain of the gRNA of the CRISPR/Cas9 system introduced into said cell. In an embodiment, the cells are contacted with one or more stem cell expander molecules, e.g., Compound 4, for a sufficient time and in a sufficient amount to cause at least a 4-fold expansion of CD34+ cells, e.g., CD34+ cells comprising an indel at or near the target site having complementarity to the targeting domain of the gRNA of the CRISPR/Cas9 system introduced into said cell. In an embodiment, the cells are contacted with one or more stem cell expander molecules, e.g., Compound 4, for a sufficient time and in a sufficient amount to cause at least a 5-fold expansion of CD34+ cells, e.g., CD34+ cells comprising an indel at or near the target site having complementarity to the targeting domain of the gRNA of the CRISPR/Cas9 system introduced into said cell. In an embodiment, the cells are contacted with one or more stem cell expander molecules for a sufficient time and in a sufficient amount to cause at least a 10-fold expansion of CD34+ cells. In an embodiment, the cells are contacted with one or more stem cell expander molecules for a sufficient time and in a sufficient amount to cause at least a 20-fold expansion of CD34+ cells. In an embodiment, the cells are contacted with one or more stem cell expander molecules for a sufficient time and in a sufficient amount to cause at least a 30-fold expansion of CD34+ cells. In an embodiment, the cells are contacted with one or more stem cell expander molecules for a sufficient time and in a sufficient amount to cause at least a 40-fold expansion of CD34+ cells. In an embodiment, the cells are contacted with one or more stem cell expander molecules for a sufficient time and in a sufficient amount to cause at least a 50-fold expansion of CD34+ cells. In an embodiment, the cells are contacted with one or more stem cell expander molecules for a sufficient time and in a sufficient amount to cause at least a 60-fold expansion of CD34+ cells. In

embodiments, the cells are contacted with the one or more stem cell expanders for a period of about 1-60 days, e.g., about 1-50 days, e.g., about 1-40 days, e.g., about 1-30 days, e.g., 1-20 days, e.g., about 1-10 days, e.g., about 7 days, e.g., about 1-5 days, e.g., about 2-5 days, e.g., about 2-4 days, e.g., about 2 days or, e.g., about 4 days.

In embodiments, the cells, e.g., HSPCs, e.g., as described herein, are cultured ex vivo for a period of about 1 hour to about 10 days, e.g., a period of about 12 hours to about 5 days, e.g., a period of about 12 hours to 4 days, e.g., a period of about 1 day to about 4 days, e.g., a period of about 1 day to about 2 days, e.g., a period of about 1 day or a period of about 2 days, prior to the step of contacting the cells with a CRISPR system, e.g., described herein. In embodiments, said culturing prior to said contacting step is in a composition (e.g., a cell culture medium) comprising a stem cell expander, e.g., described herein, e.g., compound 4, e.g., compound 4 at a concentration of about 0.25 uM to about 1 uM, e.g., compound 4 at a concentration of about 0.75-0.5 micromolar. In embodiments, the cells are cultured ex vivo for a period of no more than about about 1 day, e.g., no more than about 18, 17, 16, 15, 14, 13, 12, 11, 10, 9, 8, 7, 6, 5, 4, 3, 2, or 1 hour(s) after the step of contacting the cells with a CRISPR system, e.g., described herein, e.g., in a cell culture medium which comprises a stem cell expander, e.g., described herein, e.g., compound 4, e.g., compound 4 at a concentration of about 0.25 uM to about 1 uM, e.g., compound 4 at a concentration of about 0.75-0.5 micromolar. In other embodiments, the cells are cultured ex vivo for a period of about 1 hour to about 14 days, e.g., a period of about 12 hours to about 10 days, e.g., a period of about 1 day to about 10 days, e.g., a period of about 1 day to about 5 days, e.g., a period of about 1 day to about 4 days, e.g., a period of about 2 days to about 4 days, e.g., a period of about 2 days, about 3 days or about 4 days, after the step of contacting the cells with a CRISPR system, e.g., described herein, in a cell culture medium, e.g., which comprises a stem cell expander, e.g., described herein, e.g., compound 4, e.g., compound 4 at a concentration of about 0.25 uM to about 1 uM, e.g., compound 4 at a concentration of about 0.75-0.5 micromolar.

In embodiments, the cell culture medium is a chemically defined medium. In embodiments, the cell culture medium may additionally contain, for example, StemSpan SFEM (StemCell Technologies; Cat no. 09650). In embodiments, the cell culture medium may alternatively or additionally contain, for example, HSC Brew, GMP (Miltenyi). In embodiments, the media may be supplemented with thrombopoietin (TPO), human Flt3 ligand (Flt-3L), human stem cell factor (SCF), human interleukin-6, L-glutamine, and/or penicillin/streptomycin. In embodiments, the media is supplemented with thrombopoietin (TPO), human Flt3 ligand (Flt-3L), human stem cell factor (SCF), human interleukin-6, and L-glutamine. In other embodiments, the media is supplemented with thrombopoietin (TPO), human Flt3 ligand (Flt-3L), human stem cell factor (SCF), and human interleukin-6. In other embodiments the media is supplemented with thrombopoietin (TPO), human Flt3 ligand (Flt-3L), and human stem cell factor (SCF), but not human interleukin-6. When present in the medium, the

thrombopoietin (TPO), human Flt3 ligand (Flt-3L), human stem cell factor (SCF), human interleukin-6, and/or L-glutamine are each present in a concentration ranging from about 1 ng/mL to about 1000 ng/mL, e.g., a concentration ranging from about 10 ng/mL to about 500 ng/mL, e.g., a concentration ranging from about 10 ng/mL to about 100 ng/mL, e.g., a concentration ranging from about 25 ng/mL to about 75 ng/mL, e.g., a concentration of about 50 ng/mL. In embodiments, each of the supplemented components is at the same concentration. In other embodiments, each of the supplemented components is at a different concentration. In an embodiment, the medium comprises StemSpan SFEM (StemCell Technologies; Cat no. 09650), 50 ng/mL of thrombopoietin (Tpo), 50 ng/mL of human Flt3 ligand (Flt-3L), 50ng/mL of human stem cell factor (SCF), and 50ng/mL of human interleukin-6 (IL-6). In an embodiment, the medium comprises StemSpan SFEM (StemCell Technologies; Cat no. 09650), 50 ng/mL of thrombopoietin (Tpo), 50 ng/mL of human Flt3 ligand (Flt-3L), and 50ng/mL of human stem cell factor (SCF), and does not comprise IL-6. In embodiments, the media further comprises a stem cell expander, e.g., compound 4, e.g., compound 4 at a concentration of 0.75 μM. In embodiments, the media further comprises a stem cell expander, e.g., compound 4, e.g., compound 4 at a concentration of 0.5 μM. In embodiments, the media further comprises 1% L-glutamine and 2% penicillin/streptomycin. In embodiments, the cell culture medium is serum free.

XII. Combination Therapy

The present disclosure contemplates the use of the gRNA molecules described herein, or cells (e.g., hematopoietic stem cells, e.g., CD34+ cells) modified with the gRNA molecules described herein, in combination with one or more other therapeutic modalities and/or agents agents. Thus, in addition to the use of the gRNA molecules or cells modified with the gRNA molecules described herein, one may also administer to the subject one or more "standard" therapies for treating hemoglobinopathies.

The one or more additional therapies for treating hemoglobinopathies may include, for example, additional stem cell transplantation, e.g., hematopoietic stem cell transplantation. The stem cell transplantation may be allogeneic or autologous.

The one or more additional therapies for treating hemoglobinopathies may include, for example, blood transfusion and/or iorn chealation (e.g., removal) therapy. Known iron chealation agents include, for example, deferoxamine and deferasirox.

The one or more additional therapies for treating hemoglobinopathies may include, for example, folic acid supplements, or hydroxyurea (e.g., 5-hydroxyurea). The one or more additional therapies for treating hemoglobinopathies may be hydroxyurea. In embodiments, the hydroxyurea may be administered at a dose of, for example, 10-35mg/kg per day, e.g., 10-20 mg/kg per day. In embodiments, the hydroxyurea is adminstered at a dose of 10 mg/kg per day. In embodiments, the

hydroxyurea is adminstered at a dose of 10 mg/kg per day. In embodiments, the hydroxyurea is adminstered at a dose of 20 mg/kg per day. In embodiments, the hydroxyurea is administered before and/or after the cell (or population of cells), e.g., CD34+ cell (or population of cells) of the invention, e.g., as described herein.

The one or more additional therapeutic agents may include, for example, an anti-p-selectin antibody, e.g., SelG1 (Selexys). P-selectin antibodies are described in, for example, PCT publication WO1993/021956, PCT publication WO1995/034324, PCT publication WO2005/100402, PCT publication WO2008/069999, US patent applicatation publication US2011/0293617, US Patent No. 5800815, US Patent No. 6667036, US Patent No. 8945565, US Patent No. 8377440 and US Patent No. 9068001, the contents of each of which are incorporated herein in their entirety.

The one or more additional agents may include, for example, a small molecule which upregulates fetal hemoglobin. Examples of such molecules include TN1 (e.g., as described in Nam, T. et al., ChemMedChem 2011, 6, 777 – 780, DOI: 10.1002/cmdc.201000505, herein incorporated by reference).

The one or more additional therapies may also include irradiation or other bone marrow ablation therapeis known in the art. An example of such a therapy is busulfan. Such additional therapy may be performed prior to introduction of the cells of the invention into the subject. In an embodiment the methods of treatment described herein (e.g., the methods of treatment that include administration of cells (e.g., HSPCs) modified by the methods described herein (e.g., modified with a CRISPR system described herein, e.g., to increase HbF production)), the method does not include the step of bone marrow ablation. In embodiments, the methods include a partial bone marrow ablation step.

The therapies described herein (e.g., comprising administering a population of HSPCs, e.g., HSPCs modified using a CRISPR system described herein) may also be combined with an additional therapeutic agent. In an embodiment, the additional therapeutic agent is an HDAC inhibitor, e.g., panobinostat. In an embodiment, the additional therapeutic is a compound described in PCT Publication No. WO2014/150256, e.g., a compound described in Table 1 of WO2014/150256, e.g., GBT440. Other examples of HDAC inhibitors include, for example, suberoylanilide hydroxamic acid (SAHA). The one or more additional agents may include, for example, a DNA methylation inhibitor. Such agents have been shown to increase the HbF induction in cells having reduced BCL11a activity (e.g., Jian Xu et al, Science 334, 993 (2011); DOI: 0.1126/science.1211053, herein incorporated by reference). Other HDAC inhibitors include any HDAC inhibitor known in the art, for example, trichostatin A, HC toxin, DACI-2, FK228, DACI-14, depudicin, DACI-16, tubacin, NK57, MAZ1536, NK125, Scriptaid, Pyroxamide, MS-275, ITF−2357, MCG-D0103, CRA−024781, CI−994, and LBH589 (see, e.g., Bradner JE, et al., *PNAS*, 2010 (vol. 107:28), 12617-12622, herein incorporated by reference in its entirety).

The gRNA molecules described herein, or cells (e.g., hematopoietic stem cells, e.g., CD34+ cells) modified with the gRNA molecules described herein, and the co-therapeutic agent or co-therapy can be administered in the same formulation or separately. In the case of separate administration, the gRNA molecules described herein, or cells modified with the gRNA molecules described herein, can be administered before, after or concurrently with the co-therapeutic or co-therapy. One agent may precede or follow administration of the other agent by intervals ranging from minutes to weeks. In embodiments where two or more different kinds of therapeutic agents are applied separately to a subject, one would generally ensure that a significant period of time did not expire between the time of each delivery, such that these different kinds of agents would still be able to exert an advantageously combined effect on the target tissues or cells.

XIII. Modified Nucleosides, Nucleotides, and Nucleic Acids

Modified nucleosides and modified nucleotides can be present in nucleic acids, e.g., particularly gRNA, but also other forms of RNA, e.g., mRNA, RNAi, or siRNA. As described herein "nucleoside" is defined as a compound containing a five-carbon sugar molecule (a pentose or ribose) or derivative thereof, and an organic base, purine or pyrimidine, or a derivative thereof. As described herein, "nucleotide" is defined as a nucleoside further comprising a phosphate group.

Modified nucleosides and nucleotides can include one or more of:

(i) alteration, e.g., replacement, of one or both of the non-linking phosphate oxygens and/or of one or more of the linking phosphate oxygens in the phosphodiester backbone linkage;

(ii) alteration, e.g., replacement, of a constituent of the ribose sugar, e.g., of the 2' hydroxyl on the ribose sugar;

(iii) wholesale replacement of the phosphate moiety with "dephospho" linkers;

(iv) modification or replacement of a naturally occurring nucleobase, including with a non-canonical nucleobase;

(v) replacement or modification of the ribose-phosphate backbone;

(vi) modification of the 3' end or 5' end of the oligonucleotide, e.g., removal, modification or replacement of a terminal phosphate group or conjugation of a moiety, cap or linker; and

(vii) modification or replacement of the sugar.

The modifications listed above can be combined to provide modified nucleosides and nucleotides that can have two, three, four, or more modifications. For example, a modified nucleoside or nucleotide can have a modified sugar and a modified nucleobase. In an embodiment, every base of a gRNA is modified, e.g., all bases have a modified phosphate group, e.g., all are phosphorothioate groups. In an

embodiment, all, or substantially all, of the phosphate groups of a unimolecular or modular gRNA molecule are replaced with phosphorothioate groups. In embodiments, one or more of the five 3'-terminal bases and/or one or more of the fige 5'-terminal bases of the gRNA are modified with a phosphorothioate group.

In an embodiment, modified nucleotides, e.g., nucleotides having modifications as described herein, can be incorporated into a nucleic acid, e.g., a "modified nucleic acid." In some embodiments, the modified nucleic acids comprise one, two, three or more modified nucleotides. In some embodiments, at least 5% (e.g., at least about 5%, at least about 10%, at least about 15%, at least about 20%, at least about 25%, at least about 30%, at least about 35%, at least about 40%, at least about 45%, at least about 50%, at least about 55%, at least about 60%, at least about 65%, at least about 70%, at least about 75%, at least about 80%, at least about 85%, at least about 90%, at least about 95%, or about 100%) of the positions in a modified nucleic acid are a modified nucleotides.

Unmodified nucleic acids can be prone to degradation by, e.g., cellular nucleases. For example, nucleases can hydrolyze nucleic acid phosphodiester bonds. Accordingly, in one aspect the modified nucleic acids described herein can contain one or more modified nucleosides or nucleotides, e.g., to introduce stability toward nucleases.

In some embodiments, the modified nucleosides, modified nucleotides, and modified nucleic acids described herein can exhibit a reduced innate immune response when introduced into a population of cells, both in vivo and ex vivo. The term "innate immune response" includes a cellular response to exogenous nucleic acids, including single stranded nucleic acids, generally of viral or bacterial origin, which involves the induction of cytokine expression and release, particularly the interferons, and cell death. In some embodiments, the modified nucleosides, modified nucleotides, and modified nucleic acids described herein can disrupt binding of a major groove interacting partner with the nucleic acid. In some embodiments, the modified nucleosides, modified nucleotides, and modified nucleic acids described herein can exhibit a reduced innate immune response when introduced into a population of cells, both in vivo and ex vivo, and also disrupt binding of a major groove interacting partner with the nucleic acid.

Definitions of Chemical Groups

As used herein, "alkyl" is meant to refer to a saturated hydrocarbon group which is straight-chained or branched. Example alkyl groups include methyl (Me), ethyl (Et), propyl (e.g. , n-propyl and isopropyl), butyl (e.g. , n-butyl, isobutyl, t-butyl), pentyl (e.g. , n-pentyl, isopentyl, neopentyl), and the like. An alkyl group can contain from 1 to about 20, from 2 to about 20, from 1 to about 12, from 1 to about 8, from 1 to about 6, from 1 to about 4, or from 1 to about 3 carbon atoms.

As used herein, "aryl" refers to monocyclic or polycyclic (e.g. , having 2, 3 or 4 fused rings) aromatic hydrocarbons such as, for example, phenyl, naphthyl, anthracenyl,

phenanthrenyl, indanyl, indenyl, and the like. In some embodiments, aryl groups have from 6 to about 20 carbon atoms.

As used herein, "alkenyl" refers to an aliphatic group containing at least one double bond. As used herein, "alkynyl" refers to a straight or branched hydrocarbon chain containing 2- 12 carbon atoms and characterized in having one or more triple bonds. Examples of alkynyl groups include, but are not limited to, ethynyl, propargyl, and 3-hexynyl.

As used herein, "arylalkyl" or "aralkyl" refers to an alkyl moiety in which an alkyl hydrogen atom is replaced by an aryl group. Aralkyl includes groups in which more than one hydrogen atom has been replaced by an aryl group. Examples of "arylalkyl" or "aralkyl" include benzyl, 2-phenylethyl, 3-phenylpropyl, 9-fluorenyl, benzhydryl, and trityl groups.

As used herein, "cycloalkyl" refers to a cyclic, bicyclic, tricyclic, or polycyclic non- aromatic hydrocarbon groups having 3 to 12 carbons. Examples of cycloalkyl moieties include, but are not limited to, cyclopropyl, cyclopentyl, and cyclohexyl.

As used herein, "heterocyclyl" refers to a monovalent radical of a heterocyclic ring system. Representative heterocyclyls include, without limitation, tetrahydrofuranyl, tetrahydrothienyl, pyrrolidinyl, pyrrolidonyl, piperidinyl, pyrrolinyl, piperazinyl, dioxanyl, dioxolanyl, diazepinyl, oxazepinyl, thiazepinyl, and morpholinyl.

As used herein, "heteroaryl" refers to a monovalent radical of a heteroaromatic ring system. Examples of heteroaryl moieties include, but are not limited to, imidazolyl, oxazolyl, thiazolyl, triazolyl, pyrrolyl, furanyl, indolyl, thiophenyl pyrazolyl, pyridinyl, pyrazinyl, pyridazinyl, pyrimidinyl, indolizinyl, purinyl, naphthyridinyl, quinolyl, and pteridinyl.

Phosphate Backbone Modifications

The Phosphate Group

In some embodiments, the phosphate group of a modified nucleotide can be modified by replacing one or more of the oxygens with a different substituent. Further, the modified nucleotide, e.g., modified nucleotide present in a modified nucleic acid, can include the wholesale replacement of an unmodified phosphate moiety with a modified phosphate as described herein. In some embodiments, the modification of the phosphate backbone can include alterations that result in either an uncharged linker or a charged linker with unsymmetrical charge distribution.

Examples of modified phosphate groups include, phosphorothioate, phosphoroselenates, borano phosphates, borano phosphate esters, hydrogen phosphonates, phosphoroamidates, alkyl or aryl

phosphonates and phosphotriesters. In some embodiments, one of the non-bridging phosphate oxygen atoms in the phosphate backbone moiety can be replaced by any of the following groups: sulfur (S), selenium (Se), BR_3 (wherein R can be, e.g., hydrogen, alkyl, or aryl), C (e.g., an alkyl group, an aryl group, and the like), H, NR_2 (wherein R can be, e.g., hydrogen, alkyl, or aryl), or OR (wherein R can be, e.g., alkyl or aryl). The phosphorous atom in an unmodified phosphate group is achiral. However, replacement of one of the non-bridging oxygens with one of the above atoms or groups of atoms can render the phosphorous atom chiral; that is to say that a phosphorous atom in a phosphate group modified in this way is a stereogenic center. The stereogenic phosphorous atom can possess either the "R" configuration (herein Rp) or the "S" configuration (herein Sp).

Phosphorodithioates have both non-bridging oxygens replaced by sulfur. The phosphorus center in the phosphorodithioates is achiral which precludes the formation of oligoribonucleotide diastereomers. In some embodiments, modifications to one or both non-bridging oxygens can also include the replacement of the non-bridging oxygens with a group independently selected from S, Se, B, C, H, N, and OR (R can be, e.g., alkyl or aryl).

The phosphate linker can also be modified by replacement of a bridging oxygen, (i.e., the oxygen that links the phosphate to the nucleoside), with nitrogen (bridged phosphoroamidates), sulfur (bridged phosphorothioates) and carbon (bridged methylenephosphonates). The replacement can occur at either linking oxygen or at both of the linking oxygens.

Replacement of the Phosphate Group

The phosphate group can be replaced by non-phosphorus containing connectors. In some embodiments, the charge phosphate group can be replaced by a neutral moiety.

Examples of moieties which can replace the phosphate group can include, without limitation, e.g., methyl phosphonate, hydroxylamino, siloxane, carbonate, carboxymethyl, carbamate, amide, thioether, ethylene oxide linker, sulfonate, sulfonamide, thioformacetal, formacetal, oxime, methyleneimino, methylenemethylimino, methylenehydrazo, methylenedimethylhydrazo and methyleneoxymethylimino.

Replacement of the Ribophosphate Backbone

Scaffolds that can mimic nucleic acids can also be constructed wherein the phosphate linker and ribose sugar are replaced by nuclease resistant nucleoside or nucleotide surrogates. In some embodiments, the nucleobases can be tethered by a surrogate backbone. Examples can include, without limitation, the morpholino, cyclobutyl, pyrrolidine and peptide nucleic acid (PNA) nucleoside surrogates.

Sugar Modifications

The modified nucleosides and modified nucleotides can include one or more modifications to the sugar group. For example, the 2' hydroxyl group (OH) can be modified or replaced with a number of different "oxy" or "deoxy" substituents. In some embodiments, modifications to the 2' hydroxyl group can enhance the stability of the nucleic acid since the hydroxyl can no longer be deprotonated to form a 2'-alkoxide ion. The 2'-alkoxide can catalyze degradation by intramolecular nucleophilic attack on the linker phosphorus atom.

Examples of "oxy"-2' hydroxyl group modifications can include alkoxy or aryloxy (OR, wherein "R" can be, e.g., alkyl, cycloalkyl, aryl, aralkyl, heteroaryl or a sugar); polyethyleneglycols (PEG), $0(CH_2CH_20)_nCH2CH_2OR$ wherein R can be, e.g., H or optionally substituted alkyl, and n can be an integer from 0 to 20 (e.g., from 0 to 4, from 0 to 8, from 0 to 10, from 0 to 16, from 1 to 4, from 1 to 8, from 1 to 10, from 1 to 16, from 1 to 20, from 2 to 4, from 2 to 8, from 2 to 10, from 2 to 16, from 2 to 20, from 4 to 8, from 4 to 10, from 4 to 16, and from 4 to 20). In some embodiments, the "oxy"-2' hydroxyl group modification can include "locked" nucleic acids (LNA) in which the 2' hydroxyl can be connected, e.g., by a $Ci-_6$ alkylene or Cj-6 heteroalkylene bridge, to the 4' carbon of the same ribose sugar, where exemplary bridges can include methylene, propylene, ether, or amino bridges; O-amino (wherein amino can be, e.g., NH_2; alkylamino, dialkylamino, heterocyclyl, arylamino, diarylamino, heteroarylamino, or diheteroarylamino, ethylenediamine, or polyamino) and aminoalkoxy, $0(CH_2)_n$-amino, (wherein amino can be, e.g., NH_2; alkylamino, dialkylamino, heterocyclyl, arylamino, diarylamino, heteroarylamino, or diheteroarylamino, ethylenediamine, or polyamino). In some embodiments, the "oxy"-2' hydroxyl group modification can include the methoxyethyl group (MOE), ($OCH_2CH_2OCH_3$, e.g., a PEG derivative).

"Deoxy" modifications can include hydrogen (i.e. deoxyribose sugars, e.g., at the overhang portions of partially ds RNA); halo (e.g., bromo, chloro, fluoro, or iodo); amino (wherein amino can be, e.g., NH_2; alkylamino, dialkylamino, heterocyclyl, arylamino, diarylamino, heteroarylamino, diheteroarylamino, or amino acid); $NH(CH_2CH_2NH)_nCH2CH_2$- amino (wherein amino can be, e.g., as described herein), -NHC(0)R (wherein R can be, e.g., alkyl, cycloalkyl, aryl, aralkyl, heteroaryl or sugar), cyano; mercapto; alkyl-thio-alkyl; thioalkoxy; and alkyl, cycloalkyl, aryl, alkenyl and alkynyl, which may be optionally substituted with e.g., an amino as described herein.

The sugar group can also contain one or more carbons that possess the opposite stereochemical configuration than that of the corresponding carbon in ribose. Thus, a modified nucleic acid can include nucleotides containing e.g., arabinose, as the sugar. The nucleotide "monomer" can have an alpha linkage at the Γ position on the sugar, e.g., alpha-nucleosides. The modified nucleic acids can also include "abasic" sugars, which lack a nucleobase at C- . These abasic sugars can also be further modified at one or more of the constituent sugar atoms. The modified nucleic acids can also include one or more sugars that are in the L form, e.g. L- nucleosides.

Generally, RNA includes the sugar group ribose, which is a 5-membered ring having an oxygen. Exemplary modified nucleosides and modified nucleotides can include, without limitation, replacement of the oxygen in ribose (e.g., with sulfur (S), selenium (Se), or alkylene, such as, e.g., methylene or ethylene); addition of a double bond (e.g., to replace ribose with cyclopentenyl or cyclohexenyl); ring contraction of ribose (e.g., to form a 4-membered ring of cyclobutane or oxetane); ring expansion of ribose (e.g., to form a 6- or 7-membered ring having an additional carbon or heteroatom, such as for example, anhydrohexitol, altritol, mannitol, cyclohexanyl, cyclohexenyl, and morpholino that also has a phosphoramidate backbone). In some embodiments, the modified nucleotides can include multicyclic forms (e.g., tricyclo; and "unlocked" forms, such as glycol nucleic acid (GNA) (e.g., R-GNA or S-GNA, where ribose is replaced by glycol units attached to phosphodiester bonds), threose nucleic acid (TNA, where ribose is replaced with a-L-threofuranosyl-(3'-→2')).

Modifications on the Nucleobase

The modified nucleosides and modified nucleotides described herein, which can be incorporated into a modified nucleic acid, can include a modified nucleobase. Examples of nucleobases include, but are not limited to, adenine (A), guanine (G), cytosine (C), and uracil (U). These nucleobases can be modified or wholly replaced to provide modified nucleosides and modified nucleotides that can be incorporated into modified nucleic acids. The nucleobase of the nucleotide can be independently selected from a purine, a pyrimidine, a purine or pyrimidine analog. In some embodiments, the nucleobase can include, for example, naturally-occurring and synthetic derivatives of a base.

Uracil

In some embodiments, the modified nucleobase is a modified uracil. Exemplary nucleobases and nucleosides having a modified uracil include without limitation pseudouridine (ψ), pyridin-4-one ribonucleoside, 5-aza-uridine, 6-aza-uridine, 2-thio-5-aza-uridine, 2-thio- uridine (s2U), 4-thio-uridine (s4U), 4-thio-pseudouridine, 2-thio-pseudouridine, 5-hydroxy- u,ridine (ho^{5}U), 5-aminoallyl-uridine, 5-halo-uridine (e.g., 5-iodo-uridine or 5-bromo-uridine), 3- methyl-uridine (m^{3}U), 5-methoxy-uridine (mo^{5}U), uridine 5-oxyacetic acid (cmo^{5}U), uridine 5- oxyacetic acid methyl ester (mcmo^U), 5-carboxymethyl-uridine (cm^{5}U), 1 -carboxymethyl- pseudouridine, 5-carboxyhydroxymethyl-uridine (chm^{5}U), 5-carboxyhydroxymethyl-uridine methyl ester (mchm^{5}U), 5-methoxycarbonylmethyl-uridine (mcm^{5}U), 5- methoxycarbonylmethyl-2-thio-uridine (mcm^{5}s2U), 5-aminomethyl-2-thio-uridine (nm^{5}s2U), 5- methylaminomethyl-uridine (mnm^{5}U), 5-methylaminomethyl-2-thio-uridine (mnm^{5}s2U), 5- methylaminomethyl-2-seleno-uridine (mnm^{5}se^{2}U), 5-carbamoylmethyl-uridine (ncm^{5}U), 5- carboxymethylaminomethyl-uridine (cmnm^{5}U), 5-carboxymethylaminomethyl-2-thio-uridine (cmnm \s2U), 5-propynyl-uridine, 1 -propynyl-pseudouridine, 5-taurinomethyl-uridine (xcm^{5}U), 1 -taurinomethyl-pseudouridine, 5-taurinomethyl-2-thio-uridine(Trn^{5}s2U), l-taurinomethyl-

4- thio-pseudouridine, 5-methyl-uridine (m^5U, i.e., having the nucleobase deoxythymine), 1- methyl-pseudouridine (ιτι'ψ). 5-methyl-2-thio-uridine (m^5s2U), l-methyl-4-thio-pseudouridine (m' s \|/), 4-thio- l-methyl-pseudouridine, 3-methyl-pseudouridine (m'V), 2-thio- 1 -methyl- pseudouridine, 1 -methyl- 1 -deaza-pseudouridine, 2-thio- 1 -methyl- 1 -deaza-pseudouridine, dihydroundine (D), dihydropseudoundine, 5,6-dihydrouridine, 5-methyl-dihydrouridine (m^5D), 2- thio-dihydrouridine, 2-thio-dihydropseudouridine, 2-methoxy-uridine, 2-methoxy-4-thio- uridine, 4-methoxy-pseudouridine, 4-methoxy-2-thio-pseudouridine, N l -methyl-pseudouridine, 3- (3-amino-3-carboxypropyl)uridine (acp^3U), l-methyl-3-(3-amino-3- carboxypropy pseudouridine 5-(isopentenylaminomethyl)uridine (inm^5U), 5- (isopentenylaminomethy])-2-thio-uridine (inm^5s2U), a-thio-uridine, 2'-0-methyl-uridine (Urn), 5,2'-0-dimethyl-uridine (m^5Um), 2'-0-methyl-pseudouridine (ψπι), 2-thio-2'-0-methyl-uridine (s2Um), 5-methoxycarbonylmethyl-2'-0-methyl-uridine (mcm ^{5}Um), 5-carbamoylmethyl-2'-0-methyl-uridine (ncm ^{5}Um), 5-carboxymethylaminomethyl-2'-0-methyl-uridine (cmnm ^{5}Um), 3,2'-0-dimethyl-uridine (m^3Um), 5-(isopentenylaminomethyl)-2'-0-methyl-uridine (inm ^{5}Um), l -thio-uridine, deoxythymidine, 2'-F-ara-uridine, 2'-F-uridine, 2'-OH-ara-uridine, 5-(2- carbomethoxyvinyl) uridine, 5-[3-(l-E-propenylamino)uridine, pyrazolo[3,4-d]pyrimidines, xanthine, and hypoxanthine.

Cytosine

In some embodiments, the modified nucleobase is a modified cytosine. Exemplary nucleobases and nucleosides having a modified cytosine include without limitation 5-aza- cytidine, 6-aza-cytidine, pseudoisocytidine, 3-methyl-cytidine (m^3C), N4-acetyl-cytidine (act), 5- formyl-cytidine (f^5C), N4-methyl-cytidine (m^4C), 5-methyl-cytidine (m^5C), 5-halo-cytidine (e.g., 5-iodo-cytidine), 5-hydroxymethyl-cytidine (hm^5C), 1-methyl-pseudoisocytidine, pyrrolo- cytidine, pyrrolo-pseudoisocytidine, 2-thio-cytidine (s2C), 2-thio-5-methyl-cytidine, 4-thio- pseudoisocytidine, 4-thio-1 -methyl-pseudoisocytidine, 4-thio-l -methyl- 1-deaza- pseudoisocytidine, 1-methyl- l-deaza-pseudoisocytidine, zebularine, 5-aza-zebularine, 5-methyl- zebularine, 5-aza-2-thio-zebularine, 2-thio-zebularine, 2-methoxy-cytidine, 2-methoxy-5-methyl- cytidine, 4-methoxy-pseudoisocytidine, 4-methoxy- 1 -methyl-pseudoisocytidine, lysidine (k^2C), a-thio-cytidine, 2'-0-methyl-cytidine (Cm), 5,2'-0-dimethyl-cytidine (m^5Cm), N4-acetyl-2'-0- methyl-cytidine (ac^4Cm), N4,2'-0-dimethyl-cytidine (m^4Cm), 5-formyl-2'-0-methyl-cytidine (f ^{5}Cm), N4,N4,2'-0-trimethyl-cytidine ($m^4{}_2Cm$), 1 -thio-cytidine, 2'-F-ara-cytidine, 2'-F-cytidine, and 2'-OH-ara-cytidine.

Adenine

In some embodiments, the modified nucleobase is a modified adenine. Exemplary nucleobases and nucleosides having a modified adenine include without limitation 2-amino- purine, 2,6-diaminopurine, 2-amino-6-halo-purine (e.g., 2-amino-6-chloro-purine), 6-halo-purine (e.g., 6-chloi -purine), 2-amino-6-methyl-purine, 8-azido-adenosine, 7-deaza-adenine, 7-deaza- 8-aza-adenine, 7-deaza-2-amino-purine, 7-deaza-8-aza-2-amino-purine, 7-deaza-2,6- diaminopurine, 7-deaza-8-aza-

2,6-diaminopurine, 1-methyl-adenosine (m'A), 2-methyl-adenine (m A), N6-methyl-adenosine (m^6A), 2-methylthio-N6-methyl-adenosine ($ms2m^6A$), N6- isopentenyl-adenosine (i^6A), 2-methylthio-N6-isopentenyl-adenosine (ms^2i^6A), N6-(cis- hydroxyisopentenyl)adenosine (io^6A), 2-methylthio-N6-(cis-hydroxyisopentenyl)adenosine ($ms2io^6A$), N6-glycinylcarbamoyl-adenosine (g^6A), N6-threonylcarbamoyl-adenosine (t^6A), N6- methyl-N6-threonylcarbamoyl-adenosine (m^6t^6A), 2-methylthio-N6-threonylcarbamoyl- adenosine (ms^2g^6A), N6,N6-dimethyl-adenosine ($m^6{}_2A$), N6-hydroxynorvalylcarbamoyl- adenosine (hn^6A), 2-methylthio-N6-hydroxynorvalylcarbamoyl-adenosine ($ms2hn^6A$), N6- acetyl-adenosine (ac^6A), 7-methyl-adenine, 2-methylthio-adenine, 2-methoxy-adenine, a-thio- adenosine, 2'-0-methyl-adenosine (Am), N^6,2'-0-dimethyl-adenosine (m^5Am), N^6-Methyl-2'- deoxyadenosine, N6,N6,2'-0-trimethyl-adenosine ($m^6{}_2Am$), 1 ,2'-0-dimethyl-adenosine (m' Am), 2'-0-ribosyladenosine (phosphate) (Ar(p)), 2-amino-N6-methyl-purine, 1 -thio-adenosine, 8- azido-adenosine, 2'-F-ara-adenosine, 2'-F-adenosine, 2'-OH-ara-adenosine, and N6-(19-amino- pentaoxanonadecyl)-adenosine.

Guanine

In some embodiments, the modified nucleobase is a modified guanine. Exemplary nucleobases and nucleosides having a modified guanine include without limitation inosine (I), 1 - methyl-inosine (m 'l), wyosine (imG), methylwyosine (mimG), 4-demethyl-wyosine (imG- 14), isowyosine (imG2), wybutosine (yW), peroxywybutosine (o_2yW), hydroxywybutosine (OHyW), undemriodified hydroxywybutosine (OHyW*), 7-deaza-guanosine, queuosine (Q), epoxyqueuosine (oQ), galactosyl-queuosine (galQ), mannosyl-queuosine (manQ), 7-cyano-7- deaza-guanosine ($preQ_0$), 7-aminomethyI-7-deaza-guanosine (preQi), archaeosine (G^+), 7-deaza- 8-aza-guanosine, 6-thio-guanosine, 6-thio-7-deaza-guanosine, 6-thio-7-deaza-8-aza-guanosine, 7-methyl-guanosine (m^7G), 6-thio-7-methyl-guanosine, 7-methyl-inosine, 6-methoxy-guanosine, 1 -methyl-guanosine (m'G), N2-methyl-guanosine (m^2G), N2,N2-dimethyl-guanosine ($m^2{}_2G$), N2,7-dimethyl-guanosine (m^2,7G), N2, N2,7-dimethyl-guanosine (m^2,2,7G), 8-oxo-guanosine, 7-methyl-8-oxo-guanosine, 1 -meth thio-guanosine, N2-methyl-6-thio-guanosine, N2,N2- dimethyl-6-thio-guanosine, a-thio-guanosine, 2'-0-methyl-guanosine (Gm), N2-methyl-2'-0- methyl-guanosine (m¾m), N2,N2-dimethyl-2'-0-methyl-guanosine ($m^2{}_2Gm$), 1 -methyl-2'-0- methyl-guanosine (m'Gm), N2,7-dimethyl-2'-0-methyl-guanosine (m^2,7Gm), 2'-0-methyl- inosine (Im), 1 ,2'-0-dimethyl-inosine (m'lm), 0^6-phenyl-2'-deoxyinosine, 2'-0-ribosylguanosine (phosphate) (Gr(p)), 1 -thio-guanosine, 0^6-methy]-guanosine, 0^6-Methyl-2'-deoxyguanosine, 2'- F-ara-guanosine, and 2'-F-guanosine.

Modified gRNAs

In some embodiments, the modified nucleic acids can be modified gRNAs. In some embodiments, gRNAs can be modified at the 3' end. In this embodiment, the gRNAs can be modified at the 3' terminal U ribose. For example, the two terminal hydroxyl groups of the U ribose can be oxidized to

aldehyde groups and a concomitant opening of the ribose ring to afford a modified nucleoside, wherein U can be an unmodified or modified uridine.

In another embodiment, the 3' terminal U can be modified with a 2' 3' cyclic phosphate, wherein U can be an unmodified or modified uridine. In some embodiments, the gRNA molecules may contain 3' nucleotides which can be stabilized against degradation, e.g., by incorporating one or more of the modified nucleotides described herein. In this embodiment, e.g., uridines can be replaced with modified uridines, e.g., 5-(2-amino)propyl uridine, and 5-bromo uridine, or with any of the modified uridines described herein; adenosines and guanosines can be replaced with modified adenosines and guanosines, e.g., with modifications at the 8-position, e.g., 8-bromo guanosine, or with any of the modified adenosines or guanosines described herein. In some embodiments, deaza nucleotides, e.g., 7- deaza-adenosine, can be incoiporated into the gRNA. In some embodiments, O- and N-alkylated nucleotides, e.g., N6-methyl andenosine, can be incorporated into the gRNA. In some embodiments, sugar-modified ribonucleotides can be incorporated, e.g., wherein the 2' OH- group is replaced by a group selected from H, -OR, -R (wherein R can be, e.g., methyl, alkyl, cycloalkyl, aryl, aralkyl, heteroaryl or sugar), halo, -SH, -SR (wherein R can be, e.g., alkyl, cycloalkyl, aryl, aralkyl, heteroaryl or sugar), amino (wherein amino can be, e.g., NH_2; alkylamino, dialkylamino, heterocyclyl, arylamino, diarylamino, heteroarylamino, diheteroarylamino, or amino acid); or cyano (-CN). In some embodiments, the phosphate backbone can be modified as described herein, e.g., with a phosphothioate group. In some embodiments, the nucleotides in the overhang region of the gRNA can each independently be a modified or unmodified nucleotide including, but not limited to 2'-sugar modified, such as, 2-F 2'-0-methyl, thymidine (T), 2'-O-methoxyethyl-5-methyluridine (Teo), 2'-O-methoxyethyladenosine (Aeo), 2'-O-methoxyethyl- 5-methylcytidine (m5Ceo), and any combinations thereof.

In an embodiment, a one or more or all of the nucleotides in single stranded overhang of an RNA molecule, e.g., a gRNA molecule, are deoxynucleotides.

Pharmaceutical Compositions

Pharmaceutical compositions of the present invention may comprise a gRNA molecule described herein, e.g., a plurality of gRNA molecules as described herein, or a cell (e.g., a population of cells, e.g., a population of hematopoietic stem cells, e.g., of CD34+ cells) comprising one or more cells modified with one or more gRNA molecules described herein, in combination with one or more pharmaceutically or physiologically acceptable carriers, diluents or excipients. Such compositions may comprise buffers such as neutral buffered saline, phosphate buffered saline and the like; carbohydrates such as glucose, mannose, sucrose or dextrans, mannitol; proteins; polypeptides or amino acids such as glycine; antioxidants; chelating agents such as EDTA or glutathione; adjuvants

(e.g., aluminum hydroxide); and preservatives. Compositions of the present invention are in one aspect formulated for intravenous administration.

Pharmaceutical compositions of the present invention may be administered in a manner appropriate to the disease to be treated (or prevented). The quantity and frequency of administration will be determined by such factors as the condition of the patient, and the type and severity of the patient's disease, although appropriate dosages may be determined by clinical trials.

In one embodiment, the pharmaceutical composition is substantially free of, e.g., there are no detectable levels of a contaminant, e.g., selected from the group consisting of endotoxin, mycoplasma, mouse antibodies, pooled human serum, bovine serum albumin, bovine serum, culture media components, unwanted CRISPR system components, a bacterium and a fungus. In one embodiment, the bacterium is at least one selected from the group consisting of Alcaligenes faecalis, Candida albicans, Escherichia coli, Haemophilus influenza, Neisseria meningitides, Pseudomonas aeruginosa, Staphylococcus aureus, Streptococcus pneumonia, and Streptococcus pyogenes group A.

The administration of the subject compositions may be carried out in any convenient manner, including by aerosol inhalation, injection, ingestion, transfusion, implantation or transplantation. The compositions described herein may be administered to a patient transarterially, subcutaneously, intradermally, intratumorally, intranodally, intramedullary, intramuscularly, by intravenous (i.v.) injection, or intraperitoneally. In one aspect, the compositions of the present invention are administered to a patient by intradermal or subcutaneous injection. In one aspect, the cell compositions of the present invention are administered by i.v. injection.

The dosage of the above treatments to be administered to a patient will vary with the precise nature of the condition being treated and the recipient of the treatment. The scaling of dosages for human administration can be performed according to art-accepted practices.

Cells

The invention also relates to cells comprising a gRNA molecule of the invention, or nucleic acid encoding said gRNA molecules.

In an aspect the cells are cells made by a process described herein.

In embodiments, the cells are hematopoietic stem cells (e.g., hematopoietic stem and progenitor cells; HSPCs), for example, CD34+ stem cells. In embodiments, the cells are CD34+/CD90+ stem cells. In embodiments, the cells are CD34+/CD90- stem cells. In embodiments, the cells are human hematopoietic stem cells. In embodiments, the cells are autologous. In embodiments, the cells are allogeneic.

In embodiments, the cells are derived from bone marrow, e.g., autologous bone marrow. In embodiments, the cells are derived from peripheral blood, e.g., mobilized peripheral blood, e.g., autologous mobilized peripheral blood. In embodiments employing moblized peripheral blood, the cells are isoalted from patients who have been administered a mobilization agent. In embodiments, the mobilization agent is G-CSF. In embodiments, the mobilization agent is Plerixafor® (AMD3100). In embodiments, the cells are derived from umbilical cord blood, e.g., allogeneic umbilical cord blood.

In embodiments, the cells are mammallian. In embodiments, the cells are human.

In an aspect, the invention provides a cell comprising a modification or alteration, e.g., an indel, at or near (e.g., within 20, 19, 18, 17, 16, 15, 14, 13, 12, 11, 10, 9, 8, 7, 6, 5, 4, 3, 2 or 1 nucleotides of) a nucleic acid sequence having complementarity to a gRNA molecule or gRNA molecules, e.g., as described herein, introduced into said cells, e.g., as part of a CRISPR system as described herein. In embodiments, the cell is a CD34+ cell. In embodiments, the altered or modified cell, e.g., CD34+ cell, maintains the ability to differentiate into cells of multiple lineages, e.g., maintains the ability to differentiate into cells of the erythroid lineage. In embodiments, the altered or modified cell, e.g., CD34+ cell, has undergone or is able to undergo at least 2, at least 3, at least 4, at least 5, at least 6, at least 7, at least 8, at least 9 or at least 10 or more doublings in culture, e.g., in culture comprising a stem cell expander, e.g., Compound 4. In embodiments, the altered or modified cell, e.g., CD34+ cell, has undergone or is able to undergo at least 5, e.g., about 5, doublings in culture, e.g., in culture comprising a stem cell expander molecule, e.g., as described herein, e.g., Compound 4. In embodiments the altered or modified cell, e.g., CD34+ cell, exhibits and/or is able to differentiate into a cell, e.g., into a cell of the erythroid lineage, e.g., into a red blood cell, that exhibits increased fetal hemoglobin level (e.g., expression level and/or protein level), e.g., at least a 20% increase in fetal hemoglobin protein level, relative to a similar unmodified or unaltered cell. In embodiments the altered or modified cell, e.g., CD34+ cell, exhibits and/or is able to differentiate into a cell, e.g., into a cell of the erythroid lineage, e.g., into a red blood cell, that exhibits increased fetal hemoglobin level (e.g., expression level and/or protein level), relative to a similar unmodified or unaltered cell, e.g., produces at least 6 picograms, e.g., at least 7 picograms, at least 8 picograms, at least 9 picograms, or at least 10 picograms of fetal hemoglobin. In embodiments the altered or modified cell, e.g., CD34+ cell, exhibits and/or is able to differentiate into a cell, e.g., into a cell of the erythroid lineage, e.g., into a red blood cell, that exhibits increased fetal hemoglobin level (e.g., expression level and/or protein level), relative to a similar unmodified or unaltered cell, e.g., produces about 6 to about 12, about about 6 to about 7, about 7 to about 8, about 8 to about 9, about 9 to about 10, about 10 to about 11 or about 11 to about 12 picograms of fetal hemoglobin.

In an aspect, the invention provides a population of cells comprising cells having a modification or alteration, e.g., an indel, at or near (e.g., within 20, 19, 18, 17, 16, 15, 14, 13, 12, 11, 10, 9, 8, 7, 6, 5, 4, 3, 2 or 1 nucleotides of) a nucleic acid sequence having complementarity to a gRNA molecule or gRNA molecules, e.g., as described herein, introduced into said cells, e.g., as part of a CRISPR system as described herein. In embodiments, at least 50%, e.g., at least 60%, at least 70%, at least 80% or at least 90% of the cells of the population have the modification or alteration (e.g., have at least one modification or alteration) , e.g., as measured by NGS, e.g., as described herein, e.g., at day two following introduction of the gRNA and/or CRISPR system of the invention. In embodiments, at least 90%, e.g., at least 91%, at least 92%, at least 93%, at least 94%, at least 95%, at least 96%, at least 97%, at least 98% or at least 99% of the cells of the population have the modification or alteration (e.g., have at least one modification or alteration), e.g., as measured by NGS, e.g., as described herein, e.g., at day two following introduction of the gRNA and/or CRISPR system of the invention. In embodiments, the population of cells comprise CD34+ cells, e.g., comprise at least about 50%, at least about 60%, at least about 70%, at least about 80%, at least about 90%, at least about 95% or at least about 98% CD34+ cells. In embodiments, the population of cells comprising the altered or modified cells, e.g., CD34+ cells, maintain the ability to produce, e.g., differentiate into, cells of multiple lineages, e.g., maintains the ability to produce, e.g., differentiate into, cells of the erythroid lineage. In embodiments, the population of cells, e.g., population of CD34+ cells, has undergone or is able to undergo at least 2, at least 3, at least 4, at least 5, at least 6, at least 7, at least 8, at least 9 or at least 10 or more population doublings in culture, e.g., in culture comprising a stem cell expander, e.g., Compound 4. In embodiments, the population of altered or modified cells, e.g., population of CD34+ cells, has undergone or is capable of undergoing at least 5, e.g., about 5, population doublings in culture, e.g., in culture comprising a stem cell expander molecule, e.g., as described herein, e.g., Compound 4. In embodiments the population of cells comprising altered or modified cells, e.g., CD34+ cells, exhibits and/or is able to differentiate into a population of cells, e.g., into a population of cells of the erythroid lineage, e.g., into a population of red blood cells, that exhibits increased fetal hemoglobin level (e.g., expression level and/or protein level), e.g., at least a 20% increase in fetal hemoglobin protein level, relative to a similar unmodified or unaltered cells. In embodiments the population of cells comprising altered or modified cells, e.g., CD34+ cells, exhibits and/or is able to differentiate into a population of cells, e.g., into a population of cells of the erythroid lineage, e.g., into a population of red blood cells, that exhibits increased fetal hemoglobin level (e.g., expression level and/or protein level), relative to a similar unmodified or unaltered cells, e.g., comprises cells that produce at least 6 picograms, e.g., at least 7 picograms, at least 8 picograms, at least 9 picograms, or at least 10 picograms of fetal hemoglobin per cell. In embodiments the population of altered or modified cells, e.g., CD34+ cells, exhibits and/or is able to differentiate into a population of cells, e.g., into a population of cells of the erythroid lineage, e.g., into a population of red blood cells, that exhibits increased fetal hemoglobin level (e.g., expression level and/or protein

level), relative to a similar unmodified or unaltered cell, e.g., comprises cells that produce about 6 to about 12, about about 6 to about 7, about 7 to about 8, about 8 to about 9, about 9 to about 10, about 10 to about 11 or about 11 to about 12 picograms of fetal hemoglobin per cell.

In embodiments, the population of cells, e.g., as described herein, comprises at least about 1e3 cells. In embodiments, the population of cells, e.g., as described herein, comprises at least about 1e4 cells. In embodiments, the population of cells, e.g., as described herein, comprises at least about 1e5 cells. In embodiments, the population of cells, e.g., as described herein, comprises at least about 1e6 cells. In embodiments, the population of cells, e.g., as described herein, comprises at least about 1e7 cells. In embodiments, the population of cells, e.g., as described herein, comprises at least about 1e8 cells. In embodiments, the population of cells, e.g., as described herein, comprises at least about 1e9 cells. In embodiments, the population of cells, e.g., as described herein, comprises at least about 1e10 cells. In embodiments, the population of cells, e.g., as described herein, comprises at least about 1e11 cells. In embodiments, the population of cells, e.g., as described herein, comprises at least about 1e12 cells. In embodiments, the population of cells, e.g., as described herein, comprises at least about 1e13 cells per kilogram body weight of the patient to which they are to be administered. In embodiments, the population of cells, e.g., as described herein, comprises at least about 1e6 cells per kilogram body weight of the patient to which they are to be administered. In embodiments, the population of cells, e.g., as described herein, comprises at least about 2e6 cells per kilogram body weight of the patient to which they are to be administered. In embodiments, the population of cells, e.g., as described herein, comprises at least about 3e6 cells per kilogram body weight of the patient to which they are to be administered. In embodiments, the population of cells, e.g., as described herein, comprises at least about 4e6 cells per kilogram body weight of the patient to which they are to be administered. In embodiments, the population of cells, e.g., as described herein, comprises at least about 5e6 cells per kilogram body weight of the patient to which they are to be administered. In embodiments, the population of cells, e.g., as described herein, comprises at least about 6e6 cells per kilogram body weight of the patient to which they are to be administered. In embodiments, the population of cells, e.g., as described herein, comprises at least about 7e6 cells per kilogram body weight of the patient to which they are to be administered. In embodiments, the population of cells, e.g., as described herein, comprises at least about 8e6 cells per kilogram body weight of the patient to which they are to be administered. In embodiments, the population of cells, e.g., as described herein, comprises at least about 9e6 cells per kilogram body weight of the patient to which they are to be administered. In embodiments, the population of cells, e.g., as described herein, comprises at least about 1e7 cells per kilogram body weight of the patient to which they are to be administered. In embodiments, the population of cells, e.g., as described herein, comprises at least about 2e7 cells per kilogram body weight of the patient to which they are to be administered. In embodiments, the population of cells, e.g., as described herein, comprises at least about 3e7 cells per kilogram body weight of the patient to

which they are to be administered. In embodiments, the population of cells, e.g., as described herein, comprises at least about 4e7 cells per kilogram body weight of the patient to which they are to be administered. In embodiments, the population of cells, e.g., as described herein, comprises at least about 5e7 cells per kilogram body weight of the patient to which they are to be administered. In embodiments, the population of cells, e.g., as described herein, comprises at least about 6e7 cells per kilogram body weight of the patient to which they are to be administered. In embodiments, the population of cells, e.g., as described herein, comprises at least about 7e7 cells per kilogram body weight of the patient to which they are to be administered. In embodiments, the population of cells, e.g., as described herein, comprises at least about 8e7 cells per kilogram body weight of the patient to which they are to be administered. In embodiments, the population of cells, e.g., as described herein, comprises at least about 9e7 cells per kilogram body weight of the patient to which they are to be administered. In embodiments, the population of cells, e.g., as described herein, comprises at least about 1e8 cells per kilogram body weight of the patient to which they are to be administered. In any of the aforementioned embodiments, the population of cells may comprise at least about 50% (for example, at least about 60%, at least about 70%, at least about 80%, at least about 90%, at least about 95% or at least about 99%) HSPCs, e.g., CD34+ cells. In any of the aforementioned embodiments, the population of cells may comprise about 60% HSPCs, e.g., CD34+ cells. In an embodiment, the population of cells, e.g., as described herein, comprises about 3e7 cells and comprises about 2e7 HSPCs, e.g., CD34+ cells.

In embodiments, the population of cells, e.g., as described herein, comprises at least about 1e6 HSPCs, e.g., CD34+ cells, per kilogram body weight of the patient to which they are to be administered. In embodiments, the population of cells, e.g., as described herein, comprises at least about 1.5e6 HSPCs, e.g., CD34+ cells, per kilogram body weight of the patient to which they are to be administered. In embodiments, the population of cells, e.g., as described herein, comprises at least about 2e6 HSPCs, e.g., CD34+ cells, per kilogram body weight of the patient to which they are to be administered. In embodiments, the population of cells, e.g., as described herein, comprises at least about 3e6 HSPCs, e.g., CD34+ cells, per kilogram body weight of the patient to which they are to be administered. In embodiments, the population of cells, e.g., as described herein, comprises at least about 4e6 HSPCs, e.g., CD34+ cells, per kilogram body weight of the patient to which they are to be administered. In embodiments, the population of cells, e.g., as described herein, comprises at least about 5e6 HSPCs, e.g., CD34+ cells, per kilogram body weight of the patient to which they are to be administered. In embodiments, the population of cells, e.g., as described herein, comprises at least about 6e6 HSPCs, e.g., CD34+ cells, per kilogram body weight of the patient to which they are to be administered. In embodiments, the population of cells, e.g., as described herein, comprises at least about 7e6 HSPCs, e.g., CD34+ cells, per kilogram body weight of the patient to which they are to be administered. In embodiments, the population of cells, e.g., as described herein, comprises at least

about 8e6 HSPCs, e.g., CD34+ cells, per kilogram body weight of the patient to which they are to be administered. In embodiments, the population of cells, e.g., as described herein, comprises at least about 9e6 HSPCs, e.g., CD34+ cells, per kilogram body weight of the patient to which they are to be administered. In embodiments, the population of cells, e.g., as described herein, comprises at least about 1e7 HSPCs, e.g., CD34+ cells, per kilogram body weight of the patient to which they are to be administered. In embodiments, the population of cells, e.g., as described herein, comprises at least about 2e7 HSPCs, e.g., CD34+ cells, per kilogram body weight of the patient to which they are to be administered. In embodiments, the population of cells, e.g., as described herein, comprises at least about 3e7 HSPCs, e.g., CD34+ cells, per kilogram body weight of the patient to which they are to be administered. In embodiments, the population of cells, e.g., as described herein, comprises at least about 4e7 HSPCs, e.g., CD34+ cells, per kilogram body weight of the patient to which they are to be administered. In embodiments, the population of cells, e.g., as described herein, comprises at least about 5e7 HSPCs, e.g., CD34+ cells, per kilogram body weight of the patient to which they are to be administered. In embodiments, the population of cells, e.g., as described herein, comprises at least about 6e7 HSPCs, e.g., CD34+ cells, per kilogram body weight of the patient to which they are to be administered. In embodiments, the population of cells, e.g., as described herein, comprises at least about 7e7 HSPCs, e.g., CD34+ cells, per kilogram body weight of the patient to which they are to be administered. In embodiments, the population of cells, e.g., as described herein, comprises at least about 8e7 HSPCs, e.g., CD34+ cells, per kilogram body weight of the patient to which they are to be administered. In embodiments, the population of cells, e.g., as described herein, comprises at least about 9e7 HSPCs, e.g., CD34+ cells, per kilogram body weight of the patient to which they are to be administered. In embodiments, the population of cells, e.g., as described herein, comprises at least about 1e8 HSPCs, e.g., CD34+ cells, per kilogram body weight of the patient to which they are to be administered. In embodiments, the population of cells, e.g., as described herein, comprises at least about 2e8 HSPCs, e.g., CD34+ cells, per kilogram body weight of the patient to which they are to be administered. In embodiments, the population of cells, e.g., as described herein, comprises at least about 3e8 HSPCs, e.g., CD34+ cells, per kilogram body weight of the patient to which they are to be administered. In embodiments, the population of cells, e.g., as described herein, comprises at least about 4e8 HSPCs, e.g., CD34+ cells, per kilogram body weight of the patient to which they are to be administered. In embodiments, the population of cells, e.g., as described herein, comprises at least about 5e8 HSPCs, e.g., CD34+ cells, per kilogram body weight of the patient to which they are to be administered.

In embodiments, the population of cells, e.g., as described herein, comprises about 1e6 HSPCs, e.g., CD34+ cells, per kilogram body weight of the patient to which they are to be administered. In embodiments, the population of cells, e.g., as described herein, comprises about 1.5e6 HSPCs, e.g., CD34+ cells, per kilogram body weight of the patient to which they are to be

administered. In embodiments, the population of cells, e.g., as described herein, comprises about 2e6 HSPCs, e.g., CD34+ cells, per kilogram body weight of the patient to which they are to be administered. In embodiments, the population of cells, e.g., as described herein, comprises about 3e6 HSPCs, e.g., CD34+ cells, per kilogram body weight of the patient to which they are to be administered. In embodiments, the population of cells, e.g., as described herein, comprises about 4e6 HSPCs, e.g., CD34+ cells, per kilogram body weight of the patient to which they are to be administered. In embodiments, the population of cells, e.g., as described herein, comprises about 5e6 HSPCs, e.g., CD34+ cells, per kilogram body weight of the patient to which they are to be administered. In embodiments, the population of cells, e.g., as described herein, comprises about 6e6 HSPCs, e.g., CD34+ cells, per kilogram body weight of the patient to which they are to be administered. In embodiments, the population of cells, e.g., as described herein, comprises about 7e6 HSPCs, e.g., CD34+ cells, per kilogram body weight of the patient to which they are to be administered. In embodiments, the population of cells, e.g., as described herein, comprises about 8e6 HSPCs, e.g., CD34+ cells, per kilogram body weight of the patient to which they are to be administered. In embodiments, the population of cells, e.g., as described herein, comprises about 9e6 HSPCs, e.g., CD34+ cells, per kilogram body weight of the patient to which they are to be administered. In embodiments, the population of cells, e.g., as described herein, comprises about 1e7 HSPCs, e.g., CD34+ cells, per kilogram body weight of the patient to which they are to be administered. In embodiments, the population of cells, e.g., as described herein, comprises about 2e7 HSPCs, e.g., CD34+ cells, per kilogram body weight of the patient to which they are to be administered. In embodiments, the population of cells, e.g., as described herein, comprises about 3e7 HSPCs, e.g., CD34+ cells, per kilogram body weight of the patient to which they are to be administered. In embodiments, the population of cells, e.g., as described herein, comprises about 4e7 HSPCs, e.g., CD34+ cells, per kilogram body weight of the patient to which they are to be administered. In embodiments, the population of cells, e.g., as described herein, comprises about 5e7 HSPCs, e.g., CD34+ cells, per kilogram body weight of the patient to which they are to be administered. In embodiments, the population of cells, e.g., as described herein, comprises about 6e7 HSPCs, e.g., CD34+ cells, per kilogram body weight of the patient to which they are to be administered. In embodiments, the population of cells, e.g., as described herein, comprises about 7e7 HSPCs, e.g., CD34+ cells, per kilogram body weight of the patient to which they are to be administered. In embodiments, the population of cells, e.g., as described herein, comprises about 8e7 HSPCs, e.g., CD34+ cells, per kilogram body weight of the patient to which they are to be administered. In embodiments, the population of cells, e.g., as described herein, comprises about 9e7 HSPCs, e.g., CD34+ cells, per kilogram body weight of the patient to which they are to be administered. In embodiments, the population of cells, e.g., as described herein, comprises about 1e8 HSPCs, e.g., CD34+ cells, per kilogram body weight of the patient to which they are to be administered. In embodiments, the population of cells, e.g., as described herein, comprises about 2e8

HSPCs, e.g., CD34+ cells, per kilogram body weight of the patient to which they are to be administered. In embodiments, the population of cells, e.g., as described herein, comprises about 3e8 HSPCs, e.g., CD34+ cells, per kilogram body weight of the patient to which they are to be administered. In embodiments, the population of cells, e.g., as described herein, comprises about 4e8 HSPCs, e.g., CD34+ cells, per kilogram body weight of the patient to which they are to be administered. In embodiments, the population of cells, e.g., as described herein, comprises about 5e8 HSPCs, e.g., CD34+ cells, per kilogram body weight of the patient to which they are to be administered.

In embodiments, the population of cells, e.g., as described herein, comprises from about 2e6 to about 10e6 HSPCs, e.g., CD34+ cells, per kilogram body weight of the patient to which they are to be administered. In embodiments, the population of cells, e.g., as described herein, comprises from 2e6 to 10e6 HSPCs, e.g., CD34+ cells, per kilogram body weight of the patient to which they are to be administered.

The cells of the invention may comprise a gRNA molecule of the present invention, or nucleic acid encoding said gRNA molecule, and a Cas9 molecule of the present invention, or nucleic acid encoding said Cas9 molecule. In an embodiment, the cells of the invention may comprise a ribonuclear protein (RNP) complex which comprises a gRNA molecule of the invention and a Cas9 molecule of the invention.

The cells of the invention are preferrably modified to comprise a gRNA molecule of the invention ex vivo, for example by a method described herein, e.g., by electroporation.

The cells of the invention include cells in which expression of one or more genes has been altered, for example, reduced or inhibited, by introduction of a CRISPR system comprising a gRNA of the invention. For example, the cells of the present invention may have a reduced level of BCL11a expression relative to unmodified cells. As another example, the cells of the present invention may have an increased level of fetal hemoglobin expression relative to unmodified cells. As another example, the cells of the present invention may have reduced level of beta globin exprsesion relative to unmodified cells. Alternatively, or in addition, a cell of the invention may give rise, e.g., differentiate into, another type of cell, e.g., an erythrocyte, that has a reduced level of BCL11a expression relative to cells differentiated from unmodified cells. Alternatively, or in addition, a cell of the invention may give rise, e.g., differentiate into, another type of cell, e.g., an erythrocyte, that has an increased level of fetal hemoglobin expression relative to cells differentiated from unmodified cells. Alternatively, or in addition, a cell of the invention may give rise, e.g., differentiate into, another type of cell, e.g., an erythrocyte, that has a reduced level of beta globin expression relative to cells differentiated from unmodified cells.

The cells of the invention include cells in which expression of one or more genes has been altered, for example, reduced or inhibited, by introduction of a CRISPR system comprising a gRNA of the invention. For example, the cells of the present invention may have a reduced level of hemeoglobin beta, for example a mutated or wild-type hemoglobin beta, expression relative to unmodified cells. In another aspect, the invention provides cells which are derived from, e.g., differentiated from, cells in which a CRISPR system comprising a gRNA of the invention has been introduced. In such aspects, the cells in which the CRISPR system comprising the gRNA of the invention has been introduced may not exhibit the reduced level of hemoglobin beta, for example a mutated or wild-type hemoglobin beta, but the cells derived from, e.g., differentiated from, said cells exhibit the reduced level of hemoglobin beta, for example a mutated or wild-type hemoglobin beta. In embodiments, the derivation, e.g., differentation, is accomplished in vivo (e.g., in a patient). In embodiments the cells in which the CRISPR system comprising the gRNA of the invention has been introduced are CD34+ cells and the cells derived, e.g., differentiated, therefrom are of the erythroid lineage, e.g., red blood cells.

The cells of the invention include cells in which expression of one or more genes has been altered, for example, increased or promoted, by introduction of a CRISPR system comprising a gRNA of the invention. For example, the cells of the present invention may have an increased level of fetal hemoglobin expression relative to unmodified cells. In another aspect, the invention provides cells which are derived from, e.g., differentiated from, cells in which a CRISPR system comprising a gRNA of the invention has been introduced. In such aspects, the cells in which the CRISPR system comprising the gRNA of the invention has been introduced may not exhibit the increased level of fetal hemoglobin but the cells derived from, e.g., differentiated from, said cells exhibit the increased level of fetal hemoglobin. In embodiments, the derivation, e.g., differentation, is accomplished in vivo (e.g., in a patient). In embodiments the cells in which the CRISPR system comprising the gRNA of the invention has been introduced are CD34+ cells and the cells derived, e.g., differentiated, therefrom are of the erythroid lineage, e.g., red blood cells.

In another aspect, the invention relates to cells which include an indel at (e.g., within) or near (e.g., within 20, 19, 18, 17, 16, 15, 14, 13, 12, 11, 10, 9, 8, 7, 6, 5, 4, 3, 2 or 1 nucleotides of) a nucleic acid sequence having complementarity to the gRNA molecule or gRNA molecules introduced into said cells. In embodiments, the indel is a frameshift indel. In embodiments, the indel is an indel listed in Table 15. In embodiments, the indel is an indel listed in Table 26, Table 27 or Table 37. In embodiments the invention pertains to a population of cells, e.g., as described herein, wherein the population of cells comprises cells having an indel listed in Table 15. In embodiments the invention pertains to a population of cells, e.g., as described herein, wherein the population of cells comprises cells having an indel listed in Table 26, Table 27 or Table 37.

In an aspect, the invention relates to a population of cells, e.g., a population of HSPCs, which comprises cells which include an indel, e.g., as described herein, e.g., an indel or pattern of indels described in Figure 25, Table 15, Table 26, Table 27 or Table 37, at or near (e.g., within 20, 19, 18, 17, 16, 15, 14, 13, 12, 11, 10, 9, 8, 7, 6, 5, 4, 3, 2 or 1 nucleotides of) a nucleic acid sequence having complementarity to a gRNA molecule or gRNA molecules, e.g., as described herein, introduced into said cells, e.g., as described herein. In embodiments, the indel is a frameshift indel. In embodiments, 20%-100% of the cells of the population include said indel or indels. In embodiments, 30%-100% of the cells of the population include said indel or indels. In embodiments, 40%-100% of the cells of the population include said indel or indels. In embodiments, 50%-100% of the cells of the population include said indel or indels. In embodiments, 60%-100% of the cells of the population include said indel or indels. In embodiments, 70%-100% of the cells of the population include said indel or indels. In embodiments, 80%-100% of the cells of the population include said indel or indels. In embodiments, 90%-100% of the cells of the population include said indel or indels. In embodiments, the population of cells retains the ability to differentiate into multiple cell types, e.g., maintains the ability to differentiate into cells of erythroid lineage, e.g., red blood cells. In embodiments, the edited and differentiated cells (e.g., red blood cells) maintain the ability to proliferate, e.g., proliferate at least 5-fold, at least 10-fold, at least 15-fold, at least 20-fold, at least 25-fold, at least 30-fold, at least 35-fold, at least 40-fold, at least 45-fold, at least 50-fold or more after 7 days in erythroid differentiation medium (EDM), e.g., as described in the Examples, and/or, proliferate at least 30-fold, at least 35-fold, at least 40-fold, at least 45-fold, at least 50-fold, at least 55-fold, at least 60-fold, at least 65-fold, at least 70-fold, at least 75-fold, at least 80-fold, at least 85-fold, at least 90-fold, at least 95-fold, at least 100-fold, at least 110-fold, at least 120-fold, at least 130-fold, at least 140-fold, at least 150-fold, at least 200-fold, at least 300-fold, at least 400-fold, at least 500-fold, at least 600-fold, at least 700-fold, at least 800-fold, at least 900-fold, at least 1000-fold, at least 1100-fold, at least 1200-fold, at least 1300-fold, at least 1400-fold, at least 1500-fold or more after 21 days in erythroid differentiation medium (EDM), e.g., as described in the Examples,

In an embodiment, the invention provides a population of cells, e.g., CD34+ cells, of which at least 90%, e.g., at least 95%, e.g., at least 98%, of the cells of the population comprise an indel, e.g., as described herein (without being bound by theory, it is believed that introduction of a gRNA molecule or CRISPR system as described herein into a populaiton of cells produces a pattern of indels in said population, and thus, each cell of the population which comprises an indel may not exhibit the same indel), at or near a site complementary to the targeting domain of a gRNA molecule described herein; whrein said cells maintain the ability to differentiate into cells of an erythroid lineage, e.g., red blood cells; and/or wherein said cells differentiated from the population of cells have an increased level of fetal hemoglobin (e.g., the population has a higher % F cells) relative to cells differentiated from a

similar population of unmodified cells. In embodiments, the population of cells has undergone at least a 5-fold expansion ex vivo, e.g., in the media comprising Compound 4.

In embodiments, the indel is less than about 50 nucleotides, e.g., less than about 45, less than about 40, less than about 35, less than about 30 or less than about 25 nucelotides. In embodiments, the indel is less than about 25 nucleotides. In embodiments, the indel is less than about 20 nucleotides. In embodiments, the indel is less than about 15 nucelotides. In embodiments, the indel is less than about 10 nucleotides. In embodiments, the indel is less than about 9 nucleotides. In embodiments, the indel is less than about 9 nucleotides. In embodiments, the indel is less than about 7 nucleotides. In embodiments, the indel is less than about 6 nucleotides. In embodiments, the indel is less than about 5 nucleotides. In embodiments, the indel is less than about 4 nucleotides. In embodiments, the indel is less than about 3 nucleotides. In embodiments, the indel is less than about 2 nucleotides. In any of the aforementioned embodiments, the indel is at least 1 nucleotide. In embodiments, the indel is 1 nucleotide.

In an aspect, the invention provides a population of modified HSPCs or erythroid cells differentiated from said HSPCs (e.g., differentiated ex vivo or in a patient), e.g., as described herein, wherein at least 15%, at least 20%, at least 25%, at least 30%, at least 35%, at least 40%, at least 45%, at least 50%, at least 55%, at least 60%, at least 65%, at least 70%, at least 75%, at least 80%, at least 85%, at least 90%, or at least 95% of the cells are F cells. In embodiments, the population of cells contains (or is capable of differentiating, e.g., in vivo, into a population of erythrocytes that contains) a higher percent of F cells than a similar population of cells which have not had a gRNA molecule or gRNA molecules, e.g., as described herein, introduced into said cells. In embodiments, the population of cells has (or is capable of differentiating, e.g., in vivo, into a population of erythrocytes that has) at least a 20% increase, e.g, at least 21% increase, at least 22% increase, at least 23% increase, at least 24% increase, at least 25% increase, at least 26% increase, at least 27% increase, at least 28% increase, or at least 29% increase, in F cells relative to the similar population of cells which have not had a gRNA molecule or gRNA molecules, e.g., as described herein, introduced into said cells. In embodiments, the population of cells has (or is capable of differentiating, e.g., in vivo, into a population of erythrocytes that has) at least a 30% increase, e.g., at least a 35% increase, at least a 40% increase, at least a 45% increase, at least a 50% increase, at least a 55% increase, at least a 60% increase, at least a 65% increase, at least a 70% increase, at least a 75% increase, at least a 80% increase, at least a 85% increase, at least a 90% increase or at least a 95% increase, in F cells relative to the similar population of cells which have not had a gRNA molecule or gRNA molecules, e.g., as described herein, introduced into said cells. In embodiments, the population of cells has (or is capable of differentiating, e.g., in vivo, into a population of erythrocytes that has) at a 10-90%, a 20%-80%, a 20%-70%, a 20%-60%, a 20%-50%, a 20%-40%, a 20%-30%, a 25%-80%, a 25%-70%, a 25%-60%, a 25%-50%, a 25%-40%, a 25%-35%, a 25%-30%, a 30%-80%, a 30%-70%, a 30%-60%,

a 30%-50%, a 30%-40%, or a 30%-35% increase in F cells relative to the similar population of cells which have not had a gRNA molecule or gRNA molecules, e.g., as described herein, introduced into said cells.In embodiments, the population of cells, e.g., as produced by a method described herein, comprises a sufficient number or cells and/or a sufficient increase in % F cells to treat a hemoglobinopathy, e.g., as described herein, e.g., sickle cell disease and/or beta thalassemia, in a patient in need thereof when introduced into said patient, e.g., in a therapeutically effective amount. In embodiments, the increase in F cells is as measured in an erythroid differentiation assay, e.g., as described herein.

In embodiments, including in any of the embodiments and aspects described herein, the invention relates to a cell, e.g., a population of cells, e.g., as modified by any of the gRNA, methods and/or CRISPR systems described herein, comprising F cells that produce at least 6 picograms fetal hemoglobin per cell. In embodiments, the F cells produce at least 7 picograms fetal hemoglobin per cell. In embodiments, the F cells produce at least 8 picograms fetal hemoglobin per cell. In embodiments, the F cells produce at least 9 picograms fetal hemoglobin per cell. In embodiments, the F cells produce at least 10 picograms fetal hemoglobin per cell. In embodiments, the F cells produce an average of between 6.0 and 7.0 picograms, between 7.0 and 8.0, between 8.0 and 9.0, between 9.0 and 10.0, between 10.0 and 11.0, or between 11.0 and 12.0 picograms of fetal hemoglobin per cell.

In embodiments, including in any of the aforementioned embodiments, the cell and/or population of cells of the invention includes, e.g., consists of, cells which do not comprise nucleic acid encoding a Cas9 molecule.

Methods of Treatment

Delivery Timing

In an embodiment, one or more nucleic acid molecules (e.g., DNA molecules) other than the components of a Cas system, e.g., the Cas9 molecule component and/or the gRNA molecule component described herein, are delivered. In an embodiment, the nucleic acid molecule is delivered at the same time as one or more of the compoments of the Cas system are delivered. In an embodiment, the nucleic acid molecule is delivered before or after (e.g., less than about 30 minutes, 1 hour, 2 hours, 3 hours, 6 hours, 9 hours, 12 hours, 1 day, 2 days, 3 days, 1 week, 2 weeks, or 4 weeks) one or more of the components of the Cas system are delivered. In an embodiment, the nucleic acid molecule is delivered by a different means than one or more of the components of the Cas system, e.g., the Cas9 molecule component and/or the gRNA molecule compoment, are delivered. The nucleic acid molecule can be delivered by any of the delivery methods described herein. For example, the nucleic acid molecule can be delivered by a viral vector, e.g., an integration-deficient lentivirus, and the Cas9 molecule component and/or the gRNA molecule component can be delivered by

electroporation, e.g., such that the toxicity caused by nucleic acids (e.g., DNAs) can be reduced. In an embodiment, the nucleic acid molecule encodes a therapeutic protein, e.g., a protein described herein. In an embodiment, the nucleic acid molecule encodes an RNA molecule, e.g, an RNA molecule described herein.

Bi-modal or Differential Delivery of Components

Separate delivery of the components of a Cas system, e.g., the Cas9 molecule component and the gRNA molecule component, and more particularly, delivery of the components by differing modes, can enhance performance, e.g., by improving tissue specificity and safety. In an embodiment, the Cas9 molecule and the gRNA molecule are delivered by different modes, or as sometimes referred to herein as differential modes. Different or differential modes, as used herein, refer modes of delivery, that confer different pharmacodynamic or pharmacokinetic properties on the subject component molecule, e.g., a Cas9 molecule, gRNA molecule, template nucleic acid, or payload. E.g., the modes of delivery can result in different tissue distribution, different half-life, or different temporal distribution, e.g., in a selected compartment, tissue, or organ.

Some modes of delivery, e.g., delivery by a nucleic acid vector that persists in a cell, or in progeny of a cell, e.g., by autonomous replication or insertion into cellular nucleic acid, result in more persistent expression of and presence of a component. Examples include viral, e.g., adeno associated virus or lentivirus, delivery.

By way of example, the components, e.g., a Cas9 molecule and a gRNA molecule, can be delivered by modes that differ in terms of resulting half life or persistent of the delivered component the body, or in a particular compartment, tissue or organ. In an embodiment, a gRNA molecule can be delivered by such modes. The Cas9 molecule component can be delivered by a mode which results in less persistence or less exposure of its to the body or a particular compartment or tissue or organ.

More generally, in an embodiment, a first mode of delivery is used to deliver a first component and a second mode of delivery is used to deliver a second component. The first mode of delivery confers a first pharmacodynamic or pharmacokinetic property. The first pharmacodynamic property can be, e.g., distribution, persistence, or exposure, of the component, or of a nucleic acid that encodes the component, in the body, a compartment, tissue or organ. The second mode of delivery confers a second pharmacodynamic or pharmacokinetic property. The second pharmacodynamic property can be, e.g., distribution, persistence, or exposure, of the component, or of a nucleic acid that encodes the component, in the body, a compartment, tissue or organ.

In an embodiment, the first pharmacodynamic or pharmacokinetic property, e.g., distribution, persistence or exposure, is more limited than the second pharmacodynamic or pharmacokinetic property.

In an embodiment, the first mode of delivery is selected to optimize, e.g., minimize, a pharmacodynamic or pharmacokinetic property, e.g., distribution, persistence or exposure.

In an embodiment, the second mode of delivery is selected to optimize, e.g., maximize, a pharmacodynamic or pharmcokinetic property, e.g., distribution, persistence or exposure.

In an embodiment, the first mode of delivery comprises the use of a relatively persistent element, e.g., a nucleic acid, e.g., a plasmid or viral vector, e.g., an AAV or lentivirus. As such vectors are relatively persistent product transcribed from them would be relatively persistent.

In an embodiment, the second mode of delivery comprises a relatively transient element, e.g., an RNA or protein.

In an embodiment, the first component comprises gRNA, and the delivery mode is relatively persistent, e.g., the gRNA is transcribed from a plasmid or viral vector, e.g., an AAV or lentivirus. Transcription of these genes would be of little physiological consequence because the genes do not encode for a protein product, and the gR As are incapable of acting in isolation. The second component, a Cas9 molecule, is delivered in a transient manner, for example as mRNA or as protein, ensuring that the full Cas9 molecule/gRNA molecule complex is only present and active for a short period of time.

Furthermore, the components can be delivered in different molecular form or with different delivery vectors that complement one another to enhance safety and tissue specificity.

Use of differential delivery modes can enhance performance,' safety and efficacy. For example, the likelihood of an eventual off-target modification can be reduced. Delivery of immunogenic components, e.g., Cas9 molecules, by less persistent modes can reduce immunogenicity, as peptides from the bacterially-derived Cas enzyme are displayed on the surface of the cell by MHC molecules. A two-part deliveiy system can alleviate these drawbacks.

Differential delivery modes can be used to deliver components to different, but overlapping target regions. The formation active complex is minimized outside the overlap of the target regions. Thus, in an embodiment, a first component, e.g., a gRNA molecule is delivered by a first delivery mode that results in a first spatial, e.g., tissue, distribution. A second component, e.g., a Cas9 molecule is delivered by a second delivery mode that results in a second spatial, e.g., tissue, distribution. In an embodiment, the first mode comprises a first element selected from a liposome, nanoparticle, e.g., polymeric nanoparticle, and a nucleic acid, e.g., viral vector. The second mode comprises a second element selected from the group. In an embodiment, the first mode of delivery comprises a first targeting element, e.g., a cell specific receptor or an antibody, and the second mode of delivery does not include that element. In an embodiment, the second mode of delivery comprises a second targeting element, e.g., a second cell specific receptor or second antibody.

When the Cas9 molecule is delivered in a virus delivery vector, a liposome, or polymeric nanoparticle, there is the potential for delivery to and therapeutic activity in multiple tissues, when it may be desirable to only target a single tissue. A two-part delivery system can resolve this challenge and enhance tissue specificity. If the gRNA molecule and the Cas9 molecule are packaged in separated delivery vehicles with distinct but overlapping tissue tropism, the fully functional complex is only be formed in the tissue that is targeted by both vectors.

Candidate Cas molecules, e.g., Cas9 molecules, candidate gRNA molecules, candidate Cas9 molecule/gRNA molecule complexes, and candidate CRISPR systems, can be evaluated by art-known methods or as described herein. For example, exemplary methods for evaluating the endonuclease activity of Cas9 molecule are described, e.g., in Jinek el al., SCIENCE 2012; 337(6096):8 16-821.

EXAMPLES

Example 1

Guide Selection and Design

Initial guide selection was performed *in silico* using a human reference genome and user defined genomic regions of interest (e.g., a gene, an exon of a gene, non-coding regulatory region, etc), for identifying PAMs in the regions of interest. For each identified PAM, analyses were performed and statistics reported. gRNA molecules were further selected and rank-ordered based on a number of methods for determining efficiency and efficacy, e.g., as described herein.

Throughout the Examples, in the experiments below, either sgRNA molecules or dgRNA molecules were used. Unless indicated otherwise, where dgRNA molecules were used, the gRNA includes the following:

crRNA: [targeting domain]-[SEQ ID NO: 6607]

tracr (trRNA): SEQ ID NO: 6660

Unless indicated otherwise, in experiments employing a sgRNA molecule, the following sequence was used:

[targeting domain]-[SEQ ID NO: 6601]-UUUU

Unless inidicated otherwise, in experiments employing a sgRNA molecule labeled “BC”, the following sequence was used:

[targeting domain]-[SEQ ID NO: 6604]-UUUU

Transfection of HEK-293 Cas9GFP Cells for Primary Guide Screening

Transfection of Cas9GFP-expressing HEK293 cells (HEK-293_Cas9GFP) was used for primary screening of target specific crRNAs. In this example, target specific crRNAs were designed and selected for primary screening using defined criteria including *in silico* off-target detection, e.g., as described herein. Selected crRNAs were chemically synthesized and delivered in a 96 well format. HEK-293-Cas9GFP cells were transfected with target crRNAs in a 1:1 ratio with stock trRNA. The transfection was mediated using lipofection technology according to manufacturer's protocol (Lipofectamine 2000, Life Technologies). Transfected cells were lysed 24h following lipofection and editing (e.g., cleavage) was detected within lysates with the T7E1 assay and/or next generation sequencing (NGS; below).

T7E1 Assay

The T7E1 assay was used to detect mutation events in genomic DNA such as insertions, deletions and substitutions created through non-homologous end joining (NHEJ) following DNA cleavage by Cas9 (See Cho et al., Targeted genome engineering in human cells with the Cas9 RNA-guided endonuclease. *Nature Biotechnology.* 2013; **31**, 230–232).

Genomic DNA regions that have been targeted for cutting by CRISPR/Cas9 were amplified by PCR, denatured at 95°C for 10 minutes, and then re-annealed by ramping down from 95°C to 25°C at 0.5°C per second. If mutations were present within the amplified region, the DNA combined to form heteroduplexes. The re-annealed heteroduplexes were then digested with T7E1 (New England Biolabs) at 37°C for 25 minutes or longer. T7E1 endonuclease recognizes DNA mismatches, heteroduplexes and nicked double stranded DNA and generates a double stranded break at these sites. The resulting DNA fragments were analyzed using a Fragment Analyzer and quantified to determine cleavage efficiency.

Next-Generation Sequencing (NGS) and Analysis for On-Target Cleavage Efficiency and Indel Formation

To determine the efficiency of editing (e.g., cleaving) the target location in the genome, deep sequencing was utilized to identify the presence of insertions and deletions introduced by non-homologous end joining.

PCR primers were first designed around the target site, and the genomic area of interest PCR amplified. Additional PCR was performed according to manufacturer's protocols (Illumina) to add the necessary chemistry for sequencing. The amplicons were then sequenced on an Illumina MiSeq instrument. The reads were then aligned to the human reference genome (e.g., hg38) after eliminating those having low quality scores. From the resulting files containing the reads mapped to the reference genome (BAM files), reads which overlap the target region of interest were selected and the number

of wild type reads versus the number of reads which contain an insertion or deletion was calculated. The editing percentage was then defined as the total number of reads with insertions or deletions over the total number of reads, including wild type. To determine the pattern of insertions and/or deletions that resulted from the edit, the aligned reads with indels were selected and the number of a reads with a given indel were summed. This information was then displayed as a list as well as visualized in the form on histograms which represent the frequency of each indel.

RNP generation

The addition of crRNA and trRNA to Cas9 protein results in the formation of the active Cas9 ribonucleoprotein complex (RNP), which mediates binding to the target region specified by the crRNA and specific cleavage of the targeted genomic DNA. This complex was formed by loading trRNA and crRNA into Cas9, which is believed to cause conformational changes to Cas9 allowing it to bind and cleave dsDNA.

The crRNA and trRNA were separately denatured at 95°C for 2 minutes, and allowed to come to room temperature. Cas9 protein (10mg/ml) was added to 5X CCE buffer (20mM HEPES, 100mM KCl, 5mM $MgCl_2$, 1mM DTT, 5% glycerol), to which trRNA and the various crRNAs were then added (in separate reactions) and incubated at 37°C for 10 minutes, thereby forming the active RNP complex. The complex was delivered by electroportation and other methods into a wide variety of cells, including HEK-293 and CD34+ hematopoietic cells.

Delivery of RNPs to CD34+ HSCs

Cas9 RNPs were delivered into CD34+ HSCs.

CD34+ HSCs were thawed and cultured (at ~500,000 cells/ml) overnight in StemSpan SFEM (StemCell Technologies) media with IL12, SCF, TPO, Flt3L and Pen/Strep added. Roughly 90,000 cells were aliquoted and pelleted per each RNP delivery reaction. The cells were then resuspended in 60ul P3 nucleofection buffer (Lonza), to which active RNP was subsequently added. The HSCs were then electroporated (e.g., nucleofected using program CA-137 on a Lonza Nucleofector) in triplicate (20 uL/electroporation). Immediately following electroporation, StemSpan SFEM media (with IL12, SCF, TPO, Flt3L and Pen/Strep) was added to the HSCs, which were cultured for at least 24 hours. HSCs were then harvested and subjected to T7E1, NGS, and/or surface marker expression analyses.

HSC Functional Assay

CD34+ HSCs may be assayed for stem cell phenotype using known techniques such as flow cytometry or the in vitro colony forming assay. By way of example, cells were assayed by the in vitro colony forming assay (CFC) using the Methocult H4034 Optimum kit (StemCell Technologies) using the manufacturer's protocol. Briefly, 500-2000 CD34+ cells in <=100ul volume are added to 1-

1.25ml methocult. The mixture was vortexed vigorously for 4-5 seconds to mix thoroughly, then allowed to rest at room temperature for at least 5 minutes. Using a syringe, 1-1.25ml of MethoCult + cells was transferred to a 35mm dish or well of a 6-well plate. Colony number and morphology was assessed after 12-14 days as per the manufacturer's protocol.

***In vivo* xeno-transplantation**

HSCs are functionally defined by their ability to self-renew and for multi-lineage differentiation. This functionality can only be assessed in vivo. The gold-standard for determining human HSC function is through xeno-transplantation into the NOD-SCID gamma mouse (NSG) that through a series of mutations is severely immunocompromised and thus can act as a recipient for human cells. HSCs following editing will be transplanted into NSG mice to validate that the induced edit does not impact HSC function. Monthly peripheral blood analysis will be used to assess human chimerism and lineage development and secondary transplantation following 20 weeks will be used to establish the presence of functional HSCs.

Results

The results of editing using gRNA molecules (e.g., dgRNA molecules as describe above) described herein, in HEK293_Cas9GFP cells, as assayed by T7E1 ("T7") and/or NGS are summarized in Figure 1 (gRNAs molecules to +58 BCL11a enhancer region) and Figure 2 (gRNA moleucles to +62 BCL11a enhancer region), and in the tables below, as indicated. Average editing in CD34+ HSPCs are reported in, for example, Table 10 (gRNAs molecules to +58 BCL11a enhancer region), Table 11 (gRNAs molecules to +62 BCL11a enhancer region), Table 12B (gRNAs molecules to +55 BCL11a enhancer region), and Table 13 (gRNAs molecules to the French HPFH region), below. Where T7E1 assay results are reported, "2" indicates high efficiency cutting; "1" indicates low efficiency cutting, and "0" indicates no cutting. In general, T7E1 results correlate with the quantitative cutting assayed by NGS. Top 15 gRNAs (as ranked by highest % editing in CD34+ cells) are shown in Figure 11 (+58 BCL11a enhancer region) and Figure 12 (+62 BCL11a enhancer region).

Table 10: Bcl11a +58 enhancer region crRNA 1^{0} Screen results in CD34+ HSPCs (by NGS, n=3).

Targeting Domain ID	Average % Editing (n=3)	StDev
CR000242	1.4%	0.3%
CR000243	n/a	n/a
CR000244	3.7%	1.0%
CR000245	24.7%	1.4%

CR000246	24.2%	0.3%
CR000247	3.6%	0.6%
CR000248	6.4%	0.5%
CR000249	13.3%	0.6%
CR000250	4.8%	0.5%
CR000251	4.7%	0.5%
CR000252	2.7%	0.5%
CR000253	9.0%	0.6%
CR000255	n/a	n/a
CR000256	1.3%	0.2%
CR000257	2.4%	0.4%
CR000258	2.0%	0.0%
CR000259	3.9%	0.4%
CR000260	32.7%	2.3%
CR000261	17.9%	0.9%
CR000264	2.1%	0.2%
CR000266	2.9%	0.1%
CR000267	3.9%	0.1%
CR000268	6.3%	0.6%
CR000269	4.4%	0.2%
CR000270	2.7%	0.9%
CR000271	7.2%	1.4%
CR000272	11.9%	2.9%
CR000273	3.1%	0.2%
CR000274	1.4%	0.1%
CR000275	9.6%	0.6%
CR000276	14.5%	0.5%
CR000277	8.6%	0.5%
CR000278	4.8%	0.6%
CR000279	6.5%	0.9%
CR000280	7.9%	0.8%
CR000281	3.3%	0.7%
CR000282	10.1%	1.2%
CR000283	4.7%	0.2%
CR000284	5.8%	0.1%
CR000285	8.9%	1.2%
CR000286	20.2%	1.1%
CR000287	10.1%	1.0%
CR000288	1.6%	0.1%
CR000289	3.0%	0.4%
CR000290	2.3%	0.4%
CR000291	2.8%	0.1%

CR000292	9.9%	0.9%
CR000293	n/a	n/a
CR000294	2.7%	0.5%
CR000295	1.9%	0.4%
CR000296	2.8%	0.4%
CR000297	5.7%	0.4%
CR000298	2.2%	0.2%
CR000299	2.9%	0.2%
CR000300	2.3%	0.2%
CR000301	10.2%	0.8%
CR000302	5.0%	0.6%
CR000303	3.7%	0.3%
CR000304	6.2%	0.8%
CR000305	7.7%	2.2%
CR000306	4.0%	2.2%
CR000307	8.8%	3.6%
CR000308	39.9%	1.7%
CR000309	38.3%	8.2%
CR000310	56.8%	1.0%
CR000311	46.0%	1.2%
CR000312	48.5%	1.7%
CR000313	41.2%	4.4%
CR000314	29.9%	0.9%
CR000315	32.0%	2.9%
CR000316	3.9%	1.0%
CR000317	2.8%	0.3%
CR000318	2.6%	0.2%
CR000319	7.9%	1.8%
CR000320	1.9%	0.1%
CR000321	13.2%	1.7%
CR000322	5.2%	0.8%
CR000323	20.3%	2.1%
CR000324	2.2%	0.4%
CR000325	8.4%	0.9%
CR000326	1.4%	0.2%
CR000327	6.9%	1.7%
CR000328	2.6%	0.4%
CR000329	1.1%	0.1%
CR000330	1.7%	0.2%
CR000331	22.0%	0.9%
CR000332	3.2%	1.0%
CR000333	3.8%	0.7%

CR000334	3.2%	0.1%
CR000335	2.7%	0.3%
CR000336	2.2%	0.2%
CR000337	7.2%	1.0%
CR000338	10.3%	1.8%
CR000339	4.2%	0.2%
CR000340	4.6%	0.6%
CR000341	7.5%	1.4%
CR001124	26.1%	2.0%
CR001125	8.4%	1.6%
CR001126	17.2%	5.8%
CR001127	7.4%	2.3%
CR001128	9.0%	0.9%
CR001129	16.5%	6.0%
CR001130	11.1%	8.3%
CR001131	54.1%	4.9%

Table 11: Bcl11a +62 enhancer region crRNA 1^{o} Screen results in CD34+ HSPCs (by NGS, n=3).

Targeting Domain ID	Average % Edit (n=3)	StDev
CR000171	4.4	0.7
CR000172	4.6	2.4
CR000173	3.1	0.7
CR000174	27.6	6.5
CR000175	14.7	1.0
CR000176	2.1	0.6
CR000177	7.6	2.3
CR000178	7.1	1.7
CR000179	7.7	1.8
CR000180	2.8	0.5
CR000181	25.6	3.8
CR000182	27.6	3.5
CR000183	30.5	6.9
CR000184	4.2	1.9
CR000185	11.4	0.7
CR000186	7.2	3.7
CR000187	46.3	2.2
CR000188	21.0	6.0
CR000189	22.3	2.1
CR000190	20.2	5.7

CR000191	38.2	7.9
CR000192	5.4	1.8
CR000193	14.7	2.0
CR000194	13.5	0.7
CR000195	8.2	1.2
CR000196	27.0	6.4
CR000197	6.6	0.6
CR000198	8.7	3.2
CR000199	3.3	1.3
CR000200	6.9	0.5
CR000201	1.6	0.5
CR000202	28.1	5.6
CR000203	43.7	0.5
CR000204	35.1	2.2
CR000205	53.6	0.8
CR000206	52.8	6.0
CR000207	2.5	0.3
CR000208	31.5	7.5
CR000209	13.5	2.9
CR000210	28.7	6.6
CR000211	59.3	5.5
CR000212	40.0	1.6
CR000213	13.6	7.1
CR000214	9.4	0.7
CR000215	37.0	6.9
CR000216	25.3	2.6
CR000217	7.6	1.6
CR000218	5.1	1.3
CR000221	12.4	3.5
CR000222	7.2	2.6
CR000223	8.4	2.1
CR000224	13.9	5.3
CR000225	10.3	4.4
CR000227	12.6	1.8
CR000228	13.5	4.8
CR000229	3.2	0.8

Table 12A: Bcl11a +55 enhancer region crRNA 1[0] Screen results in HEK-293-Cas9 Cells

Targeting Domain ID	Average % Edit (n=3)	StDev

CR002142	25.0	2.0
CR002143	n/a	n/a
CR002144	51.2	8.3
CR002145	51.0	3.3
CR002146	n/a	n/a
CR002147	n/a	n/a
CR002148	13.7	4.3
CR002149	22.3	4.5
CR002150	43.8	9.0
CR002151	31.1	0.6
CR002152	33.2	8.7
CR002153	24.5	7.8
CR002154	62.1	3.9
CR002155	48.2	10.9
CR002156	57.4	8.5
CR002157	46.6	4.3
CR002158	11.0	1.7
CR002159	13.7	2.3
CR002160	37.8	0.8
CR002161	61.5	4.6
CR002162	47.0	14.0
CR002163	52.2	9.6
CR002164	58.5	4.4
CR002165	61.5	6.8
CR002166	42.6	11.3
CR002167	37.8	4.7
CR002168	32.0	12.9
CR002169	48.5	6.3
CR002170	44.8	2.9
CR002171	n/a	n/a
CR002172	n/a	n/a
CR002173	n/a	n/a
CR002174	59.8	3.8
CR002175	22.1	1.3
CR002176	35.4	5.9
CR002177	n/a	n/a
CR002178	25.9	3.2
CR002179	n/a	n/a
CR002180	57.6	6.4
CR002181	63.8	3.9
CR002182	n/a	n/a
CR002183	n/a	n/a
CR002184	30.0	4.0
CR002185	n/a	n/a

CR002186	n/a	n/a
CR002187	51.6	2.9
CR002188	35.8	8.7
CR002189	62.7	6.0
CR002190	n/a	n/a
CR002191	37.4	7.4
CR002192	n/a	n/a
CR002193	6.1	1.7
CR002194	n/a	n/a
CR002195	60.0	9.4
CR002196	42.9	13.7
CR002197	52.2	2.8
CR002198	n/a	n/a
CR002199	n/a	n/a
CR002200	4.3	1.0
CR002201	1.8	0.3
CR002202	2.6	0.3
CR002203	50.7	5.3
CR002204	n/a	n/a
CR002205	n/a	n/a
CR002206	n/a	n/a
CR002207	n/a	n/a
CR002208	n/a	n/a
CR002209	n/a	n/a
CR002210	n/a	n/a
CR002211	n/a	n/a
CR002212	n/a	n/a
CR002213	n/a	n/a
CR002214	n/a	n/a
CR002215	51.7	8.9
CR002216	14.1	8.3
CR002217	50.1	10.5
CR002218	45.0	19.4
CR002219	30.7	14.7
CR002220	44.7	13.3
CR002221	n/a	n/a
CR002222	64.0	3.9
CR002223	n/a	n/a
CR002224	n/a	n/a
CR002225	n/a	n/a
CR002226	n/a	n/a
CR002227	n/a	n/a
CR002228	10.4	5.6
CR002229	n/a	n/a

n/a = not assessed

Aftter the experiment above, the same guide RNA molecules were tested again in triplicate in both HEK-293-Cas9 cells and in CD34+ cells using a newly designed set of primers for the NGS analysis. The results are reported below in Table 12B.

Table 12B: Bcl11a +55 enhancer region crRNA screen results in HEK-293-Cas9 Cells and in CD34+ HSPCs (by NGS, n=3).

ID	Editing % HEK-293-Cas9 Cells (n=3)	Editing % CD34+ HSPCs (n=3)
CR002142	2.1	2.07
CR002143	39.6	2.31
CR002144	74.3	4.70
CR002145	72.1	11.46
CR002146	77.2	5.18
CR002147	37.3	3.13
CR002148	34.6	2.02
CR002149	40.7	3.16
CR002150	64.4	4.01
CR002151	70.5	5.05
CR002152	63.6	6.59
CR002153	42.2	2.82
CR002154	71.0	17.89
CR002155	60.3	6.01
CR002156	62.3	9.43
CR002157	38.5	4.72
CR002158	12.4	2.16
CR002159	14.8	3.64
CR002160	72.8	7.97
CR002161	74.5	18.12
CR002162	64.8	4.53
CR002163	86.7	13.92
CR002164	3.2	10.23
CR002165	78.3	9.74
CR002166	67.2	7.78
CR002167	51.6	29.26
CR002168	29.9	4.15

CR002169	80.2	9.11
CR002170	83.0	16.17
CR002171	67.8	4.83
CR002172	64.3	7.59
CR002173	80.7	6.00
CR002174	78.2	26.89
CR002175	79.4	27.08
CR002176	39.5	5.14
CR002177	66.7	21.45
CR002178	52.5	12.74
CR002179	83.1	38.88
CR002180	51.3	5.46
CR002181	54.0	12.54
CR002182	67.9	28.01
CR002183	30.3	3.52
CR002184	67.1	21.31
CR002185	65.6	8.18
CR002186	58.9	8.16
CR002187	70.2	10.05
CR002188	56.6	9.92
CR002189	71.9	31.14
CR002190	27.4	6.84
CR002191	70.0	17.54
CR002192	62.6	6.92
CR002193	1.6	0.67
CR002194	82.5	24.52
CR002195	64.4	36.32
CR002196	2.1	0.96
CR002197	63.8	37.29
CR002198	67.8	16.45
CR002199	61.3	9.78
CR002200	3.1	1.10
CR002201	1.2	0.84
CR002202	2.8	0.82

CR002203	49.9	0.84
CR002204	43.2	17.48
CR002205	60.6	11.06
CR002206	48.5	9.02
CR002207	49.4	12.29
CR002208	61.7	16.56
CR002209	61.2	9.36
CR002210	57.6	27.77
CR002211	45.4	30.93
CR002212	56.0	31.55
CR002213	34.4	10.40
CR002214	11.1	1.77
CR002215	49.3	40.23
CR002216	22.1	1.80
CR002217	52.3	11.29
CR002218	73.7	11.17
CR002219	34.2	7.94
CR002220	64.8	8.63
CR002221	20.7	5.66
CR002222	78.9	30.01
CR002223	8.2	1.21
CR002224	7.8	n.d
CR002225	n.d	n.d
CR002226	2.6	n.d
CR002227	n.d	n.d
CR002228	23.2	3.65
CR002229	39.0	n.d

n.d. = not determined

Table 13: French HPFH region crRNA 1^{o} Screen results in HEK-293-Cas9 Cells and in CD34+ HSPCs (by NGS, n=3).

Targeting Domain ID	Average Edit % HEK-293-Cas9 (n=3)	Average Edit % CD34+ HSPCs (n=3)	StDev (%) for % Edit in CD34+ HSPCs
CR001016	33.1	24.0	1.2
CR001017	30.4	19.5	1.5

CR001018	46.5	53.0	3.4
CR001019	45.9	57.6	2.3
CR001020	62.1	47.7	9.3
CR001021	29.1	34.2	1.8
CR001022	66.1	66.2	2.3
CR001023	27.3	46.0	6.1
CR001024	62.5	73.4	6.9
CR001025	25.5	24.5	1.6
CR001026	61.4	72.1	2.9
CR001027	23.3	33.2	2.2
CR001028	47.7	72.1	4.9
CR001029	53.9	61.2	5.7
CR001030	49.2	49.9	29.0
CR001031	42.7	65.0	9.3
CR001032	67.6	50.1	9.7
CR001033	15.3	44.5	3.2
CR001034	28.5	52.9	2.7
CR001035	16.9	28.5	16.4
CR001036	28.0	68.3	3.7
CR001037	52.7	53.2	4.2
CR001038	1.9	23.7	20.6
CR001039	2.2	35.8	2.8
CR001040	nd	n/a	0.0
CR001041	nd	n/a	0.0
CR001042	2.7	n/a	0.0
CR001043	nd	n/a	0.0
CR001044	4.9	1.5	0.4
CR001045	38.1	31.2	2.0
CR001046	18.4	28.4	3.9
CR001047	nd	n/a	0.0
CR001048	1.6	0.2	0.3
CR001049	nd	n/a	0.0
CR001050	nd	n/a	0.0
CR001051	nd	n/a	0.0
CR001052	nd	n/a	0.0
CR001053	5.8	4.4	0.7
CR001054	9.0	4.1	0.4
CR001055	5.2	0.1	0.1
CR001056	7.7	5.0	0.3
CR001057	25.2	7.8	0.8
CR001058	41.6	29.5	6.7
CR001059	5.2	4.9	0.1

CR001060	43.5	18.7	5.2
CR001061	21.7	4.7	0.8
CR001062	12.2	5.2	1.1
CR001063	16.6	21.5	1.6
CR001064	6.0	4.2	0.7
CR001065	43.0	20.0	1.4
CR001066	11.1	4.2	0.4
CR001067	25.7	7.9	3.5
CR001068	11.3	5.9	1.6
CR001069	15.1	2.9	0.2
CR001070	38.2	11.1	3.1
CR001071	34.6	8.5	0.2
CR001072	22.8	3.5	0.4
CR001073	45.2	18.1	4.1
CR001074	40.1	38.1	2.5
CR001075	53.0	29.2	1.8
CR001076	25.6	1.8	0.1
CR001077	8.9	12.2	0.4
CR001078	10.9	17.7	3.3
CR001079	18.3	7.8	0.9
CR001080	21.3	17.4	5.6
CR001081	22.0	21.4	0.5
CR001082	5.4	8.5	0.6
CR001083	12.3	11.6	0.5
CR001084	25.4	9.5	4.5
CR001085	18.3	12.4	1.7
CR001086	25.3	4.4	2.0
CR001087	16.4	6.9	0.9
CR001088	9.6	18.4	1.9
CR001089	nd	15.8	12.9
CR001090	16.9	30.1	3.5
CR001091	11.4	0.8	0.5
CR001092	17.4	17.0	9.8
CR001093	23.0	13.0	4.5
CR001094	10.0	24.9	5.4
CR001095	22.1	34.8	3.6
CR001096	29.8	20.4	2.0
CR001097	17.9	20.5	0.5
CR001098	49.8	34.7	5.1
CR001099	24.7	39.9	1.8
CR001100	nd	33.2	2.8
CR001101	16.9	24.7	2.1

CR001102	29.4	13.9	0.7
CR001103	9.9	8.6	2.2
CR001104	11.3	3.3	0.7
CR001105	5.0	3.6	0.9
CR001106	15.7	13.1	1.6
CR001107	31.2	8.5	4.5
CR001108	16.1	3.2	0.5
CR001109	12.1	4.6	2.1
CR001110	23.5	6.0	3.0
CR001111	12.3	2.6	1.3
CR001132	18.7	3.4	0.4
CR001133	35.4	27.0	4.2
CR001134	12.3	0.3	0.2
CR001135	57.8	16.2	2.7
CR001136	7.1	1.7	0.5
CR001137	31.2	6.2	2.7
CR001138	45.4	9.6	1.2
CR001139	nd	3.3	0.3
CR001140	28.7	11.2	1.2
CR001141	3.6	1.5	0.5
CR001142	56.7	9.7	1.2
CR001143	58.4	4.6	1.3
CR001144	23.2	4.3	2.5
CR001145	4.9	0.1	0.0
CR001146	38.2	0.2	0.0
CR001147	16.0	0.1	0.1
CR001148	22.3	3.0	1.6
CR001149	19.4	6.0	3.9
CR001150	30.8	30.4	17.9
CR001151	35.8	0.8	0.2
CR001152	24.6	0.3	0.1
CR001153	5.4	0.3	0.4
CR001154	6.3	3.6	2.1
CR001155	nd	2.1	0.6
CR001156	19.6	4.8	0.8
CR001157	16.4	2.7	0.6
CR001158	36.5	5.1	3.2
CR001159	42.9	7.7	1.0
CR001160	32.5	8.5	1.9
CR001161	20.5	10.3	1.9
CR001162	35.0	30.5	4.5
CR001163	9.9	3.3	0.5

CR001164	23.3	14.4	8.8
CR001165	5.5	1.5	0.4
CR001166	49.8	27.1	4.4
CR001167	13.8	6.0	0.8
CR001168	nd	6.4	4.7
CR001169	43.9	n/a	0.0
CR001170	28.5	10.7	6.4
CR001171	37.5	2.7	2.6
CR001172	41.5	14.8	3.5
CR001173	49.5	16.7	3.9
CR001174	36.6	4.4	0.7
CR001175	17.0	5.3	1.7
CR001176	7.7	3.6	2.8
CR001177	4.0	4.1	2.3
CR001178	nd	27.0	15.6
CR001179	59.0	27.9	1.5
CR001180	nd	8.5	5.3
CR001181	30.9	5.7	0.8
CR001182	34.5	13.6	7.8
CR001183	6.9	0.4	0.3
CR001184	15.7	5.2	2.7
CR001185	18.2	7.6	1.2
CR001186	12.0	5.0	0.6
CR001187	8.3	4.1	0.3
CR001188	16.8	7.1	2.0
CR001189	13.3	3.7	1.3
CR001190	nd	5.6	1.1
CR001191	39.5	4.8	1.0
CR001192	27.5	3.9	1.3
CR001193	17.1	1.5	1.9
CR001194	17.8	5.9	4.1
CR001195	nd	16.4	9.5
CR001196	5.8	2.2	0.7
CR001197	32.4	8.1	3.1
CR001198	28.4	18.2	5.8
CR001199	40.8	7.9	4.0
CR001200	24.4	1.2	0.7
CR001201	1.7	0.3	0.1
CR001202	46.0	39.3	22.7
CR001203	11.9	3.1	1.6
CR001204	1.2	0.8	0.1
CR001205	3.0	0.2	0.1

CR001206	3.9	0.5	0.2
CR001207	7.6	2.4	1.2
CR001208	5.5	1.5	0.7
CR001209	4.4	1.7	0.2
CR001210	10.8	3.9	2.5
CR001211	6.8	3.4	2.0
CR001212	32.7	11.1	6.5
CR001213	21.6	6.2	1.5
CR001214	28.4	5.7	0.8
CR001215	9.0	1.5	0.5
CR001216	nd	2.5	1.4
CR001217	nd	n/a	0.0
CR001218	7.7	4.1	1.0
CR001219	40.0	20.3	0.6
CR001220	33.8	n/a	0.0
CR001221	41.3	n/a	0.0
CR001222	39.1	18.9	10.9
CR001223	35.9	n/a	0.0
CR001224	34.9	16.5	7.1
CR001225	55.0	24.6	1.1
CR001226	34.1	4.7	4.1
CR001227	46.4	6.4	0.6
CR003027	50.2	4.5	nd
CR003028	3.0	2.2	nd
CR003029	14.4	3.4	nd
CR003030	20.2	5.8	nd
CR003031	31.3	9.7	nd
CR003032	15.1	4.4	nd
CR003033	46.5	25.2	nd
CR003034	55.2	11.8	nd
CR003035	42.4	15.9	nd
CR003036	17.4	6.1	nd
CR003037	38.6	19.6	nd
CR003038	47.1	24.6	nd
CR003039	53.8	21.1	nd
CR003040	35.9	6.1	nd
CR003041	23.7	9.9	nd
CR003042	35.5	8.7	nd
CR003043	24.4	4.3	nd
CR003044	54.1	16.2	nd
CR003045	33.7	6.6	nd
CR003046	34.8	3.6	nd

CR003047	46.9	9.8	nd
CR003048	12.6	1.7	nd
CR003049	24.4	4.9	nd
CR003050	19.6	2.9	nd
CR003051	15.4	1.8	nd
CR003052	15.7	7.8	nd
CR003053	10.8	0.9	nd
CR003054	16.7	2.9	nd
CR003055	17.3	4.4	nd
CR003056	46.3	19.3	nd
CR003057	40.9	11.3	nd
CR003058	40.0	8.9	nd
CR003059	23.7	<2%	nd
CR003060	16.8	<2%	nd
CR003061	27.6	<2%	nd
CR003062	3.9	<2%	nd
CR003063	19.8	2.5	nd
CR003064	19.6	<2%	nd
CR003065	42.3	0.1	nd
CR003066	36.5	0.0	nd
CR003067	53.1	0.1	nd
CR003068	11.5	<2%	nd
CR003069	42.7	0.0	nd
CR003070	49.0	0.1	nd
CR003071	41.8	<2%	nd
CR003072	27.2	<2%	nd
CR003073	45.1	0.1	nd
CR003074	40.2	0.1	nd
CR003075	58.5	0.1	nd
CR003076	28.5	<2%	nd
CR003077	44.9	0.0	nd
CR003078	43.9	<2%	nd
CR003079	31.1	<2%	nd
CR003080	41.1	<2%	nd
CR003081	29.4	<2%	nd
CR003082	30.8	<2%	nd
CR003083	26.5	0.0	nd
CR003084	32.3	<2%	nd
CR003085	24.0	0.1	nd
CR003086	40.8	10.8	nd
CR003087	51.0	45.0	nd
CR003088	25.5	9.7	nd

CR003089	26.0	11.5	nd
CR003090	15.2	<2%	nd
CR003091	26.4	5.5	nd
CR003092	4.9	2.1	nd
CR003093	16.7	2.9	nd
CR003094	39.5	4.7	nd
CR003095	12.0	1.7	nd
CR003096	22.9	4.0	nd

n/a = not assayed; nd = not determined

Genome Editing at the BCL11a Enhancer Site

Synthetic sgRNA molecules containing targeting domains specific for genomic DNA within the +58 or +62 erythroid enhancer region of BCL11a were ordered. Figure 5 shows the genomic DNA targeted by the sgRNAs, which were named sgEH1 through sgEH9.

sgEH1 Targeting Domain (CR00276): AUCACAUAUAGGCACCUAUC (SEQ ID NO: 212)

sgEH2 Targeting Domain (CR00275): CACAGUAGCUGGUACCUGAU (SEQ ID NO: 211)

sgEH8 Targeting Domain (CR00273): CAGGUACCAGCUACUGUGUU (SEQ ID NO: 209)

sgEH9 (CR00277) Targeting Domain: UGAUAGGUGCCUAUAUGUGA (SEQ ID NO: 213)

RNPs containing sgEH[X] precomplexed with Cas9 were introduced into CD34+ bone marrow cells (Bone Marrow CD34+ cells ordered from Lonza , Cat # 2M-101C , Lot# 466977 , 30y, F, B (96.8%)) using electroporation (NEON electroporator). Cutting was determined in CD34+ stem cells using T7E1 and NGS. The results are summarized in Figure 6A-D, which shows overall indel formation across four experiments (two experiments from two different donors), as well as the top indel patterns. sgEH1, 2 and 9 were able to direct cutting with high efficiency.

It was surprisingly found that across multiple experiments, including those using cells from different donors, the indel pattern remained constant (See Figure 6A-D). That is, each gRNA gave a consistent pattern of indel formation. As well, deletions appeared to correlate with regions of microhomology near the cutting site.

To further investigate this phenomenon, gRNAs to the BCL11a locus were designed at tested using different biological samples as well as different delivery methods, and gRNA scaffolds. For this experiment, gRNAs with the following targeting domains were used:

G7 (also referred to as g7) Targeting domain: GUGCCAGAUGAACUUCCCAU (SEQ ID NO: 2016) (e.g., the 3' 20 nt of SEQ ID NO: 1191)

G8 (also referred to as g8) Targeting domain: CACAAACGGAAACAAUGCAA (SEQ ID NO: 2017) (e.g., the 3' 20 nt of SEQ ID NO: 1186)

In a first experiment, g7 and g8 were tested across two different biological samples. As shown in Figure 7, the pattern of top 3 most prevalent indels for each gRNA was identical. Next, gRNA molecules comprising the G7 and G8 targeting domains were tested with a different tracrRNA component. In the previous experiments, SEQ ID NO: 6601, followed by –UUUU, was directly appended to the gRNA targeting domain to form the sgRNA. In the next set of experiments, SEQ ID NO: 6604, followed by –UUUU, was directly appended to the gRNA targeting domains of g7 and g8 to create sgRNA molecules with a different scaffold (gRNAs called g7BC or g8BC). As shown in Figure 8, the indel pattern remained constant even when different sgRNA scaffolds are used. Finally, the indel pattern was compared using different delivery methods. Delivery of g7 to 293 cells via either RNP electroporation or by delivery of a g7-encoding plasmid via lipofectamine 2000 was investigated and the results reported in Figure 9. As shown, the indel pattern remained the same. Together, these results strongly suggest that indel pattern formation is sequence-dependent. gRNA molecules that target sequences where cutting results in large deletions and/or frameshift deletions may be beneficial for loss of function.

Excision with Multiple Guides

G7 and g8, above, target genomic DNA at proximal sites (PAM sequences are within 50 nucleotides of each other within the BCL11a gene). To investigate the effect of simultanesously targeting two proximal sites, CD34+ cells were transfected with RNPs comprising gRNAs with the targeting domain of G7 as well as RNPs comprising gRNAs with the targeting domain of G8. Cutting efficiency and indel pattern was assessed by NGS. As shown in Figure 10, the primary indel is a delection of the nucleotides between the two gRNA binding sites. These results demonstrate that a plurality, e.g., 2, guides that bind in proximity may be used to effect an excision of the DNA located between the two binding sites.

Genome Editing in CD34+ Stem Cells

Genome editing at the BCL11a locus was demonstrated in CD34+ primary hematopoietic stem cells. Briefly, CD34+ cells were isolated from G-CSF mobilized peripheral blood from adult donors (AllCells) using immunoselection (Miltenyi) according to the manufacturer's instructions. Cell gating is shown in Figure 3. Cells were aliquotted and cryopreserved. Thawed cells were seeded at $2x10^5$/ml in SFEM (StemCell Technologies) + 1X antibiotic/antimycotic + 50 ng/ml each cytokine (TPO, FLT3L, IL6 and SCF) + 500 nM compound 4 and cultured for 5 days at 37C, 5% CO2 in a humidified incubator. Cell concentration after 5 days was $1x10^6$/ml.

Preincubated RNP complex consisting of 150 ng each Cas9 (Genscript #265425-7) and sgRNA (TriLink, comprising the sgBCL11A_7 Targeting Domain (i.e., the targeting domain of g7): GTGCCAGATGAACTTCCCATGTTTAAGAGCTATGCTGGAAACAGCATAGCAAGTTTAAAT AAGGCTAGTCCGTTATCAACTTGAAAAAGTGGCACCGAGTCGGTGCTTTT) (SEQ ID NO: 2000) was added to $2x10^5$ cells and electroporated on the Neon system (Lifetechnologies) with pulse parameters: 1600 V, 20ms, 1 pulse, according to manufacturer's protocols. Duplicate electroporations were performed. Mock electroporations were also performed in the absence of RNP complex. After electroporation, cells were seeded into 1 ml media to recover overnight.

The day following electroporation, 1/20 of the unsorted culture was seeded in SFEM (StemCell Technologies) + 1X antibiotic/antimycotic + 50 ng/ml each TPO, FLT3L, IL6, SCF, IL3 and GCSF for 6 days. The remaining cells were stained with antibodies to human CD34 and human CD90 and sorted by flow cytometry for CD34+CD90+ and CD34+CD90- populations. CD34+CD90+ cells are known to contain hematopoietic stem cells, as defined by long-term multi-lineage engraftment in immunodeficient mice (see Majeti et al. 2007 Cell Stem Cell 1, 635-645). Cell populations selected for sorting are indicated by the gates in the representative dot plot of Figure 3. Sorted cells were cultured in SFEM (StemCell Technologies) + 1X antibiotic/antimycotic + 50 ng/ml each TPO, FLT3L, IL6, SCF, IL3 and GCSF for 6 days, at which point all cultures were harvested for analysis of genome editing.

Genomic DNA was purified from harvested cells and the targeted region was amplified with the following primers: BCL11A-7 F, gcttggctacagcacctctga (SEQ ID NO: 2018); BCL11A-7 R, ggcatggggttgagatgtgct (SEQ ID NO: 2019). PCR product was denatured and reannealed, followed by incubation with T7E1 (New England Biolabs) as per the manufacturer's recommendations. The reaction was then analyzed by agarose gel electrophoresis (Figure 4). The upper band represents uncleaved homoduplex DNA and the lower bands indicate cleavage products resulting from heteroduplex DNA. The far left lane is a DNA ladder. Band intensity was calculated by peak integration of unprocessed images by ImageJ software. % gene modification (indel) was calculated as follows: % gene modification = 100 x (1 – (1- fraction cleaved)$^{1/2}$), and is indicated below each corresponding lane of the gel.

The results are shown in Figure 4. Gene editing efficiency in the hematopoietic stem cell-containing CD34+CD90+ population was equivalent to CD34+CD90- cells or unsorted. These experiments demonstrate that gene editing can be accomplished in CD34+ HSPCs and CD34+CD90+ cells that are further enriched in HSCs.

Example 3. BCL11A erythroid enhancer editing in Hematopoietic Stem and Progenitor Cells (HSPCs) using CRISPR-Cas9 for derepression of fetal globin expression in adult erythroid cells

Methods:

Human $CD34^+$ cell culture. Human bone marrow $CD34^+$ cells were purchased from either AllCells (Cat#: ABM017F) or Lonza (Cat#: 2M-101C) and expanded for 2 to 3 days using StemSpan SFEM (StemCell Technologies; Cat no. 09650) supplemented with 50 ng/mL of thrombopoietin (Tpo, Peprotech; Cat# 300-18), 50 ng/mL of human Flt3 ligand (Flt-3L, Peprotech; Cat# 300-19), 50ng/mL of human stem cell factor (SCF, Peprotech; Cat# 300-07), human interleukin-6 (IL-6, Peprotech; Cat# 200-06), 1% L-glutamine; 2% penicillin/streptomycin, and Compound 4 (0.75 μM). After 2 to 3 days of expansion, the culture had expanded 2- to 3-fold relative to starting cell numbers purchased from AllCells and 1- to 1.5-fold from Lonza. These culture conditions were used for all CD34+ expansion steps, including both before and after introduction of the CRISPR/Cas systems as described herein.

Assembly of Cas9 and guide RNA ribonucleoprotein (RNP) complexes, preparation of HSC, and electroporation of RNP into HSC. Cas9-guide RNA ribonucleoprotein complexes (RNPs) were prepared immediately prior to electroporation. For formation of RNP using dual guide RNAs (dgRNAs), 3 μg of each of crRNA (in 2.24 μL) and tracr (in 1.25 μL) are first denatured at 95°C for 2 min in separate tubes and then cooled to room temperature. For preparation of Cas9 protein, 7.3 μg of CAS9 protein (in 1.21 μL) was mixed with 0.52 μL of 5 x CCE buffer (20 mM HEPES, 100 mM KCL, 5 mM MgCL2, 5% Glycerol and freshly added 1 mM DTT). Tracr was first mixed with the Cas9 preparation and incubated at 37°C for 5 min. The crRNA was then added to Tracr/CAS9 complexes and incubated for 5 min at 37°C. The HSC were collected by centrifugation at 200 x g for 15 min and resuspended in T buffer that comes with Neon electroporation kit (Invitrogen; Cat#: MPK1096) at a cell density of 2 x 10^7/mL. The RNP mixed with 12 μL of cells by pipetting up and down 3 times gently. To prepare single guide RNA (sgRNA) and Cas9 complexes, 2.25 μg sgRNA (in 1.5 μL) was mixed with 2.25 μg Cas9 protein (in 3 μL) and incubated at RT for 5 min. The sgRNA/Cas9 complex was then mixed with 10.5 μL of 2 x 10^7 /mL cells by pipetting up and down several times gently and incubated at RT for 2 min. The RNP/cell mixture (10 μL) was transferred into Neon electroporation probe. The electroporation was performed with Neon transfection system (Invitrogen; MPK5000S) using 1700 volts/20 milliseconds and 1 pulse. After electroporation, the cells were transferred into 0.5 mL pre-warmed StemSpan SFEM medium supplemented with growth factors and cytokines as described above and cultured at 37°C for 2 days.

Genomic DNA preparation. Genomic DNA was prepared from edited and unedited HSC at 48 hours post-electroporation. The cells were lysed in 10 mM Tris-HCL, pH 8.0; 0.05% SDS and freshly added Protease K of 25 μg/mL and incubated at 37°C for 1 hour followed by additional incubation at 85°C for 15 min to inactivate protease K.

T7E1 assay. To determine editing efficiency of HSCs, T7E1 and assay was performed. PCR was performed using Phusion Hot Start II High-Fidelity kit (Thermo Scientific; Cat#: F-549L) with the following cycling condition: 98°C for 30''; 35 cycles of 98°C for 5'', 68°C for 20', 72°C for 30"; 72°C for 5 min. The following primers were used: forward primer: 5'-AGCTCCAAACTCTCAAACCACAGGG-3' (SEQ ID NO: 2001) and reverse primer: 5'-TACAATTTTGGGAGTCCACACGGCA-3' (SEQ ID NO: 2002). The PCR products were denatured and re-annealed using the following condition: 95°C for 5 min, 95-85°C at -2°C/s, 85-25°C at -0.1°C/s, 4°C hold. After annealing, 1 µL of mismatch-sensitive T7 E1 nuclease (NEB, Cat# M0302L) was added into 10 µL of PCR product above and further incubated at 37°C for 15 min for digestion of hetero duplexes, and the resulting DNA fragments were analyzed by agarose gel (2%) electrophoresis. The editing efficiency was quantified using ImageJ software (http://rsb.info.nih.gov/ij/).

Next generation sequencing (NGS). To determine editing efficiency more precisely and patterns of insertions and deletions (indels), the PCR products were subjected to next generation sequencing (NGS). The PCR were performed in duplicate using Titanium Taq PCR kit (Clontech Laboratories; Cat#: 639210) with the following cycling condition: 98°C for 5 min; 30 cycles of 95°C for 15 seconds, 68°C for 15 seconds, 72°C 1 min; 72°C for 7 min. The following primers were used: forward primer: 5'-AGCTCCAAACTCTCAAACCACAGGG-3' (SEQ ID NO: 2001) and reverse primer: 5'-TACAATTTTGGGAGTCCACACGGCA-3' (SEQ ID NO: 2002). The PCR products were analyzed by 2% agarose gel electrophoresis and submitted for deep sequencing.

Flow cytometry analysis of HSPC culture. The HSPC were subjected to flow cytometry to characterize stem and progenitor cell populations. The percentage of $CD34^+$, $CD34^+CD90^+$ cell subsets, prior to and after genome editing was determined on aliquots of the cell cultures. The cells were incubated with anti-CD34 (BD Biosciences, Cat# 555824), anti-CD90 (Biolegend, Cat# 328109) in staining buffer, containing PBS supplemented with 0.5% BSA, at 4°C, in dark for 30 min. The cell viability is determined by 7AAD. The cells were washed with staining buffer and Multicolor FACS analysis was performed on a FACSCanto (Becton Dickinson). Flow cytometry results analyzed using Flowjo and the data were presented as percent $CD34^+$, $CD34^+CD90^+$ of the total cell population. Absolute numbers of each cell type population in the culture were calculated from the total number of cells multiplied by the percentage of each population.

In vitro erythropoiesis and FACS analysis for HbF containing erythroid cells. The genome edited HSC were subjected to *in vitro* erythroid differentiation 48 hours post-electroporation. Briefly, the edited HSC were cultured in erythroid differentiation medium (EDM) consisting of IMDM (Invitrogen, Cat# 31980-097) supplemented with 330 µg /mL human holo-transferrin (Sigma, Cat# T0665), 10 µg /mL recombinant human insulin (Sigma, Cat# I3536), 2 IU/mL heparin (Sigma, Cat # H3149), 5% human plasma (Sigma, Cat# P9523), 3 IU/mL human erythropoietin (R&D, Cat# 287-

TC), 1% L-glutamine, and 2% penicillin/streptomycin. During days 0–7 of culture, EDM was further supplemented with 10^{-6}M hydrocortisone (Sigma, Cat# H0888), 100 ng/mL human SCF (Peprotech, Cat# 300-07), and 5 ng/mL human IL-3 (Peprotech, Cat# 200-03) for 7-days. During days 7–11 of culture, EDM was supplemented with 100 ng/mL of human SCF only. During days 11–21 of culture, EDM has no additional supplements. On days 7, 14 and 21 of the culture, the cells (2-10 x 10^5) were analyzed by intracellular staining for HbF expression. Briefly, the cells were collected by centrifugation at 350 x g for 5 min and washed once with staining buffer (Biolegend, Cat# 420201). The cells were then fixed with 0.5 mL of fixation buffer (Biolegend, Cat# 420801) and washed three times with 2 mL of 1x intracellular staining permeabilization wash buffer (Biolegend, Cat# 421002) by centrifugation at 350 x g for 5 min. The cells were then incubated with 5 µL of anti-HbF antibody (Life technologies, Cat# MHFH01) in 100 µL of 1x intracellular staining perm wash buffer for 20 min at room temperature. The cells were washed twice with 2 mL of 1x intracellular staining Perm wash buffer and resuspend in 200 µL staining buffer and analyzed on FACS Canto (Becton Dickinson) for HbF expression. The results analyzed using Flowjo and data were presented as % of HbF positive cells (F-cells) in total cell population.

Gene expression assays. ~1 x 10^6 cells were used to purify RNA using RNeasy mini kit (Qiagen. Cat# 74104). 200 to 400 ng RNA was used for 1st strand synthesize using qScript cDNA synthesis kit (Quanta, Cat# 95047-500). Taq-man PCR was performed using Taq-Man Fast Advance PR Mix (Life technologies, Cat# 4444963) and GAPDH (Life technologies, ID# Hs02758991_g1), HbB (Life technologies, ID#: Hs00747223_g1), HbG2/HbG1 (Life technologies, ID# Hs00361131_g1) and BCL11A (Life technologies, ID#: Hs01093197_m1) according to suppliers protocol. The relative expression of each gene was normalized to GAPDH expression.

Colony forming unit cell assay. For colony forming unit (CFU) assay, 300 cells per 1.1 mL Methocult/35 mm dish in duplicate were plated in Methocult H4434 methylcellulose medium containing SCF, GM-CSF, IL-3, and erythropoietin (StemCell Technologies). Pen/Strep was added into the Methocult. The culture dishes were incubated in a humidified incubator at 37°C. Colonies containing at least 30 cells were counted at day 14 post-plating using StemVision (StemCell Technologies) to take the image of entire plate. The total number of colonies, number of CFU-GEMM (Granulocyte, Erythrocyte, Macrophage, Megakaryocyte), CFU-GM (Granulocyte, Macrophage), CFU-M (Macrophage), CFU-E (erythroid) and BFU-E (Burst-forming unit-erythroid) were then counted StemVision image analyzer software and confirmed by manually using StemVision Colony Marker software.

In vivo engraftment study. In vivo engraftment studies are conducted under protocol approved by IACUC. A fraction of final culture of genome edited HSC equivalent to 30,000 starting cells are

injected intravenously via the tail vein into sub-lethally irradiated (200 cGY) 6- to 8-week old NSG mice. Engraftment is performed within 24 h after irradiation. Engraftment is monitored by flow cytometric analysis of blood collected at 4, 8, and 12 weeks post-infusion using anti-human CD45 and anti-mouse CD45 antibodies. The mice are sacrificed 13 weeks post-transplantation and bone marrow, spleen and thymus collected for analysis by flow cytometry and colony forming cell unit assay. For secondary engraftment, 50% of the bone marrow from each recipient mouse is transplanted into one secondary sub-lethally irradiated NSG mouse. Engraftment is monitored by flow cytometric analysis of blood collected at 4, 8, and 12 weeks post-infusion using panleukocyte marker, CD45 using anti-human CD45 and anti-mouse CD45 antibodies. Fifteen weeks after transplantation, bone marrow and spleen were harvested from the secondary mice and analyzed by flow cytometry and colony forming cell unit assay.

Results:

Without being bound by theory, it is believed that targeted genetic disruption of BCL11A erythroid enhancer in HSC will down regulate the expression of BCL11A selectively in erythroid cell lineage and relieve repression of γ-globin expression, allowing production of the red blood cells containing elevated HbF protein, F-cells. The elevated HbF prevents sickling of the red blood cells under deoxygenated conditions and will be therapeutic/curative for the patients of both β-thalassemia and SCD. Autologous hematopoietic stem cell transplantation (HSCT) with *ex vivo* genome edited HSC from SCD patients was also combined with stem cell expansion enhancing technology, e.g., an aryl hydrocarbon receptor (AHR) inhibitor, e.g., as described in WO2010/059401 (the contents of which are incorporated by reference in their entirety), e.g., Compound 4 to improve ex vivo expansion and increase the dose of gene modified HSC delivered.

For efficient genome editing via programmable nuclease, Cas9, the successful delivery of guide RNA (gRNA) and Cas9 protein into target cells and tissues is essential. Recent reports demonstrated that Cas9 ribonucleoprotein (RNP) complexes when delivered into target cells by electroporation can accomplish efficient and specific genome editing in several different cell types. Cas9-RNP complexes cleave chromosomal DNA almost immediately after delivery and are degraded rapidly in cells, reducing off-target effects. In contrast, use of plasmid and viral vector systems used to deliver Cas9 results in prolonged expression of the enzyme aggravating off-target effects associated with the system. Additionally, delivery of RNPs into the target cells requires no additional tools which would greatly facilitate translation of genome editing for therapeutic purposes in the clinic. Purified recombinant Cas9 protein and gRNA complexes (RNPs) were delivered into cultured HSPC and an overview experiments used are shown in Figure 17.

Recombinant Cas9 protein was purified from Escherichia coli and complexed with synthetic dual gRNAs (dgRNA) that consist of crRNA and tracr or full-length single guide RNA (sgRNA) to

generate ribonucleoprotein (RNP) complexes. The list and sequences of gRNAs used in the study are shown in Table 14. The RNP complexes were electroporated into healthy or SCD patient derived bone marrow CD34+ HSPC via electroporation as described under materials and methods. The cells were expanded for 2-days in HSC expansion medium containing Compound 4 prior to the delivery of RNP complexes. Actively dividing cells may facilitate uptake of RNP complexes delivered by electroporation. To facilitate recovery from transfection process, the cells were cultured for two additional days in the modified expansion medium containing compound 4. Viability of the cells 48 hours after electroporation was determined by flow cytometry using 7AAD. The viability was relatively high with >80% of the cells viable (Figure 18) suggesting that the HSPC tolerated electroporation of the RNP complexes relatively well compared to other methods of Cas9 and gRNA delivery systems reported in the literature.

Table 14. List of gRNAs targeting BCL11A erythroid specific enhancer used in the current study.

Guide RNA targeting domain ID	Region/ strand	dgRNA tested	sgRNA tested	Target Sequence	Coordinates (hg38)	SEQ ID NO:
CR000245	+58/+	x		tcagtgagatgagatatcaa	chr2:60494483-60494502	2020
CR000246	+58/+	x		cagtgagatgagatatcaaa	chr2:60494484-60494503	2021
CR000260	+58/-	x		tgtaactaataaataccagg	chr2:60494790-60494809	2022
CR001124	+58/-	x		ttagggtgggggcgtgggtg	chr2:60495217-60495236	2023
CR001131	+58/-	x		attagggtgggggcgtgggt	chr2:60495218-60495237	2024
CR000309	+58/+	x	X	cacgcccccaccctaatcag	chr2:60495221-60495240	2025
CR000308	+58/-	x	X	tctgattagggtgggggcgt	chr2:60495222-60495241	2026
CR000310	+58/-	x	X	ttggcctctgattagggtgg	chr2:60495228-60495247	2027
CR000311	+58/-	x	X	tttggcctctgattagggtg	chr2:60495229-60495248	2028
CR000312	+58/-	x	X	gtttggcctctgattagggt	chr2:60495230-60495249	2029
CR000313	+58/-	x	X	ggtttggcctctgattaggg	chr2:60495231-60495250	2030
CR000314	+58/-	x	X	aagggtttggcctctgatta	chr2:60495234-60495253	2031
CR000315	+58/-	x	X	gaagggtttggcctctgatt	chr2:60495235-60495254	2032
CR001128 / sgEH15	+58/+		X	atcagaggccaaacccttcc	chr2:60495236-60495255	2033

CR001127 / sgEH14	+58/-		X	cacaggctccaggaagggtt	chr2:60495247-60495266	2034
CR001126 / sgEH13	+58/-	x	X	tttatcacaggctccaggaa	chr2:60495252-60495271	2035
CR001125 / sgEH12	+58/-		X	ttttatcacaggctccagga	chr2:60495253-60495272	2036
CR000316 / sgEH11	+58/-		X	ttgcttttatcacaggctcc	chr2:60495257-60495276	2037
CR000317 / sgEH4	+58/-			ctaacagttgcttttatcac	chr2:60495264-60495283	2038

The T7E1 assay is a convenient method to assess editing at specific sites in the genome. The genomic DNA was extracted from the HSPC 2-days post-electroporation. The targeted BCL11A erythroid enhancer region was amplified by polymerase chain reaction (PCR). The PCR products were subjected to T7E1 assay. The end products of T7E1 assay were subjected to 2% agarose gel electrophoresis and the percent edited alleles quantified by imageJ (http://rsb.info.nih.gov/ij/). Expected PCR product sizes and approximate expected sizes of T7E1-digested fragments are shown in Figure 19. The total editing frequencies are indicated as percentage of total edits below the agarose gel image. The genome editing at the BCL11A locus was observed in the cells treated with BCL11A Cas9 RNPs but not in mock electroporated control cells (Figure 19).

The genomic PCR products of the +58 erythroid enhancer region of BCL11A were also subjected to next generation sequencing (NGS). The NGS facilitates simultaneous monitoring of a large number of samples giving a global view of the alleles. Moreover, it provides information on the heterogeneity of insertions and deletions (indels). The sequences were compared with the sequences from control (mock) treated cells. The results of sequence analysis showed that CRISPR-Cas9 induced double stranded breaks were repaired by NHEJ resulting in variable frequencies of small deletions and insertions (indels) near Cas9 cleavage site located in +58 BCL11A erythroid enhancer region (Figure 20 and Table 15). Overall, the observed editing efficiencies was higher for sgRNAs compared to dgRNAs targeting the same sequence, with 12 out 14 sgRNA producing editing at more than 50% alleles (Figure 20 and Table 15), though (without being bound by theory) the differences in efficiency between sgRNA and dgRNA may be affected by the source of the materials.

Table 15. Genotypes identified by NGS in HSPCs edited with Cas9-RNP. The nucleotide sequence for each population is given. The target sequence targeted by each gRNA is indicated above each indel population, with the PAM sequences indicated in lower case. Dashes denote deleted bases and lowercase letters denote insertions. In the description of the gRNA, dgRNA refers to dual gRNA molecules comprising the indicated targeting domain. sgRNA indicates single gRNA molecules

comprising the indicated targeting domain. Where multiple experiments were run with the same dgRNA or sgRNA, successive experiments are labeled "dgRNA," "d1gRNA", "d2gRNA," etc.

gRNA	Variant	% Allele	Indel length	SEQ ID NO:
	CTAACAGTTGCTTTTATCACagg			2039
CR00317-dgRNA	TAGTGCAAGCTAACAG----------GCTCCAGGAAGGGTTTGGCCTCTGATTAG	5.96%	-15	2040
CR00317-dgRNA	TAGTGCAAGCTAACAGTTGCTTTTATtCACAGGCTCCAGGAAGGGTTTGGCCTCTGATTAG	5.77%	1	2041
CR00317-dgRNA	TAGTGCAAGCTAACAGTTGCT----------CCAGGAAGGGTTTGGCCTCTGATTAG	4.69%	-13	2042
CR00317-dgRNA	TAGTGCAAGCTAACAGTTGCTTTTATCA--GGCTCCAGGAAGGGTTTGGCCTCTGATTAG	0.90%	-2	2043
CR00317-dgRNA	TAGTGCAAGCTAACAGTTGCTTTTA-CACAGGCTCCAGGAAGGGTTTGGCCTCTGATTAG	0.88%	-1	2044
CR00317-dgRNA	TAGTGCAAGCTAACAGTTGCTTTT--CACAGGCTCCAGGAAGGGTTTGGCCTCTGATTAG	0.77%	-2	2045
CR00317-dgRNA	TAGTGCAAGCT----------CCAGGAAGGGTTTGGCCTCTGATTAG	0.67%	-23	2046
	ATCAGAGGCCAAACCCTTCCacc			2047
CR001128-dgRNA	AGCTAACAGTTGCTTTTATCACAGGCTCCAGGA-GGGTTTGGCCTCTGATTAGGGTGGGG	20.07%	-1	2048
CR001128-dgRNA	AGCTAACAGTTGCTTTTATCACAGGCTCCAGG-----TTTGGCCTCTGATTAGGGTGGGG	5.00%	-5	2049
CR001128-dgRNA	AGCTAACAGTTGCTTTTATCACAGGCTCCAGGAAaGGGTTTGGCCTCTGATTAGGGTGGGG	4.84%	1	2050
CR001128-dgRNA	AGCTAACAGTTGCTTTTATCACAGGCTCCAGG----GTTTGGCCTCTGATTAGGGTGGGG	4.01%	-4	2051
CR001128-dgRNA	AGCTAACAGTTGCTTTTATCACAGGCTCCAGGA--GGTTTGGCCTCTGATTAGGGTGGGG	2.99%	-2	2052
CR001128-sgRNA	AGCTAACAGTTGCTTTTATCACAGGCTCCAGGA-GGGTTTGGCCTCTGATTAGGGTGGGG	23.33%	-1	2053
CR001128-sgRNA	AGCTAACAGTTGCTTTTATCACAGGCTCCAGGAAGG-TTTGGCCTCTGATTAGGGTGGGG	5.77%	-1	2054
CR001128-sgRNA	AGCTAACAGTTGCTTTTATCACAGGCTCCAGGAAaGGGTTTGGCCTCTGATTAGGGTGGGG	5.77%	1	2055
CR001128-sgRNA	AGCTAACAGTTGCTTTTATCACAGGCTCCAGGA--GGTTTGGCCTCTGATTAGGGTGGGG	5.37%	-2	2056
CR001128-sgRNA	AGCTAACAGTTGCTTTTATCACAGGCTCCAGGAAG--TTTGGCCTCTGATTAGGGTGGGG	3.70%	-2	2057
CR001128-sgRNA	AGCTAACAGTTGCTTTTATCACAGGCTCCAGG----------CCTCTGATTAGGGTGGGG	3.62%	-10	2058
CR001128-sgRNA	AGCTAACAGTTGCTTTTATCACAGGC----------CTCTGATTAGGGTGGGG	3.54%	-17	2059
CR001128-sgRNA	AGCTAACAGTTGCTTTTATCACAGGCTCCAGGA---GTTTGGCCTCTGATTAGGGTGGGG	2.97%	-3	2060
	TTGCTTTTATCACAGGCTCCagg			2061
CR00316-sgRNA	AGCTAACAGTTGCTTTTATCACAGG-------AAGGGTTTGGCCTCTGATTAGGGTGGGG	16.03%	-7	2062
CR00316-sgRNA	AGCTAACAGTTGCTTTTATCACAGGCTtCCAGGAAGGGTTTGGCCTCTGATTAGGGTGGGG	8.25%	1	2063
CR00316-sgRNA	AGCTAACAGTTGCTTTTATC--------CAGGAAGGGTTTGGCCTCTGATTAGGGTGGGG	8.04%	-8	2064
CR00316-sgRNA	AGCTAACAGTTGCTTTTATCACAGGCcTCCAGGAAGGGTTTGGCCTCTGATTAGGGTGGGG	4.07%	1	2065
CR00316-sgRNA	AGCTAACAGTTGCTTTTATCACAGGC-CCAGGAAGGGTTTGGCCTCTGATTAGGGTGGGG	3.55%	-1	2066
CR00316-sgRNA	AGCTAACAGTTGCTTTTATCACAGGC--CAGGAAGGGTTTGGCCTCTGATTAGGGTGGGG	2.37%	-2	2067
CR00316-dgRNA	AGCTAACAGTTGCTTTTATCACAGG-------AAGGGTTTGGCCTCTGATTAGGGTGGGG	2.49%	-7	2068
CR00316-dgRNA	AGCTAACAGTTGCTTTTATCACAGGCTtCCAGGAAGGGTTTGGCCTCTGATTAGGGTGGGG	1.78%	1	2069
CR00316-dgRNA	AGCTAACAGTTGCTTTTATC--------CAGGAAGGGTTTGGCCTCTGATTAGGGTGGGG	1.32%	-8	2070
CR00316-dgRNA	AGCTAACAGTTGCTTTTATCACAGGCcTCCAGGAAGGGTTTGGCCTCTGATTAGGGTGGGG	1.26%	1	2071
CR00316-d1gRNA	AGCTAACAGTTGCTTTTATCACAGG-------AAGGGTTTGGCCTCTGATTAGGGTGGGG	6.94%	-7	2072
CR00316-d1gRNA	AGCTAACAGTTGCTTTTATC--------CAGGAAGGGTTTGGCCTCTGATTAGGGTGGGG	4.99%	-8	2073
CR00316-	AGCTAACAGTTGCTTTTATCACAGGCTtCCAGGAAGGGTTTGGCCTCTGATTAGGGTGGGG	4.69%	1	2074

d1gRNA				
CR00316-d1gRNA	AGCTAACAGT----------GATTAGGGTGGGG	2.90%	-37	2075
CR00316-d1gRNA	AGCTAACAGTTGCTTTTATCACAGGC-CCAGGAAGGGTTTGGCCTCTGATTAGGGTGGGG	1.54%	-1	2076
CR00316-d2gRNA	AGCTAACAGTTGCTTTTATCACAGG-------AAGGGTTTGGCCTCTGATTAGGGTGGGG	11.64%	-7	2077
CR00316-d2gRNA	AGCTAACAGTTGCTTTTATC--------CAGGAAGGGTTTGGCCTCTGATTAGGGTGGGG	6.04%	-8	2078
CR00316-d2gRNA	AGCTAACAGTTGCTTTTATCACAGGCTtCCAGGAAGGGTTTGGCCTCTGATTAGGGTGGGG	5.40%	1	2079
CR00316-d2gRNA	AGCTAACAGTTGCTTTTATCACAGGCcTCCAGGAAGGGTTTGGCCTCTGATTAGGGTGGGG	1.80%	1	2080
CR00316-d2gRNA	AGCTAACAGTTGCTTTTATCACAGGC-----GAAGGGTTTGGCCTCTGATTAGGGTGGGG	1.43%	-5	2081
	TTTTATCACAGGCTCCAGGA**agg**			2082
CR001125-dgRNA	AACAGTTGCTTTTATCACAGGCTCCAaGGAAGGGTTTGGCCTCTGATTAGGGTGGGGGCGT	13.50%	1	2083
CR001125-dgRNA	AACAGTTGCTTTTATCACAGGC----------CTCTGATTAGGGTGGGGGCGT	1.82%	-17	2084
CR001125-dgRNA	AACAGTTGCTTTTATCACAGG----------GTTTGGCCTCTGATTAGGGTGGGGGCGT	1.76%	-11	2085
CR001125-dgRNA	AACAGTTGCTTTTATCACAGG-------AAGGGTTTGGCCTCTGATTAGGGTGGGGGCGT	1.59%	-7	2086
CR001125-dgRNA	AACAGTTGCTTTT----------GGTGGGGGCGT	1.33%	-36	2087
CR001125-sgRNA	AACAGTTGCTTTTATCACAGGCTCCAaGGAAGGGTTTGGCCTCTGATTAGGGTGGGGGCGT	26.27%	1	2088
CR001125-sgRNA	AACAGTTGCTTTTATCACAGG----------GTTTGGCCTCTGATTAGGGTGGGGGCGT	4.64%	-11	2089
CR001125-sgRNA	AACAGTTGCTTTTATCACAGG-------AAGGGTTTGGCCTCTGATTAGGGTGGGGGCGT	4.11%	-7	2090
CR001125-sgRNA	AACAGTTGCTTTTATCACAGGC----------CTCTGATTAGGGTGGGGGCGT	2.66%	-17	2091
CR001125-sgRNA	AACAGTTGCTTTTATCACAGGCT----------TGGCCTCTGATTAGGGTGGGGGCGT	2.58%	-12	2092
CR001125-sgRNA	AACAGTTGCTTTTATCACAGGCTCC-GGAAGGGTTTGGCCTCTGATTAGGGTGGGGGCGT	1.84%	-1	2093
	TTTATCACAGGCTCCAGGAA**ggg**			2094
CR001126-dgRNA	ACAGTTGCTTTTATCACAGGCTCCAG-AAGGGTTTGGCCTCTGATTAGGGTGGGGGCGTG	9.38%	-1	2095
CR001126-dgRNA	ACAGTTGCTTTTATCACAGG----------GTTTGGCCTCTGATTAGGGTGGGGGCGTG	3.28%	-11	2096
CR001126-dgRNA	ACAGTTGCTTTTATCACAGGCTCCAGGgAAGGGTTTGGCCTCTGATTAGGGTGGGGGCGTG	2.91%	1	2097
CR001126-dgRNA	ACAGTTGCTTTTATCACAGGC----------CTCTGATTAGGGTGGGGGCGTG	2.82%	-17	2098
CR001126-dgRNA	ACAGTTGCTTTT----------GGGGGCGTG	1.61%	-39	2099
CR001126-dgRNA	ACAGTTGCTTT----------GGGGGCGTG	1.12%	-40	2100
CR001126-sgRNA	ACAGTTGCTTTTATCACAGGCTCCAG-AAGGGTTTGGCCTCTGATTAGGGTGGGGGCGTG	12.70%	-1	2101
CR001126-sgRNA	ACAGTTGCTTTTATCACAGG----------GTTTGGCCTCTGATTAGGGTGGGGGCGTG	4.37%	-11	2102
CR001126-sgRNA	ACAGTTGCTTTTATCACAGGCTCCAGGgAAGGGTTTGGCCTCTGATTAGGGTGGGGGCGTG	3.22%	1	2103
CR001126-sgRNA	ACAGTTGCTTTTATCACAGGCTCCAGaT----------AAGGTGGGGGCGTG	2.96%	-18	2104
CR001126-sgRNA	ACAGTTGCTTTTATCACAGGC----------CTCTGATTAGGGTGGGGGCGTG	2.68%	-17	2105
CR001126-sgRNA	ACAGTTGCTTTTATCACAGGCTCCAGG----GTTTGGCCTCTGATTAGGGTGGGGGCGTG	2.59%	-4	2106
CR001126-sgRNA	ACAGTTGCTTTTATCACAGGCTCCAGcGAAGGGTTTGGCCTCTGATTAGGGTGGGGGCGTG	1.80%	1	2107
CR001126-sgRNA	ACAGTTGCTTTTATCACAGGCTCC-GGAAGGGTTTGGCCTCTGATTAGGGTGGGGGCGTG	1.74%	-1	2108
	CACAGGCTCCAGGAAGGGTT**tgg**			2109
CR001127-dgRNA	TGCTTTTATCACAGGCTCCAGGAAGG-TTTGGCCTCTGATTAGGGTGGGGGCGTGGGTGG	4.00%	-1	2110
CR001127-dgRNA	TGCTTTTATCACAGGCcT----------GGGGCGTGGGTGG	2.35%	-29	2111
CR001127-dgRNA	TGCTTTTATCACAGGC----------GTGGGTGG	2.19%	-36	2112
CR001127-dgRNA	TGCTTTTATCACAGGC----------CTCTGATTAGGGTGGGGGCGTGGGTGG	1.59%	-17	2113
CR001127-	TGCTTTTATCACAGGCTCCAGGAAGG------CCTCTGATTAGGGTGGGGGCGTGGGTGG	1.48%	-6	2114

dgRNA				
CR001127-sgRNA	TGCTTTTATCACAGGCTCCAGGA-GGGTTTGGCCTCTGATTAGGGTGGGGGCGTGGGTGG	23.21%	-1	2115
CR001127-sgRNA	TGCTTTTATCACAGGCTCCAGGAAGG-TTTGGCCTCTGATTAGGGTGGGGGCGTGGGTGG	6.65%	-1	2116
CR001127-sgRNA	TGCTTTTATCACAGGC----------CTCTGATTAGGGTGGGGGCGTGGGTGG	5.20%	-17	2117
CR001127-sgRNA	TGCTTTTATCACAGGCTCCAGGAAaGGGTTTGGCCTCTGATTAGGGTGGGGGCGTGGGTGG	4.89%	1	2118
CR001127-sgRNA	TGCTTTTATCACAGGCTCCAGG----------GCGTGGGTGG	4.30%	-28	2119
CR001127-sgRNA	TGCTTTTATCACAGGCTCCAGG-----TTTGGCCTCTGATTAGGGTGGGGGCGTGGGTGG	3.72%	-5	2120
CR001127-sgRNA	TGCTTTTATCACAGGC----------GTGGGTGG	3.71%	-36	2121
CR001127-sgRNA	TGCTTTTATCACAGGCTCCAGGAAG--TTTGGCCTCTGATTAGGGTGGGGGCGTGGGTGG	3.53%	-2	2122
CR001127-sgRNA	TGCTTTTATCACAGGCTCCAGGAAGGtC----------CGTTTGCGTGGGTGG	2.29%	-17	2123
	CACGCCCCCACCCTAATCAG**agg**			2124
CR00309-sgRNA	TATCACAGGCTCCAGGAAGGGTTTGGC----------GTGGGTGGGGTAGA	11.56%	-19	2125
CR00309-sgRNA	TATCACAGGCTCCAGGAAGGGTTTGGCCTCTGAaTTAGGGTGGGGGCGTGGGTGGGGTAGA	7.29%	1	2126
CR00309-sgRNA	TATCACAGGCTCCAGGAAGGG----------CGTGGGTGGGGTAGA	6.16%	-24	2127
CR00309-sgRNA	TATCACAGGCTCCAGGAAGGG----------GGCGTGGGTGGGGTAGA	4.74%	-22	2128
CR00309-sgRNA	TATCACAGGCTCCAGGAAGGGTTTGG----------GCGTGGGTGGGGTAGA	4.34%	-18	2129
CR00309-sgRNA	TATCACAGGCTCCAGGAAGGGTTTGG----------GTGGGGTAGA	3.45%	-24	2130
CR00309-sgRNA	TATCACAGGCTCCAGG----------GGCGTGGGTGGGGTAGA	1.87%	-27	2131
	GAAGGGTTTGGCCTCTGATT**agg**			2132
CR00315-dgRNA	AGGCTCCAGGAAGGGTTTGGC----------GTGGGTGGGGTAGAAGAGGA	5.80%	-19	2133
CR00315-dgRNA	AGGCTCCAGGAAGGGTTTGG----------GCGTGGGTGGGGTAGAAGAGGA	4.08%	-18	2134
CR00315-dgRNA	AGGCTCCAGG----------GGCGTGGGTGGGGTAGAAGAGGA	2.80%	-27	2135
CR00315-dgRNA	AGGCTCCAGGAAGGGT----------GGGGTAGAAGAGGA	2.62%	-30	2136
CR00315-dgRNA	AGGCTCCAGGAAGGGTTTGGCCTCTG----------GCGTGGGTGGGGTAGAAGAGGA	2.49%	-12	2137
CR00315-dgRNA	AGGCTCCAGGAAGGG----------CGTGGGTGGGGTAGAAGAGGA	2.44%	-24	2138
CR00315-dgRNA	AGGCTCCAGGAAGGGTTTGGCCTCTGcG----------TAGAAGAGGA	1.55%	-22	2139
CR00315-dgRNA	AGGCTCCAGGAAGGGTT----------GGGTGGGGTAGAAGAGGA	1.52%	-25	2140
CR00315-sgRNA	AGGCTCCAGGAAGGGTTTGGC----------GTGGGTGGGGTAGAAGAGGA	8.40%	-19	2141
CR00315-sgRNA	AGGCTCCAGGAAGGGTTTGG----------GCGTGGGTGGGGTAGAAGAGGA	4.66%	-18	2142
CR00315-sgRNA	AGGCTCCAGGAAGGGT----------GGGGTAGAAGAGGA	3.77%	-30	2143
CR00315-sgRNA	AGGCTCCAGGAAGGGTTTGG----------GGTAGAAGAGGA	3.19%	-28	2144
CR00315-sgRNA	AGGCTCCAGGAAGGG----------GGCGTGGGTGGGGTAGAAGAGGA	2.78%	-22	2145
CR00315-sgRNA	AGGCTCCAGG----------CGTGGGTGGGGTAGAAGAGGA	2.71%	-29	2146
CR00315-sgRNA	AGGCTCCAGGAAGGG----------CGTGGGTGGGGTAGAAGAGGA	2.50%	-24	2147
CR00315-sgRNA	AGGCTCCAGG----------GTAGAAGAGGA	2.28%	-39	2148
CR00315-sgRNA	AGGCTCCAGGAAGGGTTTGG----------GTGGGGTAGAAGAGGA	2.25%	-24	2149
	AAGGGTTTGGCCTCTGATTA**ggg**			2150
CR00314-dgRNA	GGCTCCAGGAAGGGTTTGGCCTCTGATTccccATTGTGGGGGCGTGGGTGGGGTAGAAGAGGAC	0.91%	4	2151
CR00314-dgRNA	GGCTCCAGGAAGGGTTTGG----------TGGGGTAGAAGAGGAC	0.86%	-25	2152
CR00314-sgRNA	GGCTCCAGGAAGGGTTTGGC----------GTGGGTGGGGTAGAAGAGGAC	4.47%	-19	2153
CR00314-sgRNA	GGCTCCAGGAAGGG----------CGTGGGTGGGGTAGAAGAGGAC	3.89%	-24	2154
CR00314-	GGCTCCAGGAAGGGTTTGG----------GTGGGGTAGAAGAGGAC	3.75%	-24	2155

sgRNA				
CR00314-sgRNA	GGCTCCAGGAAGGGTTTGGCCTCTGA---------GGGCGTGGGTGGGGTAGAAGAGGAC	2.60%	-9	2156
CR00314-sgRNA	GGCTCCAGGAAGGGTTTGGCC----------GTGGGTGGGGTAGAAGAGGAC	2.26%	-18	2157
CR00314-sgRNA	GGCTCCAGGAAGGGTTTGGCCTCTGAaTTAGGGTGGGGGCGTGGGTGGGGTAGAAGAGGAC	2.11%	1	2158
CR00314-sgRNA	GGCTCCAGGAAGGGTTTG----------CGTGGGTGGGGTAGAAGAGGAC	2.05%	-20	2159
CR00314-sgRNA	GGCTCCAGGAAGGGTTTGG----------GGTAGAAGAGGAC	2.04%	-28	2160
CR00314-sgRNA	GGCTCCAGGAAGGGT----------GGGTGGGGTAGAAGAGGAC	2.03%	-26	2161
	GGTTTGGCCTCTGATTAGGG**tgg**			2162
CR00313-dgRNA	TCCAGGAAGGGTTTGGC----------GTGGGTGGGGTAGAAGAGGACTGG	16.00%	-19	2163
CR00313-dgRNA	TCCAGGAAGGGT----------GGGGTAGAAGAGGACTGG	5.69%	-30	2164
CR00313-dgRNA	TCCAGGAAGGGTTTGGCCTCTGATTAGG-TGGGGGCGTGGGTGGGGTAGAAGAGGACTGG	3.93%	-1	2165
CR00313-dgRNA	TCCAGGAAGGGT----------AGAAGAGGACTGG	3.57%	-35	2166
CR00313-dgRNA	TCCAGGAAGGG----------GGCGTGGGTGGGGTAGAAGAGGACTGG	2.75%	-22	2167
CR00313-dgRNA	TCCAGGAAGGG----------CGTGGGTGGGGTAGAAGAGGACTGG	2.70%	-24	2168
CR00313-dgRNA	TCCAGGAAGGGTTTGG----------GTGGGGTAGAAGAGGACTGG	2.66%	-24	2169
CR00313-dgRNA	TCCAGGAAGGGTTTGGCCTCTGATT-GGGTGGGGGCGTGGGTGGGGTAGAAGAGGACTGG	2.17%	-1	2170
CR00313-sgRNA	TCCAGGAAGGGTTTGGC----------GTGGGTGGGGTAGAAGAGGACTGG	11.86%	-19	2171
CR00313-sgRNA	TCCAGGAAGGG----------GGCGTGGGTGGGGTAGAAGAGGACTGG	3.86%	-22	2172
CR00313-sgRNA	TCCAGGAAGGGTTTGG----------GTGGGGTAGAAGAGGACTGG	3.36%	-24	2173
CR00313-sgRNA	TCCAGGAAGGGTTTGGCCTCTGATTAGG-TGGGGGCGTGGGTGGGGTAGAAGAGGACTGG	3.31%	-1	2174
CR00313-sgRNA	TCCAGGAAGGGTT----------GGGGTAGAAGAGGACTGG	2.83%	-29	2175
CR00313-sgRNA	TCCAGGAAGGGTTTGGCCT----------GGGTGGGGTAGAAGAGGACTGG	2.76%	-19	2176
CR00313-sgRNA	TCCAGGAAGGGTTTGG----------TAGAAGAGGACTGG	2.31%	-30	2177
	GTTTGGCCTCTGATTAGGGT**ggg**			2178
CR00312-dgRNA	CCAGGAAGGGTTTGGCCTCTGATTAGG-TGGGGGCGTGGGTGGGGTAGAAGAGGACTGGC	16.87%	-1	2179
CR00312-dgRNA	CCAGGAAGGGTTTGGC----------GTGGGTGGGGTAGAAGAGGACTGGC	9.86%	-19	2180
CR00312-dgRNA	CCAGGAAGGGTTTGGCCTCTGATT--GGTGGGGGCGTGGGTGGGGTAGAAGAGGACTGGC	5.65%	-2	2181
CR00312-dgRNA	CCAGGAAGGG----------CGTGGGTGGGGTAGAAGAGGACTGGC	3.83%	-24	2182
CR00312-dgRNA	CCAGGAAGGG----------GGCGTGGGTGGGGTAGAAGAGGACTGGC	3.42%	-22	2183
CR00312-dgRNA	CCAGGAAGGGTTTGG----------GTGGGGTAGAAGAGGACTGGC	2.10%	-24	2184
CR00312-dgRNA	CCAGGAAGGGTTTGGCCTCTGA----GGTGGGGGCGTGGGTGGGGTAGAAGAGGACTGGC	1.85%	-4	2185
CR00312-sgRNA	CCAGGAAGGGTTTGGCCTCTGATTAGG-TGGGGGCGTGGGTGGGGTAGAAGAGGACTGGC	13.35%	-1	2186
CR00312-sgRNA	CCAGGAAGGGTTTGGC----------GTGGGTGGGGTAGAAGAGGACTGGC	7.85%	-19	2187
CR00312-sgRNA	CCAGGAAGGGTTTGG----------GTGGGGTAGAAGAGGACTGGC	4.19%	-24	2188
CR00312-sgRNA	CCAGGAAGGGTTTGGCCTCTGATT--GGTGGGGGCGTGGGTGGGGTAGAAGAGGACTGGC	3.98%	-2	2189
CR00312-sgRNA	CCAGGAAGGGTTTGGCCTCTGATTAGGG-----GCGTGGGTGGGGTAGAAGAGGACTGGC	2.95%	-5	2190
CR00312-sgRNA	CCAGGAAGGG----------CGTGGGTGGGGTAGAAGAGGACTGGC	2.29%	-24	2191
CR00312-sgRNA	CCAGGAAGGGTTTGGCCTCTGATTAGaGGTGGGGGCGTGGGTGGGGTAGAAGAGGACTGGC	2.09%	1	2192
CR00312-d1gRNA	CCAGGAAGGGTTTGGCCTCTGATTAGG-TGGGGGCGTGGGTGGGGTAGAAGAGGACTGGC	19.22%	-1	2193
CR00312-d1gRNA	CCAGGAAGGGTTTGGCCTCTGATT--GGTGGGGGCGTGGGTGGGGTAGAAGAGGACTGGC	6.28%	-2	2194

CR00312-d1gRNA	CCAGGAAGGGTTTGG----------GTGGGGTAGAAGAGGACTGGC	5.31%	-24	2195
CR00312-d1gRNA	CCAGGAAGGGTTTGGC----------GTGGGTGGGGTAGAAGAGGACTGGC	4.22%	-19	2196
CR00312-d1gRNA	CCAGGAAGGGTTTGG----------GGGCGTGGGTGGGGTAGAAGAGGACTGGC	3.10%	-16	2197
CR00312-d1gRNA	CCAGGAAGGGTTTGGCCTCTGATTAG--TGGGGGCGTGGGTGGGGTAGAAGAGGACTGGC	2.85%	-2	2198
CR00312-d1gRNA	CCAGGAAGGG----------CGTGGGTGGGGTAGAAGAGGACTGGC	2.74%	-24	2199
CR00312-d2gRNA	CCAGGAAGGGTTTGGCCTCTGATTAGG-TGGGGGCGTGGGTGGGGTAGAAGAGGACTGGC	23.15%	-1	2200
CR00312-d2gRNA	CCAGGAAGGGTTTGGC----------GTGGGTGGGGTAGAAGAGGACTGGC	8.99%	-19	2201
CR00312-d2gRNA	CCAGGAAGGGTTTGGCCTCTGATT--GGTGGGGGCGTGGGTGGGGTAGAAGAGGACTGGC	6.82%	-2	2202
CR00312-d2gRNA	CCAGGAAGGG----------GCGTGGGTGGGGTAGAAGAGGACTGGC	2.69%	-23	2203
CR00312-d2gRNA	CCAGGAAGGG----------CGTGGGTGGGGTAGAAGAGGACTGGC	2.29%	-24	2204
CR00312-d2gRNA	CCAGGAAGGGTTTGGCCTCTGATTAG--TGGGGGCGTGGGTGGGGTAGAAGAGGACTGGC	2.25%	-2	2205
CR00312-d2gRNA	CCAGGAAGGGTTTGG----------GGGCGTGGGTGGGGTAGAAGAGGACTGGC	2.13%	-16	2206
	TTTGGCCTCTGATTAGGGTG**ggg**			2207
CR00311-dgRNA	CAGGAAGGGTTTGGCCTCTGATTAGG-TGGGGGCGTGGGTGGGGTAGAAGAGGACTGGCA	19.62%	-1	2208
CR00311-dgRNA	CAGGAAGGGTTTGGC----------GTGGGTGGGGTAGAAGAGGACTGGCA	3.01%	-19	2209
CR00311-dgRNA	CAGGAAGGGTTTGGCCTCTGATTAG--TGGGGGCGTGGGTGGGGTAGAAGAGGACTGGCA	2.77%	-2	2210
CR00311-dgRNA	CAGGAAGGGTTTGGCCTCTGATTAGGG-----GCGTGGGTGGGGTAGAAGAGGACTGGCA	2.23%	-5	2211
CR00311-dgRNA	CAGGAAGGGTTTGG----------GTGGGGTAGAAGAGGACTGGCA	2.21%	-24	2212
CR00311-dgRNA	CAGGAAGGGTTTGG----------TGGGGGCGTGGGTGGGGTAGAAGAGGACTGGCA	2.05%	-13	2213
CR00311-dgRNA	CAGGAAGGGTTTGGCCTCTG-------TGGGGGCGTGGGTGGGGTAGAAGAGGACTGGCA	1.88%	-7	2214
CR00311-dgRNA	CAGGAAGGGT----------GGGGTAGAAGAGGACTGGCA	1.76%	-30	2215
CR00311-sgRNA	CAGGAAGGGTTTGGCCTCTGATTAGG-TGGGGGCGTGGGTGGGGTAGAAGAGGACTGGCA	28.21%	-1	2216
CR00311-sgRNA	CAGGAAGGGTTTGGC----------GTGGGTGGGGTAGAAGAGGACTGGCA	4.88%	-19	2217
CR00311-sgRNA	CAGGAAGGGT----------GGGGTAGAAGAGGACTGGCA	2.72%	-30	2218
CR00311-sgRNA	CAGGAAGGGTTTGGCCTCTGATTAG--TGGGGGCGTGGGTGGGGTAGAAGAGGACTGGCA	2.62%	-2	2219
CR00311-sgRNA	CAGGAAGGGTTTGGCCTCTGATTAGGG----GGCGTGGGTGGGGTAGAAGAGGACTGGCA	2.35%	-4	2220
CR00311-sgRNA	CAGGAAGGGTTTGGCCTCTGATTAGGG-----GCGTGGGTGGGGTAGAAGAGGACTGGCA	2.06%	-5	2221
CR00311-d1gRNA	CAGGAAGGGTTTGGCCTCTGATTAGG-TGGGGGCGTGGGTGGGGTAGAAGAGGACTGGCA	31.34%	-1	2222
CR00311-d1gRNA	CAGGAAGGGTTTGGCCTCTGATTAG--TGGGGGCGTGGGTGGGGTAGAAGAGGACTGGCA	4.00%	-2	2223
CR00311-d1gRNA	CAGGAAGGGTTTGGCCT----------AAGAGGACTGGCA	2.84%	-30	2224
CR00311-d1gRNA	CAGGAAGGGTTTGG----------GAGGACTGGCA	2.41%	-35	2225
CR00311-d1gRNA	CAGGAAGGGTTT----------AGAAGAGGACTGGCA	2.35%	-33	2226
CR00311-d1gRNA	CAGGAAGGGTTTGGCCTC----------GAGGACTGGCA	2.11%	-31	2227
CR00311-d1gRNA	CAGGAAGGGTTTGGCCTCTGATTAGGG----GGCGTGGGTGGGGTAGAAGAGGACTGGCA	2.03%	-4	2228
CR00311-d1gRNA	CAGGAAGGGTTTGGCCTCTGATTAGGG---GGGCGTGGGTGGGGTAGAAGAGGACTGGCA	1.71%	-3	2229
CR00311-d2gRNA	CAGGAAGGGTTTGGCCTCTGATTAGG-TGGGGGCGTGGGTGGGGTAGAAGAGGACTGGCA	30.20%	-1	2230
CR00311-d2gRNA	CAGGAAGGGTTTGGC----------GTGGGTGGGGTAGAAGAGGACTGGCA	7.57%	-19	2231
CR00311-d2gRNA	CAGGAAGGGTTTGGCCTCTGATTAG--TGGGGGCGTGGGTGGGGTAGAAGAGGACTGGCA	3.57%	-2	2232
CR00311-d2gRNA	CAGGAAGGGTTTGG----------GGTAGAAGAGGACTGGCA	2.39%	-28	2233
CR00311-	CAGGAAGGGTTTGGCCTCTGATTAGGG-----GCGTGGGTGGGGTAGAAGAGGACTGGCA	2.10%	-5	2234

d2gRNA				
CR00311-d2gRNA	CAGGAAGGGTTTGGCCTCTGATTAGGG----GGCGTGGGTGGGGGTAGAAGAGGACTGGCA	1.50%	-4	2235
CR00311-d2gRNA	CAGGAAGGGTTTGG----------GGGCGTGGGTGGGGTAGAAGAGGACTGGCA	1.49%	-16	2236
	TTGGCCTCTGATTAGGGTGG**ggg**			2237
CR00310-sgRNA	AGGAAGGGTTTGGCCTCTGATTAGGG----GGCGTGGGTGGGGTAGAAGAGGACTGGCAG	7.70%	-4	2238
CR00310-sgRNA	AGGAAGGGTTTGGCCTCTGATTAGGG------CGTGGGTGGGGTAGAAGAGGACTGGCAG	7.13%	-6	2239
CR00310-sgRNA	AGGAAGGGTTTGGCCTCTGATTAGGG-----GCGTGGGTGGGGTAGAAGAGGACTGGCAG	6.34%	-5	2240
CR00310-sgRNA	AGGAAGGGTTTGGCCTCTGATTAGG-TGGGGGCGTGGGTGGGGTAGAAGAGGACTGGCAG	5.38%	-1	2241
CR00310-sgRNA	AGGAAGGGTTTGGCCTCTGATTAG--TGGGGGCGTGGGTGGGGTAGAAGAGGACTGGCAG	3.73%	-2	2242
CR00310-sgRNA	AGGAAGGGTTTGGCCTCTGATT-----GGGGGCGTGGGTGGGGTAGAAGAGGACTGGCAG	3.54%	-5	2243
CR00310-dgRNA	AGGAAGGGTTTGGCCTCTGATTAGGGTGGGGGCGTGGGTGGG-TAGAAGAGGACTGGCAG	0.67%	-1	2244
	TCTGATTAGGGTGGGGGCGT**ggg**			2245
CR00308-sgRNA	GGTTTGGCCTCTGATTAGGGTGGGG----------TAGAAGAGGACTGGCAGACCTCT	16.28%	-12	2246
CR00308-sgRNA	GGTTTGGCCTCTGATTAGGGTGGGGG----------TAGAAGAGGACTGGCAGACCTCT	5.59%	-11	2247
CR00308-sgRNA	GGTTTGGCCTCTGATTAGGGTGGG--------TGGGGTAGAAGAGGACTGGCAGACCTCT	4.51%	-8	2248
CR00308-sgRNA	GGTTTGGCCTCTGAT----------GGGGTAGAAGAGGACTGGCAGACCTCT	3.54%	-18	2249
CR00308-sgRNA	GGTTTGGCCTCTGATTtA----------CTGGCAGACCTCT	2.76%	-29	2250
CR00308-sgRNA	GGTTTGGCCTCTGATTgG-------CCGTGGGTGGGGGTAGAAGAGGACTGGCAGACCTCT	2.27%	-7	2251
CR00308-sgRNA	GGTTTGGCCTCTGATTAGGG----------GTAGAAGAGGACTGGCAGACCTCT	2.26%	-16	2252
CR00308-sgRNA	GGTTTGGCCTCTGATcC--AAGAGCCCGTGGGTGGGGTAGAAGAGGACTGGCAGACCTCT	1.99%	-2	2253
CR00308-dgRNA	GGTTTGGCCTCTGATTAGGGTGGGGGCGTGGGTGGG-TAGAAGAGGACTGGCAGACCTCT	0.42%	-1	2254
	ATTAGGGTGGGGGCGTGGGT**ggg**			2255
CR001131-dgRNA	TGGCCTCTGATTAGGGTGGGG----------TAGAAGAGGACTGGCAGACCTCTCCAT	44.62%	-12	2256
CR001131-dgRNA	TGGCCTCTGATTAGGGTGGGGG----------TAGAAGAGGACTGGCAGACCTCTCCAT	3.19%	-11	2257
CR001131-dgRNA	TGGCCTCTGATTAGGGTGGGGGCGTGG-TGGGGTAGAAGAGGACTGGCAGACCTCTCCAT	1.72%	-1	2258
CR001131-dgRNA	TGGCCTCTGATTAGGGTGGGGGCG----------AAGAGGACTGGCAGACCTCTCCAT	1.04%	-12	2259
	TTAGGGTGGGGGCGTGGGTG**ggg**			2260
CR001124-dgRNA	GGCCTCTGATTAGGGTGGGG----------TAGAAGAGGACTGGCAGACCTCTCCATC	8.52%	-12	2261
CR001124-dgRNA	GGCCTCTGATTAGGGTGGGGGCGTGG-TGGGGTAGAAGAGGACTGGCAGACCTCTCCATC	2.12%	-1	2262
CR001124-dgRNA	GGCCTCTGATTAGGGTGGGGG----------TAGAAGAGGACTGGCAGACCTCTCCATC	1.33%	-11	2263
	TGTAACTAATAAATACC**agg**			2264
CR00260-dgRNA	CTGCTGAGGTGTAACTAATAAATACC-GGAGGCAGCATTTTAGTTCACAAGCTCGGAGCA	26.54%	-1	2265
CR00260-dgRNA	CTGCTGAGGTGTAACTAATAAATAC-AGGAGGCAGCATTTTAGTTCACAAGCTCGGAGCA	12.39%	-1	2266
CR00260-dgRNA	CTGCTGAGGTGTAACTAATAAATACCcAGGAGGCAGCATTTTAGTTCACAAGCTCGGAGCA	12.32%	1	2267
CR00260-dgRNA	CTGCTGAGGTGTAACTAATAAATACC--GAGGCAGCATTTTAGTTCACAAGCTCGGAGCA	2.37%	-2	2268
CR00260-dgRNA	CTGCTGAGGTGTAACTAATAAAT--CAGGAGGCAGCATTTTAGTTCACAAGCTCGGAGCA	1.89%	-2	2269
CR00260-dgRNA	CTGCTGAGGTGTAACTAATAAATA---GGAGGCAGCATTTTAGTTCACAAGCTCGGAGCA	1.28%	-3	2270
	CAGTGAGATGAGATATCAAA**ggg**			2271
CR00246-dgRNA	GGGAGATGGAATGAACACTTTTCGTCCCCTTTGgATATCTCATCTCACTGAGCTCTGGGCC	7.56%	1	2272

CR00246-dgRNA	GGGAGATGGAATGAACACTTTTCGTCCCCTTTGAT--CTCATCTCACTGAGCTCTGGGCC	4.46%	-2	2273
CR00246-dgRNA	GGGAGATGGAATGAACACTTTTCGTCCCCTTTG------CATCTCACTGAGCTCTGGGCC	3.50%	-6	2274
CR00246-dgRNA	GGGAGATGGAATGAACACTTTTCGTCCCCTTT-----CTCATCTCACTGAGCTCTGGGCC	2.98%	-5	2275
CR00246-dgRNA	GGGAGATGGAATGAACACTTTTCGTCCCCTTT-ATATCTCATCTCACTGAGCTCTGGGCC	2.97%	-1	2276
CR00246-dgRNA	GGGAGATGGAATGAACACTTTTCGTCCCCTTTG---TCTCATCTCACTGAGCTCTGGGCC	2.96%	-3	2277
CR00246-dgRNA	GGGAGATGGAATGAACACTTTTCGTCCCCTTT--TATCTCATCTCACTGAGCTCTGGGCC	2.93%	-2	2278
CR00246-dgRNA	GGGAGATGGAATGAACACTTTTCGTCCCCTTTG-TATCTCATCTCACTGAGCTCTGGGCC	2.70%	-1	2279
	TCAGTGAGATGAGATATCAA**agg**			2280
CR00245-dgRNA	GGAGATGGAATGAACACTTTTCGTCCCCTTTGAaTATCTCATCTCACTGAGCTCTGGGCCG	22.36%	1	2281
CR00245-dgRNA	GGAGATGGAATGAACACTTTTCGTCCCCTTTGA-ATCTCATCTCACTGAGCTCTGGGCCG	8.97%	-1	2282
CR00245-dgRNA	GGAGATGGAATGAACACTTTTCGTCCCCTTTGAT--CTCATCTCACTGAGCTCTGGGCCG	4.03%	-2	2283
CR00245-dgRNA	GGAGATGGAATGAACACTTTTCGTCCCCTTTG-TATCTCATCTCACTGAGCTCTGGGCCG	2.45%	-1	2284
CR00245-dgRNA	GGAGATGGAATGAACACTTTTCGTCCCCTT--ATATCTCATCTCACTGAGCTCTGGGCCG	1.85%	-2	2285
CR00245-dgRNA	GGAGATGGAATGAACACTTTTCGTCCCCTTTGA-----CATCTCACTGAGCTCTGGGCCG	1.38%	-5	2286
	GTGCCAGATGAACTTCCCAT**tgg**			2287
g7BCL11a-BC-1sgRNA	CTGTGGGCAGTGCCAGATGAACTTCC-ATTGGGGGGACATTCTTATTTTTTATCGAGCACAA	15.63%	-1	2288
g7BCL11a-BC-1sgRNA	CTGTGGGCAGTGCCAGATGAACTTC--ATTGGGGGGACATTCTTATTTTTTATCGAGCACAA	7.36%	-2	2289
g7BCL11a-BC-1sgRNA	CTGTGGGCAGTGCCAGATGAACTTCCCcATTGGGGGGACATTCTTATTTTTTATCGAGCACAA	6.88%	1	2290
g7BCL11a-BC-1sgRNA	CTGTGGGCAGTGCCAGATGAAC-----ATTGGGGGGACATTCTTATTTTTTATCGAGCACAA	2.81%	-5	2291
g7BCL11a-BC-1sgRNA	CTGTGGGCAGTGCCAGATGAACTTCC--TTGGGGGGACATTCTTATTTTTTATCGAGCACAA	2.59%	-2	2292
g7BCL11a-BC-2sgRNA	CTGTGGGCAGTGCCAGATGAACTTCC-ATTGGGGGGACATTCTTATTTTTTATCGAGCACAA	18.89%	-1	2293
g7BCL11a-BC-2sgRNA	CTGTGGGCAGTGCCAGATGAACTTC--ATTGGGGGGACATTCTTATTTTTTATCGAGCACAA	9.14%	-2	2294
g7BCL11a-BC-2sgRNA	CTGTGGGCAGTGCCAGATGAACTTCCCcATTGGGGGGACATTCTTATTTTTTATCGAGCACAA	5.52%	1	2295
g7BCL11a-BC-2sgRNA	CTGTGGGCAGTGCCAGATGAACTTCC--TTGGGGGGACATTCTTATTTTTTATCGAGCACAA	4.39%	-2	2296
g7BCL11a-BC-2sgRNA	CTGTGGGCAGTGCCAGATGAACT---CATTGGGGGGACATTCTTATTTTTTATCGAGCACAA	3.18%	-3	2297

To determine whether CD34+ HSPC have retained their multilineage potential to differentiate into effector cells after ex vivo manipulations including genome editing, in vitro colony forming cell (CFC) unit assays were performed for select gRNAs. The genome edited cells were suspended in cytokine-supplemented methylcellulose and maintained for 14 days at 37°C in a humidified atmosphere of 5% CO2. Discrete colonies developed which were classified and counted based on the number and types of mature cells using morphological and phenotypic criteria (STEMvision) that they contain and scored for contribution to colony forming unit-erythroid (CFU-E), burst forming unit-erythroid (BFU-E), colony-forming unit - granulocyte/macrophage (CFU-GM) and colony-forming

unit - granulocyte/erythrocyte/macrophage/megakaryocyte (CFU-GEMM; Figure 21). The colony forming potential of mock transfected cells was the highest followed by gRNAs targeting +58 erythroid enhancer of BCL11A. A similar number and types of colonies were observed for gRNAs targeting BCL11A erythroid enhancer. The guide RNA targeting exon 2 of BCL11A gave the least number of colonies (Figure 22).

Relative mRNA expression levels of BCL11A, gamma- and beta-globin chains in unilineage erythroid cultures were quantified by Real-Time PCR. The transcript levels were normalized against human GAPDH transcript levels. The BCL11A mRNA levels were reduced in genome edited HSPC. In contrast, BCL11A mRNA levels remained the same in unedited or edited HSPC at the exon 2 of BCL11A on days 7 and 14 of erythroid differentiation (Figure 23). Gamma globin mRNA levels increased and correspondingly beta-globin mRNA decreased gradually in edited HSPC during erythroid differentiation (Figure 23). Increase in HbF and decrease in beta-globin (sickled globin) levels in erythrocytes derived from genome edited cells likely to have therapeutic implications by reduced sickling.

The genome edited and unedited HSPC at various stages (day 7, 14 and 21) of erythroid differentiation were analyzed by flow cytometry for expression levels of fetal globin and two erythroid cell surface markers, transferrin receptor (CD71) and glycophorin A (CD235a) using antibodies conjugated to fluorescent dyes. The live cells were identified and gated by exclusion of 7AAD. Genome editing did not adversely affect erythroid differentiation as the cultured cells showed similar levels of CD71 and CD235A positivity consistent with late stage erythroblasts. Genome editing of +58 erythroid enhancer region resulted in a larger increase in HbF containing cells (up to 67%) than other gRNAs and the mock electroporated cells (Figure 24). Very high induction of HbF positive cells by g7 gRNA targeting exon 2 of BCL11A was observed. However, the cell proliferation and colony forming potential of exon 2 targeted cells was dramatically reduced (Figures 21 and 22).

Upon deep sequencing of the targeted region, we noticed that GATA1 and TAL1 binding motifs were intact in the genome edited target region (Figure 25). Recent literature demonstrated the importance of GATA1 binding site in regulation of BCL11A expression and derepression of fetal globin. Viestra et al., Nature Methods. 2015, 12:927. In contrast to the literature reports, which showed the importance of the two motifs for maintenance of BCL11A levels in adult erythroid cells, our findings demonstrate that sequences upstream of the two transcription factor binding sites are also important in regulation of BCL11a gene expression, and genome editing exclusively at these upstream sites leads to upregulation of HbF, even when the GATA1 and TAL1 binding sites remain intact.

Example 3.1

Methods:

Human $CD34^+$ cell culture. Human CD34+ cells were isolated from G-CSF mobilized peripheral blood from adult donors (AllCells) using immunoselection (Miltenyi) according to the manufacturer's instructions and expanded for 3 days using StemSpan SFEM (StemCell Technologies; Cat no. 09650) supplemented with 50 ng/mL each of thrombopoietin (Tpo), Flt3 ligand (Flt-3L, Life Technologies, Cat. #PHC9413), human stem cell factor (SCF, Life Technologies, Cat. #PHC2113) and human interleukin-6 (IL-6, Life Technologies, Cat. #PHC0063), as well as 1x antibiotic/antimycotic (Gibco, Cat. #10378-016) and 500 nM compound 4.

Assembly of Cas9 and guide RNA ribonucleoprotein (RNP) complexes, preparation of HSPC, and electroporation of RNP into HSPC. Cas9-guide RNA ribonucleoprotein complexes (RNPs) were prepared immediately prior to electroporation. For formation of RNP using dual guide RNAs (dgRNAs), 3 µg of each of crRNA (in 2.24 µL) and tracr (in 1.25 µL) are first denatured at 95°C for 2 min in separate tubes and then cooled to room temperature. For preparation of Cas9 protein, 6 µg of CAS9 protein (in 1 µL) was mixed with 0.5 µL of 5 x CCE buffer (20 mM HEPES, 100 mM KCL, 5 mM MgCL2, 5% Glycerol and freshly added 1 mM DTT). Tracr was first mixed with the Cas9 preparation and incubated at 37°C for 5 min. The crRNA was then added to Tracr/CAS9 complexes and incubated for 5 min at 37°C. For the None/control condition, vehicle rather than crRNA was added to the Tracr/CAS9 complexes. The HSPC were collected by centrifugation and resuspended in P3 Primary Cell Solution (Lonza cat. No. PBP3-00675) at a cell density of 2.5 x 10^6/mL. The RNP was mixed with 20 µL of cells by pipetting up and down and incubated at RT for 2 min. The RNP/cell mixture (20 µL) was electroporated using code CM-137 on the 4D-Nucleofector (Lonza). Duplicate 20 µL electroporations were performed. For the experiments in this Example 3.1, the tracr used was SEQ ID NO: 7808, and the crRNA had the following format and sequence, with 2'O-Methyl (m) and Phosphorothioate Bond (*) modifications indicated: mN*mN*mN*rNrNrNrNrNrNrNrNrNrNrNrNrNrNrNrGrUrUrUrUrArGrArGrCrUrArU*mG*mC*mU (SEQ ID NO: 2298), where N's are the nucleotides of the indicated targeting domain (e.g., as indicated by the CRxxxxx identifier).

In vitro erythropoiesis and FACS analysis for HbF containing erythroid cells. After electroporation, the cells were immediately transferred into 250 µL pre-warmed erythroid differentiation medium (EDM) consisting of IMDM (Hyclone, Cat. #SH30228.01), 330 µg /mL human holo-transferrin (Invitria Cat# 777TRF029), 10 µg /mL recombinant human insulin (Gibco Cat#A1138211), 2 IU/mL heparin (Sigma, part #H3393), 5% human AB serum (Sigma, Cat# H4522), 125 ng/mL human erythropoietin (Peprotech #10779-058), and 1x antibiotic/antimycotic (Gibco, Cat. #10378-016). EDM was further supplemented with 1 µM hydrocortisone (Sigma H8672), 100 ng/mL human SCF (Life Technologies, Cat. #PHC2113), and 5 ng/mL human IL-3 (Peprotech #10779-598). After 2

days, the cell culture was diluted in fresh medium. Cultures were maintained for a total of 7 days, at which time the cells were analyzed by intracellular staining for HbF expression. Briefly, the cells were washed once with PBS, resuspended in LIVE/DEAD® Fixable Violet Dead Cell Stain (ThermoFisher L34963; 1:1000 in PBS) and incubated for 30 min. Cell were then washed and stained with anti-CD71-BV711 (Fisher Scientific Company Llc. BDB563767) and anti-CD235a-APC (BD 551336) antibodies for 30 min. The cells were then washed, followed by fixation with fixation buffer (Biolegend, Cat# 420801) and permeabilized with 1x intracellular staining permeabilization wash buffer (Biolegend, Cat# 421002) according to the manufacturer's instructions. The cells were then incubated with 0.5 µL of anti-HbF-PE antibody (Life Technologies, part #MHFH04) in 50 µL of 1x intracellular staining perm wash buffer for 20 min at room temperature. The cells were washed twice with 2 mL of 1x intracellular staining Perm wash buffer and resuspend in staining buffer and analyzed on an LSRFortessa flow cytometer (BD Biosciences) for HbF expression. The results were analyzed using Flowjo and data were presented as % of HbF positive cells (F-cells) in the viable CD71 positive erythroid cell population.

Genomic DNA preparation and next generation sequencing (NGS). Genomic DNA was prepared from edited and unedited HSPC at 48 hours post-electroporation using Quick Extract DNA Extraction Solution (Epicentre Cat # QE09050). To determine editing efficiency and patterns of insertions and deletions (indels), PCR products were generated using primers flanking the target sites, which were then subjected to next generation sequencing (NGS). Percent editing of corresponding sequences in unedited samples was typically less than 1% and never exceeded 3%.

Results:

Without being bound by theory, it is believed that targeted genetic disruption of the BCL11A erythroid enhancer region will relieve repression of γ-globin expression, allowing production of the red blood cells containing elevated HbF protein, (cells expressing fetal hemoglobin, e.g., expressing elevated levels of fetal hemoglobin, are sometimes referred to herein as "F-cells." In embodiments, a cell is considered an F-cell if it produces as least 6 picograms fetal hemoglobin per cell). The elevated HbF prevents sickling of the red blood cells under deoxygenated conditions and will be therapeutic/curative for the patients of both β-thalassemia and SCD. Autologous hematopoietic stem cell transplantation (HSCT) with *ex vivo* genome edited HSC from SCD patients was also combined with stem cell expansion enhancing technology, e.g., an aryl hydrocarbon receptor (AHR) inhibitor, e.g., as described in WO2010/059401 (the contents of which are incorporated by reference in their entirety), e.g., Compound 4, to improve ex vivo expansion and increase the dose of gene modified HSC delivered.

For efficient genome editing via programmable nuclease, Cas9, the successful delivery of guide RNA (gRNA) and Cas9 protein into target cells and tissues is essential. Recent reports demonstrated that

Cas9 ribonucleoprotein (RNP) complexes when delivered into target cells by electroporation can accomplish efficient and specific genome editing in several different cell types. Cas9-RNP complexes cleave chromosomal DNA almost immediately after delivery and are degraded rapidly in cells, reducing off-target effects. In contrast, use of plasmid and viral vector systems used to deliver Cas9 results in prolonged expression of the enzyme aggravating off-target effects associated with the system. Additionally, delivery of RNPs into the target cells requires no additional tools which would greatly facilitate translation of genome editing for therapeutic purposes in the clinic. Purified recombinant Cas9 protein and gRNA complexes (RNPs) were delivered into cultured HSPC and an overview experiments used are shown in Figure 17.

Recombinant Cas9 protein was purified from Escherichia coli and complexed with synthetic dual gRNAs (dgRNA) that consist of crRNA and tracr to generate ribonucleoprotein (RNP) complexes. The list and of gRNAs used in the study are shown in Table 17 (e.g., gRNAs comprising the targeting domain of the incidated CRxxxxxx identifier). The RNP complexes were electroporated into CD34+ HSPC via electroporation as described under materials and methods. The cells were expanded prior to the delivery of RNP complexes. Actively dividing cells may facilitate uptake of RNP complexes delivered by electroporation.

Table 17. List of gRNAs targeting the BCL11A erythroid specific enhancer region used in the current study. All gRNA molecules were tested in duplicate in the dgRNA format as described in the materials and methods.

Guide RNA targeting domain ID	% HbF+ (F cells), average of replicates	% HbF+ (F cells), standard deviation	% edited, average of replicates	% edited, standard deviation
CR000308	27.7	0.5	52.8	0.7
CR000309	43.1	1.4	74.8	7.5
CR000310	28.6	0.1	65.1	3.6
CR000311	27.2	0.7	50.5	1.9
CR000312	47.9	1.0	87.8	0.9
CR000313	36.8	1.2	66.6	2.7
CR000314	32.7	0.1	39.8	0.5
CR000316_EH11	34.4	0.8	52.9	1.3
CR000317_EH4	50.7	0.4	82.7	2.5
CR001124	28.6	0.1	2.5	0.1
CR001125_EH12	42.3	0.4	94.0	0.9
CR001126_EH13	44.6	1.7	76.7	6.1
CR001127_EH14	33.3	0.1	26.1	3.3
CR001128_EH15	46.4	1.2	84.6	5.6
CR001129	25.3	0.8	3.6	0.4
CR001130	27.1	0.8	11.8	1.7
CR001131	28.6	0.0	35.6	8.5
None/control	22.4	0.6	n/a	n/a
g8	66.3	0.7	94.2	1.1

The genome edited and unedited HSPC were analyzed by flow cytometry for expression levels of fetal globin and two erythroid cell surface markers, transferrin receptor (CD71) and glycophorin A (CD235a) using antibodies conjugated to fluorescent dyes. The live cells were identified and gated by exclusion of Live Dead Violet. BCL11A erythroid specific enhancer region targeting resulted in increased percentage of erythroid cells containing HbF (up to 50.7%) compared to mock electroporated cells (22.4%) (Table 17). Induction of HbF positive cells by dgRNA including the targeting domain of g8 targeting exon 2 of BCL11A was also observed in parallel. Genomic PCR products of the BCL11A erythroid enhancer region were also subjected to next generation sequencing (NGS) to determine the percentage of edited alleles in the cell population. The dgRNA treatments that resulted in greater than 40% HbF+ cells had a range of 74.8% to 94.0% editing (Table 17). For the same targeting domain, the dgRNA in this Example differed in tracr and crRNA sequence from that in Example 3; however, the editing and HbF induction were similar across dgRNA formats for most targeting domains. Of note, CR000317_EH4 in the dgRNA format in the current study resulted in a high HbF induction to 50.7 % HbF+ cells. An increase in HbF-containing erythrocytes derived from genome edited cells is likely to have positive therapeutic implications by reduced sickling.

Example 3.2. Optimization of gRNA editing and fetal hemoglobin upregulation using gRNAs targeting the +58 region of the BCL11a enhancer in HSPCs.

Based on the % editing results from the comprehensive screen of gRNAs targeting the +58 region of the BCL11a Enhancer, 8 gRNA targeting domains were selected for further study and optimization. To test the effect of modificaitons to the gRNA molecules on % editing, erythroid differentiation, and fetal hemoglobin expression, different versions of the eight gRNA molecules targeting sites within the +58 region of the BCL11a enhancer region were designed. The following versions of of gRNAs comprising the targeting domain of CR00309, CR00311, CR00312, CR00316, CR01125, CR01126, CR01127, and CR01128 were made:

dgRNA (all sequences other than those of the targeting domain as described in Example 1):

1. Unmodified crRNA and unmodified tracr ("Unmodified" or "Unmod")
2. Unmodified crRNA and unmodified tracr, but with only the 5'-18nt of the indicated targeting domain (not the full 20 nt) ("18nt")
3. Three 3' nt and three 5' nt of crRNA modified with phosphorothioate linkages, and unmodified tracr ("PS")
4. Additional inverted abasic residue at both 5'- and 3'- end of crRNA, and unmodified tracr ("Invd")

5. Three 3' nt and three 5' nt of crRNA modified with phosphorothioate linkages and with 2'-Omethyl groups, and unmodified tracr ("OMePS")
6. Three 3' nt and three 5' nt of crRNA modified with 2'-fluoro group, and unmodified tracr ("F")
7. Three 3' nt and three 5' nt of crRNA modified with phosphorothioate linkages and with 2'-fluoro group, and unmodified tracr ("F-PS")

sgRNA (all sequences other than targeting domain are as described in Example 1):

1. Unmodified sgRNA ("Unmodified" or "Unmod")
2. Targeting domain consisting of only the 5'-18nt of the indicated targeting domain (not the full 20 nt) ("18nt")
3. Three 3' nt and three 5' nt of sgRNA modified with phosphorothioate linkages ("PS")
4. Additional inverted abasic residue at both 5'- and 3'- end of sgRNA ("Invd")
5. Three 3' nt and three 5' nt of sgRNA modified with phosphorothioate linkages and with 2'-Omethyl groups ("OMePS")
6. Three 3' nt and three 5' nt of sgRNA modified with 2'-fluoro group ("F")
7. Three 3' nt and three 5' nt of sgRNA modified with phosphorothioate linkages and with 2'-fluoro group ("F-PS")

All other reagents and methods were as described in Example 3. All results were run in duplicate, and the results are reported in Figures 28-32. Figure 28A and Figure 28B show the % editing, as measured by NGS, in CD34+ cells 2 days after electroporation of RNP comprising the indicated dual guide RNAs (dgRNAs). Figure 29 shows the % editing, as measured by NGS, in CD34+ cells 2 days after electroporation of RNP comprising the indicated single guide RNAs (sgRNAs). Figure 30 shows the % HbF positive cells as measured by flow cytometry at day 14 following transfer of edited CD34+ cells to erythroid differentiation medium, after electroporation of RNP comprising the indicated dual guide RNAs (dgRNAs). Figure 31 shows the % HbF positive cells as measured by flow cytometry at day 14 following transfer of edited CD34+ cells to erythroid differentiation medium, after electroporation of RNP comprising the indicated single guide RNAs (sgRNAs). Figure 32 shows the fold-expansion of edited cells after 14 days in the erythroid differentiation medium. These results indicate that many of the selected gRNA molecules, in both dgRNA and sgRNA formats, are capable of achieving genome editing at the target site with greater than 90% efficiency, and in some cases, with greater than 98% efficiency, when delivered to CD34+ cells as RNP via electroporation. As well, many of the selected gRNAs were able to achieve a greater than 20% increase in % F cells relative to unmodified cells ("mock"). Finally, although genome editing of BCL11A erythroid enhancer in HSPC lowered the expansion capabilities of erythroid cells, with the effect more pronounced with some gRNAs (e.g., CR00309) than other gRNAs (e.g., CR00312), most

edited cell populations differentiated into erythrocytes were non-the-less capable of achieving between 500-1500 population doublings in 14 days in erythroid differentiation medium ex vivo, indicating that the edited cells may be therapeutically useful in treating hemoglobinopathies such as sickle cell disease or beta thalassemia in patients.

Example 4. HPFH region editing in Hematopoietic Stem and Progenitor Cells (HSPCs) using CRISPR-Cas9 for derepression of fetal globin expression in adult erythroid cells

Methods:

Human $CD34^+$ cell culture. Human CD34+ cells were isolated from G-CSF mobilized peripheral blood from adult donors (AllCells) using immunoselection (Miltenyi) according to the manufacturer's instructions and expanded for 4 to 6 days using StemSpan SFEM (StemCell Technologies; Cat no. 09650) supplemented with 50 ng/mL each of thrombopoietin (Tpo), Flt3 ligand (Flt-3L, Life Technologies, Cat. #PHC9413), human stem cell factor (SCF, Life Technologies, Cat. #PHC2113) and human interleukin-6 (IL-6, Life Technologies, Cat. #PHC0063), as well as 1x antibiotic/antimycotic (Gibco, Cat. #10378-016) and 500 nM compound 4. Throughout this example (including its subexamples), where the protocol indicates that cells were "expanded," this medium was used. This medium is also referred to as "stem cell expansion medium," or "expansion medium" throughout this example (including its subexamples).

Assembly of Cas9 and guide RNA ribonucleoprotein (RNP) complexes, preparation of HSPC, and electroporation of RNP into HSPC. Cas9-guide RNA ribonucleoprotein complexes (RNPs) were prepared immediately prior to electroporation. For formation of RNP using dual guide RNAs (dgRNAs), 3 µg of each of crRNA (in 2.24 µL) and tracr (in 1.25 µL) are first denatured at 95°C for 2 min in separate tubes and then cooled to room temperature. For preparation of Cas9 protein, 6 µg of CAS9 protein (in 0.8 to 1 µL) was mixed with 0.5 µL of 5 x CCE buffer (20 mM HEPES, 100 mM KCL, 5 mM MgCL2, 5% Glycerol and freshly added 1 mM DTT). Tracr was first mixed with the Cas9 preparation and incubated at 37°C for 5 min. The crRNA was then added to Tracr/CAS9 complexes and incubated for 5 min at 37°C. For the None/control condition, vehicle rather than crRNA was added to the Tracr/CAS9 complexes. The HSPC were collected by centrifugation and resuspended in T buffer that comes with Neon electroporation kit (Invitrogen; Cat#: MPK1096) at a cell density of 5 x 10^6/mL. The RNP was mixed with 20 µL of cells by pipetting up and down and incubated at RT for 2 min. The RNP/cell mixture (10 µL) was transferred into Neon electroporation probe. The electroporation was performed with Neon transfection system (Invitrogen; MPK5000S) using 1700 volts/20 milliseconds and 1 pulse. Duplicate 10 µL electroporations were performed.

In vitro erythropoiesis and FACS analysis for HbF containing erythroid cells. After electroporation, the cells were immediately transferred into 250 µL pre-warmed erythroid differentiation medium

(EDM) consisting of IMDM (Hyclone, Cat. #SH30228.01), 330 µg /mL human holo-transferrin (Invitria Cat# 777TRF029), 10 µg /mL recombinant human insulin (Gibco Cat#A1138211), 2 IU/mL heparin (Sigma, part #H3393), 5% human AB serum (Sigma, Cat# H4522), 125 ng/mL human erythropoietin (Peprotech #10779-058), and 1x antibiotic/antimycotic (Gibco, Cat. #10378-016). EDM was further supplemented with 1 µM hydrocortisone (Sigma H8672), 100 ng/mL human SCF (Life Technologies, Cat. #PHC2113), and 5 ng/mL human IL-3 (Peprotech #10779-598). After 2 days, the cell culture was diluted in fresh medium. Cultures were maintained for a total of 7 days, at which time the cells were analyzed by intracellular staining for HbF expression. Briefly, the cells were washed once with PBS, resuspended in LIVE/DEAD® Fixable Violet Dead Cell Stain (ThermoFisher L34963; 1:1000 in PBS) and incubated for 30 min. Cell were then washed and stained with anti-CD71-BV711 (Fisher Scientific Company Llc. BDB563767) and anti-CD235a-APC (BD 551336) antibodies for 30 min. The cells were then washed, followed by fixation with fixation buffer (Biolegend, Cat# 420801) and permeabilized with 1x intracellular staining permeabilization wash buffer (Biolegend, Cat# 421002) according to the manufacturers instructions. The cells were then incubated with 0.5 µL of anti-HbF-PE antibody (Life Technologies, part #MHFH04) in 50 µL of 1x intracellular staining perm wash buffer for 20 min at room temperature. The cells were washed twice with 2 mL of 1x intracellular staining Perm wash buffer and resuspend in staining buffer and analyzed on an LSRFortessa flow cytometer (BD Biosciences) for HbF expression. The results were analyzed using Flowjo and data were presented as % of HbF positive cells (F-cells) in the viable CD71 positive erythroid cell population.

Gene expression analysis. After 7 days of *in vitro* erythropoiesis as described, approximately 1 x 10^5 cells were used to purify RNA using the Zymo Research ZR-96 quick RNA Kit (Zymo Cat# R1053). Up to 1µg RNA was used for 1st strand synthesis using Quantiscript Reverse Transcription Kit (Qiagen, Cat# 205313). Taq-man quantitative real-time PCR was performed using the 2x Taq-Man Fast Advance PR Mix (Life technologies, Cat# 4444963) and Taq-Man Gene Expression Assays for GAPDH (Life technologies, ID# Hs02758991_g1, VIC), HBB (Life technologies, ID# Hs00747223_g1, VIC) and HBG2/HBG1 (Life technologies, ID# Hs00361131_g1, FAM), according to the suppliers protocol. The relative expression of each gene was normalized to GAPDH expression and reported as fold of None/control RNP-delivered samples by the ΔΔCt method. Alternatively, after conversion to a GAPDH normalized relative quantity of transcript (2^-ΔCt), the HBG2/HBG1 expression level was calculated as a percentage of the sum of HBB and HBG2/HBG1 expression.

Genomic DNA preparation and next generation sequencing (NGS). Genomic DNA was prepared from edited and unedited HSPC at 48 hours post-electroporation using Quick Extract DNA Extraction Solution (Epicentre Cat # QE09050). To determine editing efficiency and patterns of insertions and deletions (indels), PCR products were generated using primers flanking the target sites, which were then subjected to next generation sequencing (NGS) as described in the literature. Percent editing of

corresponding sequences in unedited samples (electroporated with RNPs consisting of Cas9 and Tracr only) was typically less than 1% and never exceeded 3%.

Results:

Without being bound by theory, it is believed that targeted genetic disruption of the HPFH region will relieve repression of γ-globin expression, allowing production of the red blood cells containing elevated HbF protein, (cells expressing fetal hemoglobin are sometimes referred to herein as "F-cells"). The elevated HbF prevents sickling of the red blood cells under deoxygenated conditions and will be therapeutic/curative for the patients of both β-thalassemia and SCD. Autologous hematopoietic stem cell transplantation (HSCT) with *ex vivo* genome edited HSC from SCD patients was also combined with stem cell expansion enhancing technology, e.g., an aryl hydrocarbon receptor (AHR) inhibitor, e.g., as described in WO2010/059401 (the contents of which are incorporated by reference in their entirety), e.g., Compound 4 to improve ex vivo expansion and increase the dose of gene modified HSC delivered.

For efficient genome editing via programmable nuclease, Cas9, the successful delivery of guide RNA (gRNA) and Cas9 protein into target cells and tissues is essential. Recent reports demonstrated that Cas9 ribonucleoprotein (RNP) complexes when delivered into target cells by electroporation can accomplish efficient and specific genome editing in several different cell types. Cas9-RNP complexes cleave chromosomal DNA almost immediately after delivery and are degraded rapidly in cells, reducing off-target effects. In contrast, use of plasmid and viral vector systems used to deliver Cas9 results in prolonged expression of the enzyme aggravating off-target effects associated with the system. Additionally, delivery of RNPs into the target cells requires no additional tools which would greatly facilitate translation of genome editing for therapeutic purposes in the clinic. Purified recombinant Cas9 protein and gRNA complexes (RNPs) were delivered into cultured HSPC and an overview experiments used are shown in Figure 17.

Recombinant Cas9 protein was purified from Escherichia coli and complexed with synthetic dual gRNAs (dgRNA) that consist of crRNA and tracr to generate ribonucleoprotein (RNP) complexes. The list and sequences of gRNAs used in the study are shown in Table 16. The RNP complexes were electroporated into CD34+ HSPC via electroporation as described under materials and methods. The cells were expanded prior to the delivery of RNP complexes. Actively dividing cells may facilitate uptake of RNP complexes delivered by electroporation.

Table 16. List of gRNAs targeting the HPFH region used in the current study. All gRNA molecules were tested in duplicate in the dgRNA format described above, except for g8 (crRNA consisting of mN*mN*mN*rNrNrNrNrNrNrNrNrNrNrNrNrNrNrNrNrGrUrUrUrUrArGrArGrCrUrArU*mG*mC*mU (SEQ ID NO: 2299), where N's are the residues of the targeting domain, and modifications are

indicated as follows: 2'O-Methyl (m) and Phosphorothioate Bond (*); with the tracr sequence SEQ ID NO: 7808) and None/control. The g8 and None/control were tested in 16 replicates each.

Guide RNA targeting domain ID	% HbF+ (F cells), average of replicates	% HbF+ (F cells), standard deviation	% CD71+, average of replicates	% CD71+, standard deviation	% edited, average of replicates	% edited, standard deviation
CR001030	51.4	5.2	84.4	0.6	84.5	1.6
CR001095	49.3	1.8	82.7	2.5	66.1	1.4
CR001043	44.8	2.0	84.1	0.8	80.0	0.7
CR001029	43.7	1.3	82.2	0.7	86.6	2.7
CR001142	43.4	0.6	83.9	0.1	76.9	0.4
CR001028	42.9	1.3	84.8	0.5	91.7	0.5
CR001212	42.6	5.8	83.1	0.9	81.6	1.5
CR001036	42.4	1.3	82.6	0.6	91.5	5.0
CR001135	42.4	0.7	83.7	0.1	84.4	13.3
CR001221	41.8	1.7	80.8	0.4	83.9	1.4
CR001158	41.7	1.3	81.7	0.2	72.4	2.7
CR001090	41.3	0.1	85.5	0.8	87.2	1.2
CR001169	41.3	1.5	82.4	2.6	80.2	2.5
CR001089	40.9	0.6	82.8	6.6	81.7	0.3
CR001031	40.8	0.1	81.5	1.8	90.7	1.8
CR001092	40.8	2.2	84.1	0.1	43.0	1.1
CR001034	40.7	1.0	84.5	0.0	72.7	3.8
CR001068	40.7	2.3	85.7	0.4	90.5	0.9
CR001168	40.2	3.4	82.6	0.1	74.2	7.1
CR001171	40.1	1.6	83.4	0.4	63.8	1.6
CR001217	40.1	0.8	81.9	0.1	80.9	0.8
CR001023	39.6	3.2	82.2	0.8	90.2	0.7
CR001093	39.3	0.3	86	1.1	38.3	14.5
CR001080	39.2	3.4	87.1	1.1	32.4	1.1
CR001164	38.6	2.0	84.4	0.4	92.0	0.7
CR001178	38.6	1.2	82.6	2.4	61.1	0.6
CR001032	38.4	9.2	82.4	0.6	57.6	32.9
CR001100	38.4	1.8	81.7	0.2	29.6	2.4
CR001156	38.4	1.2	81.6	0.3	91.2	3.6
CR001159	38.4	1.8	81.8	0.2	65.5	0.7
CR001042	38.2	0.4	83.1	1.0	90.8	0.3
CR001065	38.2	0.0	85.2	2.0	86.5	0.2
CR001133	38.1	0.0	83.6	0.5	92.1	0.8
CR001173	38	1.5	81.7	1.1	72.5	5.0
CR001161	37.7	4.6	82.3	1.7	54.8	10.7
CR001138	37.6	7.6	83.7	0.7	69.4	28.9
CR001037	37.4	1.3	81.2	0.8	90.5	1.5
CR001098	37.4	1.2	85.6	1.5	95.0	0.2
CR001150	37.3	2.0	84.8	0.4	52.8	7.5
CR001160	37.3	0.5	81.4	1.5	65.9	1.6
CR001197	37.3	1.1	83.3	1.6	83.8	2.8
CR001170	37.2	1.3	83.7	1.2	47.3	0.3
CR001226	37	1.0	82.5	1.3	65.3	2.0
CR001018	36.9	0.8	80.9	0.8	97.2	0.0

CR001109	36.8	0.3	84.7	1.4	91.0	2.4
CR001219	36.8	0.6	82.5	0.1	75.9	0.2
CR001047	36.7	0.6	83.2	0.3	70.8	1.5
CR001101	36.6	3.3	81.7	0.1	50.6	3.8
CR001046	36.5	1.0	84	0.3	76.9	4.2
CR001021	36.4	0.3	82.2	0.4	79.5	2.9
CR001060	36.3	3.2	84.1	1.1	50.0	0.4
CR001074	36.3	1.6	87.3	1.8	56.5	4.9
CR001097	36.3	0.2	87.1	1.3	58.5	2.1
CR001099	36.1	4.0	85.8	1.8	89.8	0.3
CR001172	36.1	1.7	82.2	0.7	71.1	3.7
CR001195	36.1	0.8	83.4	0.2	67.2	2.7
CR001075	36	1.9	87.2	0.1	56.8	2.6
CR001143	35.9	3.7	83.5	0.4	56.7	9.2
CR001063	35.8	1.3	84.3	0.4	71.7	1.9
CR001225	35.5	0.4	83.1	0.5	81.1	4.2
CR001027	35.4	0.9	81.9	0.8	71.1	0.5
CR001073	35.4	1.6	86.5	1.6	56.3	5.9
CR001180	35.3	1.1	79.6	1.4	86.2	4.0
CR001182	35.3	0.8	81.8	0.2	72.5	3.9
CR001162	35.2	9.1	85	0.0	62.6	35.7
CR001026	35.1	1.0	82.4	0.2	97.0	0.3
CR001078	35	1.1	85	1.7	12.7	1.8
CR001025	34.9	0.3	81.9	1.5	55.5	3.8
CR001187	34.9	2.5	79.4	2.3	70.1	3.7
CR001081	34.8	1.4	87.5	4.0	27.0	0.7
CR001137	34.8	13.6	83.8	1.6	41.5	39.8
CR001174	34.8	0.5	81.8	0.6	34.1	3.2
CR001058	34.6	1.0	83.3	1.5	71.4	6.2
CR001188	34.6	1.3	82.6	1.2	64.0	2.2
CR001079	34.4	2.5	89.2	0.2	12.8	2.0
CR001179	34.4	3.2	82	0.4	81.4	4.3
CR001214	34	2.2	82.1	1.5	58.1	1.0
CR001139	33.9	1.9	83	2.5	70.3	0.4
CR001222	33.9	1.6	80.6	0.8	35.5	1.4
CR001096	33.8	0.1	85.6	2.2	77.5	1.0
CR001148	33.6	2.1	84.5	0.4	50.9	4.0
CR001140	33.5	0.4	84	1.4	66.3	1.5
CR001191	33.5	2.5	83.2	0.3	83.4	5.1
CR001227	33.5	2.3	79	0.2	56.3	0.1
CR001110	33.4	0.4	85.2	0.1	70.3	0.1
CR001220	33.4	1.7	81.4	0.4	72.4	3.3
CR001224	33.4	3.1	82.2	1.3	71.3	2.3
CR001033	33.2	0.3	81.9	0.6	63.6	8.1
CR001051	33.2	0.6	82.2	0.6	42.2	0.5
CR001106	33.2	0.2	82.6	3.0	46.9	2.0
CR001020	32.9	8.9	81.9	1.3	67.7	29.4
CR001022	32.9	0.8	82.4	1.6	91.5	0.3
CR001045	32.9	0.4	80.5	0.0	88.5	0.4
CR001198	32.9	0.5	81.3	1.8	96.8	0.5
CR001084	32.8	1.7	87.5	0.1	55.1	5.4
CR001111	32.6	1.0	84.2	2.5	78.1	1.4
CR001087	32.5	0.1	87.6	0.7	89.6	2.6

CR001107	32.5	0.4	83.3	1.8	46.5	2.2
CR001108	31.8	1.8	84.7	0.6	75.2	3.3
CR001205	31.7	2.3	81.3	6.2	2.7	1.7
CR001085	31.6	2.1	86	0.3	31.2	1.2
CR001166	31.5	0.5	83.6	0.8	86.9	0.3
CR001019	31.3	2.3	80.6	0.9	35.1	4.0
CR001076	31.3	0.5	86.6	0.2	96.3	0.3
CR001016	31.2	1.2	80.2	0.7	95.0	1.9
CR001035	31.1	1.8	83.5	1.3	80.0	0.9
CR001192	31	2.5	79.9	0.7	60.4	5.1
CR001091	30.7	2.8	85.3	0.6	72.4	7.6
CR001105	30.7	0.1	84.8	0.1	12.1	1.1
CR001185	30.7	0.7	82.7	0.4	36.7	0.2
CR001190	30.7	0.1	82.4	0.7	53.2	0.8
CR001024	30.6	0.4	81.8	0.7	97.0	0.6
CR001132	30.5	2.3	84.6	0.1	26.4	2.2
CR001189	30.4	1.9	83.1	0.3	42.0	0.6
CR001040	30.1	8.3	77.5	2.2	73.6	33.6
CR001146	30.1	1.5	83.8	0.1	88.1	2.1
CR001070	29.8	0.9	82.7	0.4	44.9	0.8
CR001213	29.8	1.8	81.9	0.2	48.4	4.4
CR001017	29.6	11.8	81.3	1.5	44.3	36.8
CR001077	29.5	0.9	87.2	2.5	14.3	0.5
CR001083	29.4	1.1	84.3	9.1	26.6	10.6
CR001082	29	0.7	87.6	1.5	17.7	0.0
CR001175	29	1.1	81.7	0.1	6.3	0.7
CR001144	28.9	0.4	82.6	0.9	38.8	1.1
CR001194	28.8	4.3	81.8	0.6	70.2	1.9
CR001157	28.5	1.1	81	1.3	29.2	4.2
CR001163	28.4	0.6	83.5	0.7	13.4	3.0
CR001151	28.2	0.6	84.6	1.6	51.8	2.3
CR001181	28.2	0.2	80.3	0.8	46.0	0.5
CR001061	28	2.9	82.6	0.4	53.6	5.8
CR001152	27.8	0.8	84.9	0.2	37.0	1.9
CR001094	27.7	9.2	74.6	12.7	85.2	2.1
CR001202	27.7	6.3	84	2.3	61.7	8.4
CR001149	27.6	1.7	84.1	0.6	10.8	1.3
CR001207	27.6	5.7	83.3	0.1	31.5	17.5
CR001134	27.2	1.6	83.2	1.3	2.3	0.2
CR001206	27.2	1.8	84.4	0.2	11.1	0.4
CR001067	27	18.4	84.2	2.6	6.0	0.8
CR001167	27	0.5	81.7	0.2	32.3	0.1
CR001209	27	0.8	81.5	2.5	14.8	0.2
CR001165	26.9	0.5	81.6	1.3	12.9	2.1
CR001044	26.8	7.2	78.2	4.3	28.5	20.7
CR001052	26.6	0.3	82.5	1.5	26.5	0.9
CR001062	26.6	0.7	78.7	2.8	39.1	5.3
CR001071	26.6	1.0	84.2	0.4	15.1	1.1
CR001210	26.6	2.1	80.1	3.3	58.6	2.2
CR001223	26.6	0.9	80.2	0.8	40.3	1.9
CR001057	26.5	6.5	82.4	0.1	25.0	18.9
CR001147	26.5	1.3	83.5	0.4	33.1	2.7
CR001186	26.4	2.1	79.6	3.8	40.5	2.1

CR001103	26.1	0.2	84.3	0.0	51.2	3.6
CR001199	25.9	0.8	80.9	1.5	89.3	1.4
CR001216	25.7	1.0	77.7	0.0	43.2	2.7
CR001041	25.6	1.8	78.9	4.8	22.4	2.1
CR001053	25.5	1.4	82.4	1.9	38.4	0.3
CR001086	25.4	0.6	84.4	0.9	30.4	0.6
CR001050	25.1	0.4	80.6	1.1	4.9	0.2
CR001136	25.1	0.7	82.3	1.0	9.1	1.1
CR001203	25.1	4.0	83.4	1.8	22.0	13.1
CR001211	24.8	1.1	83.3	0.4	5.0	1.0
CR001066	24.4	0.4	86.1	0.1	15.2	1.8
CR001145	24.4	1.0	83.5	0.9	16.4	8.9
CR001049	24.3	0.3	83.9	1.9	3.7	0.0
CR001176	24.3	0.6	81.9	0.6	29.0	1.4
CR001218	24.1	0.2	81.9	0.1	21.6	2.4
CR001141	23.8	0.5	82.8	0.4	4.1	0.8
CR001196	23.6	0.8	82.5	0.6	18.2	2.9
CR001184	23.5	0.4	81.1	0.4	43.5	1.6
CR001204	23.3	1.1	81.5	0.7	0.5	0.2
CR001069	23.1	1.1	85	0.0	16.2	0.3
CR001072	23	0.3	84.2	0.7	15.6	0.3
CR001102	22.8	1.7	84.7	1.6	58.1	4.8
CR001153	22.8	1.3	82.8	0.1	17.2	2.6
CR001177	22.8	0.5	82.2	0.9	2.0	0.2
CR001104	22.7	1.7	84.8	1.1	29.4	5.0
CR001064	22.6	1.1	82.1	1.0	35.8	5.2
CR001200	22.6	0.1	82	0.0	9.8	0.7
CR001154	22.4	0.0	82.2	1.3	8.0	1.1
CR001055	22.3	1.0	83.4	1.1	19.0	0.8
CR001054	22	1.1	83.5	1.0	11.3	1.4
CR001039	21.9	0.2	80.8	0.2	16.6	1.5
CR001183	21.6	0.7	81.4	0.8	13.3	0.1
CR001155	21.4	0.0	81.6	0.8	5.0	1.0
CR001059	21.1	0.6	82.5	1.2	4.6	0.3
CR001056	20.8	0.9	83.2	0.2	3.7	0.9
CR001193	20.5	0.9	80.4	0.9	4.8	0.2
CR001208	20.5	0.1	81.1	0.9	12.6	3.0
CR001201	20.1	1.7	81.7	0.6	10.7	0.7
CR001048	19.3	3.0	82.3	1.1	0.4	0.3
CR001215	19.2	0.2	81.2	2.3	5.6	2.2
CR001038	19.1	0.1	80.8	1.3	6.5	1.1
CR001088	18.8	5.9	67.3	2.7	74.6	2.3
None/control	21.0	2.0	82.9	1.9	n/a	n/a
g8	59.2	3.0	74.3	4.4	95.1	1.8

The genome edited and unedited HSPC were analyzed by flow cytometry for expression levels of fetal globin and two erythroid cell surface markers, transferrin receptor (CD71) and glycophorin A (CD235a) using antibodies conjugated to fluorescent dyes. The live cells were identified and gated by exclusion of Live Dead Violet. Genome editing did not adversely affect erythroid differentiation as the cultured cells showed percentages of CD71+ cells consistent with erythroblasts similar to

uneditied cells. HPFH region targeting resulted in increased percentage of erythroid cells containing HbF (up to 51.4%) compared to mock electroporated cells (21.0%) (Table 16). Induction of HbF positive cells by dgRNA including the targeting domain of g8 targeting exon 2 of BCL11A was also observed in parallel. Genomic PCR products of the HPFH region were also subjected to next generation sequencing (NGS) to determine the percentage of edited alleles in the cell population. High genome editing percentages at the HFPH locus was observed in many of the cell cultures electroporated with RNPs containing Cas9, crRNA of the given targeting domain and Tracr (Table 16), but not in control cells with no targeting domain delivered (RNPs containing only Cas9 and Tracr). In particular, the dgRNA treatments that resulted in greater than 40% HbF+ cells had a range of 43.0% to 91.7% edited alleles (Table 16).

Table 18. Gene expression analysis of select cultures edited with gRNAs targeting the HPFH region in the current study. All gRNA molecules were tested in duplicate in the dgRNA format. Fetal gamma-globin (γ-globin, HBG2/HBG1 genes), adult beta-globin (β-globin, HBB gene) and Glyceraldehyde-3-Phosphate Dehydrogenase (GAPDH gene) expression were determined and reported as described in Materials and Methods.

Guide RNA targeting domain ID	Number of electroporation replicates	γ-globin expression, fold over control (average of replicates)	β-globin expression, fold over control (average of replicates)	% globin expression, γ / (γ + β) (average of replicates)
CR001030	2	3.8	0.91	26.6
CR001142	2	1.6	0.76	20.0
CR001212	2	2.2	0.58	18.6
CR001036	2	2.6	0.91	19.7
CR001221	2	2.3	0.79	15.2
CR001217	2	1.9	0.72	13.8
None/control	5	1	1	7.7

Some cultures in this study were also analyzed for hemoglobin gene expression. Of these targeting domains, fetal gamma-globin gene expression was induced 1.6 to 3.8-fold over None/control, which was accompanied by a modest reduction in adult beta-globin expression (0.58 to 0.91-fold of None/control) (Table 18). These effects together resulted in gamma-globin expression levels ranging from 13.8% to 26.6% of the total beta-type globins (γ / [γ + β]) in the cell population (Table 17), with relative fetal globin induction across targeting domains similar to that observed for HbF protein induction (Table 16). Either an increase in HbF / gamma-globin or an increase in HbF / gamma-globin together with a decrease in beta-globin (sickled globin) levels in erythrocytes derived from genome edited cells is likely to have therapeutic implications by reduced sickling.

Example 4.2

Methods: Methods are as in Example 4, with the following exceptions.

Assembly of Cas9 and guide RNA ribonucleoprotein (RNP) complexes, preparation of HSPC, and electroporation of RNP into HSPC. The HSPC collected by centrifugation were resuspended in P3 Primary Cell Solution (Lonza cat. No. PBP3-00675) at a cell density of 2.5 x 10^6/mL. The RNP was mixed with 20 µL of cells by pipetting up and down and incubated at RT for 2 min. The RNP/cell mixture (20 µL) was electroporated using code CM-137 on the 4D-Nucleofector (Lonza).

Results:

Without being bound by theory, it is believed that targeted genetic disruption of the HPFH region will relieve repression of γ-globin expression, allowing production of the red blood cells containing elevated HbF protein, (cells expressing fetal hemoglobin are sometimes referred to herein as "F-cells"). The elevated HbF prevents sickling of the red blood cells under deoxygenated conditions and will be therapeutic/curative for the patients of both β-thalassemia and SCD. Autologous hematopoietic stem cell transplantation (HSCT) with *ex vivo* genome edited HSC from SCD patients was also combined with stem cell expansion enhancing technology, e.g., an aryl hydrocarbon receptor (AHR) inhibitor, e.g., as described in WO2010/059401 (the contents of which are incorporated by reference in their entirety), e.g., Compound 4 to improve ex vivo expansion and increase the dose of gene modified HSC delivered.

For efficient genome editing via programmable nuclease, Cas9, the successful delivery of guide RNA (gRNA) and Cas9 protein into target cells and tissues is essential. Recent reports demonstrated that Cas9 ribonucleoprotein (RNP) complexes when delivered into target cells by electroporation can accomplish efficient and specific genome editing in several different cell types. Cas9-RNP complexes cleave chromosomal DNA almost immediately after delivery and are degraded rapidly in cells, reducing off-target effects. In contrast, use of plasmid and viral vector systems used to deliver Cas9 results in prolonged expression of the enzyme aggravating off-target effects associated with the system. Additionally, delivery of RNPs into the target cells requires no additional tools which would greatly facilitate translation of genome editing for therapeutic purposes in the clinic. Purified recombinant Cas9 protein and gRNA complexes (RNPs) were delivered into cultured HSPC and an overview experiments used are shown in Figure 17.

Recombinant Cas9 protein was purified from Escherichia coli and complexed with synthetic dual gRNAs (dgRNA) that consist of crRNA and tracr to generate ribonucleoprotein (RNP) complexes. The list of gRNAs used in the study are shown in Table 19. The RNP complexes were electroporated into CD34+ HSPC via electroporation as described under materials and methods. The cells were expanded prior to the delivery of RNP complexes. Actively dividing cells may facilitate uptake of RNP complexes delivered by electroporation.

Table 19. List of gRNAs targeting the HPFH region used in the current study. All gRNA molecules were tested in the dgRNA format (except for g8 which was tested in the dgRNA format using : crRNA consisting of mN*mN*mN*rNrNrNrNrNrNrNrNrNrNrNrNrNrNrNrNrGrUrUrUrUrArGrArGrCrUrArU*mG*mC*mU (SEQ ID NO: 2300), where N's are the residues of the targeting domain, and modifications are indicated as follows: 2'O-Methyl (m) and Phosphorothioate Bond (*); with the tracr sequence SEQ ID NO: 7808).

Guide RNA targeting domain ID	% HbF+ (F cells)	% CD71+
CR003037	46.6	80.3
CR003033	45.4	75.9
CR003038	42.9	77.6
CR003035	42.1	77.8
CR003087	42.1	76.7
CR003085	41.8	77.6
CR003052	39.9	80.5
CR003080	38.0	80.1
CR003081	35.3	80.6
CR003031	34.8	77.7
CR003056	34.3	78.3
CR003070	33.9	81.2
CR003089	33.8	77.8
CR003065	33.0	76.4
CR003075	33.0	75.2
CR003088	33.0	77.3
CR003041	32.1	76.2
CR003039	31.9	75.7
CR003044	30.6	77.7
CR003084	29.7	77.2
CR003073	29.5	76.9
CR003066	29.3	77.9
CR003082	29.3	78.6
CR003067	29.2	78.1
CR003074	29.1	77.5
CR003095	28.8	80.4
CR003083	28.3	76.6
CR003030	27.9	78.4
CR003069	27.7	78.9
CR003055	27.6	78.9
CR003058	27.6	78.8
CR003054	27.5	79.0
CR003029	27.1	78.4
CR003086	27.1	76.6
CR003063	27.0	76.0
CR003071	26.5	79.5
CR003079	26.5	78.0
CR003042	26.4	77.0
CR003045	26.3	78.0
CR003034	25.9	76.8

CR003027	25.7	79.2
CR003043	25.0	76.0
CR003032	24.9	77.9
CR003040	24.9	75.7
CR003028	24.8	78.6
CR003048	24.8	80.4
CR003057	24.7	79.0
CR003096	24.6	78.9
CR003077	24.4	77.7
CR003036	24.3	76.8
CR003049	24.3	78.4
CR003047	24.0	78.2
CR003059	23.9	80.2
CR003051	23.7	77.2
CR003053	23.7	76.9
CR003091	23.7	80.2
CR003093	23.7	79.2
CR003060	23.6	78.9
CR003072	23.6	77.7
CR003076	23.6	78.0
CR003078	23.6	78.0
CR003064	23.4	75.9
CR003046	23.3	80.5
CR003092	22.9	81.7
CR003090	22.7	79.7
CR003050	22.6	77.2
CR003062	22.1	76.5
CR003061	21.5	76.3
CR003068	21.5	78.8
CR003094	21.0	79.6
None/control replicate 1	18.9	77.0
None/control replicate 2	21.1	79.7
g8 replicate 1	56.8	65.4
g8 replicate 2	56.4	65.8

The genome edited and unedited HSPC were analyzed by flow cytometry for expression levels of fetal globin and two erythroid cell surface markers, transferrin receptor (CD71) and glycophorin A (CD235a) using antibodies conjugated to fluorescent dyes. The live cells were identified and gated by exclusion of Live Dead Violet. Genome editing did not adversely affect erythroid differentiation as the cultured cells showed percentages of CD71+ cells consistent with erythroblasts similar to uneditied cells. HPFH region targeting resulted in increased percentage of erythroid cells containing HbF (up to 46.6%) compared to mock electroporated cells (18.9 and 21.1%) (Table 19). Induction of HbF positive cells by dgRNA including the targeting domain of g8 targeting exon 2 of BCL11A was also observed in parallel.

Finally, the indel pattern created at or near the target site for dgRNAs comprising the targeting domains of CR003031, CR003033, CR003035, CR003037, CR003038, CR003052, CR003085 were assessed by NGS. The top 5 most frequent indels at each location are shown in Table 27.

Table 27. 5 most frequent indels at each taget sequence after exposure to RNP comprising the indicated gRNA molecule. Each gRNA was tested in dgRNA. Capital letters are the naturally occurring nucleotides at and near the target sequence. Deletions relative to the unmodified target sequence are shown as "-"; insertions are shown as lowercase letters.

dgRNA targeting domain	Variant Read (Genomic Sequence)	SEQ ID NO:	% of all reads	Indel Length
CR003031	ACTGTTGATTAGAGGTAGGGAAATGATTTTAATCTGTGACCTTGG------- GCAAGTAGCTATCTAATGACTAAAATGG	2301	9.74%	-7
CR003031	ACTGTTGATTAGAGGTAGGGAAATGATTTTAATCTGTGACCTTGGTtGAATGGGC AAGTAGCTATCTAATGACTAAAATGG	2302	7.82%	1
CR003031	ACTGTTGATTAGAGGTAGGGAAATGATTTTAATCTGTGACCTTG--- AATGGGCAAGTAGCTATCTAATGACTAAAATGG	2303	2.19%	-3
CR003031	ACTGTTGATTAGAGGTAGGGAAATGATTTTAATCTGTGACCTTG- TGAATGGGCAAGTAGCTATCTAATGACTAAAATGG	2304	1.37%	-1
CR003031	ACTGTTGATTAGAGGTAGGGAAATGATTTTAATCTGTGA--------- ATGGGCAAGTAGCTATCTAATGACTAAAATGG	2305	1.33%	-9
CR003031			...	...
CR003033	ATGGGCAAGTAGCTATCTAATGACTAAAATGGAA---------- GAGAAACAGTTTTAGTATAACAAGTGAAATACCCAT	2306	25.21%	-10
CR003033	ATGGGCAAGTAGCTATCTAATGACTAAAATGGAAAAaCACTGGAAGAGAAACAGT TTTAGTATAACAAGTGAAATACCCAT	2307	7.77%	1
CR003033	ATGGGCAAGTAGCTATCTAATGACTAAAATGGAA-- CACTGGAAGAGAAACAGTTTTAGTATAACAAGTGAAATACCCAT	2308	5.72%	-2
CR003033	ATGGGCAAGTAGCTATCTAATGACTAAAATGGAAAAC-- TGGAAGAGAAACAGTTTTAGTATAACAAGTGAAATACCCAT	2309	2.94%	-2
CR003033	ATGGGCAAGTAGCTATCTAATGACTAAAATGGAAAACcACTGGAAGAGAAACAGT TTTAGTATAACAAGTGAAATACCCAT	2310	1.68%	1
CR003033			...	...
CR003035	CACTGGAAGAGAAACAGTTTTAGTATAACAAGTGAAATACCCATG--- AGTCTGAGGTGCCTATAGGACATCTATATAAA	2311	10.87%	-3
CR003035	CACTGGAAGAGAAACAGTTTTAGTATAACAAGTGAAATACCCAT- CTGAGTCTGAGGTGCCTATAGGACATCTATATAAA	2312	2.62%	-1
CR003035	CACTGGAAGAGAAACAGTTTTAGTATAACAAGTGAAATACCCA-- CTGAGTCTGAGGTGCCTATAGGACATCTATATAAA	2313	2.04%	-2
CR003035	CACTGGAAGAGAAACAGTTTTAGTATAACAAGTGAAATACCCATG-- GAGTCTGAGGTGCCTATAGGACATCTATATAAA	2314	1.79%	-2
CR003035	CACTGGAAGAGAAACAGTTTTAGTATAACAAGTGAAATACCC---- TGAGTCTGAGGTGCCTATAGGACATCTATATAAA	2315	1.77%	-4
CR003035			...	...
CR003037	TAACAAGTGAAATACCCATGCTGAGTCTGAGG---------- ACATCTATATAAATAAGCCCAGTACATTGTTTGATATA	2316	7.19%	-10
CR003037	TAACAAGTGAAATACCCATGCTGAGTCTGAGGTGCC- ATAGGACATCTATATAAATAAGCCCAGTACATTGTTTGATATA	2317	6.13%	-1
CR003037	TAACAAGTGAAATACCCATGCTGAGTCTGAGGTGCCcTATAGGACATCTATATAA ATAAGCCCAGTACATTGTTTGATATA	2318	4.17%	1
CR003037	TAACAAGTGAAATACCCATGCTGAGTCTGAGGTGCCTtATAGGACATCTATATAA ATAAGCCCAGTACATTGTTTGATATA	2319	3.89%	1
CR003037	TAACAAGTGAAATACCCATGCTGAGTCTGAGGTGC-	2320	3.72%	-1

	TATAGGACATCTATATAAATAAGCCCAGTACATTGTTTGATATA			
CR003037			...	...
CR003038	TAGTATAACAAGTGAAATACCCATGCTGAGTCTGAGGTGCCTATA---------- -TAAATAAGCCCAGTACATTGTTTG	2321	14.85%	-11
CR003038	TAGTATAACAAGTGAAATACCCATGCTGAGTCTGAGGTGCCTATAG- ACATCTATATAAATAAGCCCAGTACATTGTTTG	2322	6.25%	-1
CR003038	TAGTATAACAAGTGAAATACCCATGCTGAGTCTGAGGTGCCTAT- GGACATCTATATAAATAAGCCCAGTACATTGTTTG	2323	3.99%	-1
CR003038	TAGTATAACAAGTGAAATACCCATGCTGAGTCTGAGGTGCCTATAGGgACATCTA TATAAATAAGCCCAGTACATTGTTTG	2324	2.83%	1
CR003038	TAGTATAACAAGTGAAATACCCATGCTGAGTCTGAGGTGCCTATAaGGACATCTA TATAAATAAGCCCAGTACATTGTTTG	2325	2.76%	1
CR003038			...	...
CR003052	TCAGAGGTTAGAAATCAGAGTTGGGAATTGGGATTA-- CAGGCTGTATTTAAGAGTTTAGATATAACTGTGAATCCAAGA	2326	14.04%	-2
CR003052	TCAGAGGTTAGAAATCAGAGTTGGGAATTGGGATTAaTACAGGCTGTATTTAAGA GTTTAGATATAACTGTGAATCCAAGA	2327	2.94%	1
CR003052	TCAGAGGTTAGAAATCAGAGTTGGGAATTGGGATT- TACAGGCTGTATTTAAGAGTTTAGATATAACTGTGAATCCAAGA	2328	2.41%	-1
CR003052	TCAGAGGTTAGAAATCAGAGTTGGGAATTGGGATTATtACAGGCTGTATTTAAGA GTTTAGATATAACTGTGAATCCAAGA	2329	2.37%	1
CR003052	TCAGAGGTTAGAAATCAGAGTTGGGAATTGGGATTAaaTACAGGCTGTATTTAAG AGTTTAGATATAACTGTGAATCCAAGA	2330	2.28%	2
CR003052			...	...
CR003085	TGTAAGGAGGATGAGCCACATGGTATGGGAGGTAT- CTAAGGACTCTAGGGTCAGAGAAATATGGGTTATATCCTTCTAC	2331	12.03%	-1
CR003085	TGTAAGGAGGATGAGCCACATGGTATGGGAGG---------- ACTCTAGGGTCAGAGAAATATGGGTTATATCCTTCTAC	2332	8.70%	-10
CR003085	TGTAAGGAGGATGAGCCACATGGTATGGGA---------- CTCTAGGGTCAGAGAAATATGGGTTATATCCTTCTAC	2333	4.42%	-13
CR003085	TGTAAGGAGGATGAGCCACATGGTATGGGAGGTATAaCTAAGGACTCTAGGGTCA GAGAAATATGGGTTATATCCTTCTAC	2334	4.38%	1
CR003085	TGTAAGGAGGATGAGCCACATGGTATGGGAGGTA----- AGGACTCTAGGGTCAGAGAAATATGGGTTATATCCTTCTAC	2335	3.41%	-5
CR003085			...	...
CR003087	GATGAGCCACATGGTATGGGAGGTATACTAAGGACTtCTAGGGTCAGAGAAATAT GGGTTATATCCTTCTACAAAATTCAC	2336	24.73%	1
CR003087	GATGAGCCACATGGTATGGGAGGTATACTA---------- GGGTCAGAGAAATATGGGTTATATCCTTCTACAAAATTCAC	2337	15.83%	-9
CR003087	GATGAGCCACATGGTATGGGAGGTATACTAAGG--------- GTCAGAGAAATATGGGTTATATCCTTCTACAAAATTCAC	2338	8.50%	-8
CR003087	GATGAGCCACATGGTATGGGAGGTATACTAAGGACT-- AGGGTCAGAGAAATATGGGTTATATCCTTCTACAAAATTCAC	2339	7.07%	-2
CR003087	GATGAGCCACATGGTATGGGAGGTATACTAAGG---------- TCAGAGAAATATGGGTTATATCCTTCTACAAAATTCAC	2340	1.75%	-9
CR003087			...	...

These results suppor the conclusion from earlier experiments described herein that small indels (e.g., in this case, indels from 1-20 nucleotides) in the HPFH region targeted by the indicated gRNA molecule can have a significant impact on expression and production of HbF. An increase in HbF-containing erythrocytes derived from genome edited cells is likely to have therapeutic implications by reduced sickling.

Example 4.3

Methods: Methods are as in Example 4, with the following exceptions.

Human $CD34^+$ cell culture. Human CD34+ cells were expanded for 3 days prior to RNP delivery in expansion medium.

Assembly of Cas9 and guide RNA ribonucleoprotein (RNP) complexes, preparation of HSPC, and electroporation of RNP into HSPC. The HSPC collected by centrifugation were resuspended in P3 Primary Cell Solution (Lonza cat. No. PBP3-00675) at a cell density of 6.4 x 10^6/mL. The RNP was mixed with 20 µL of cells by pipetting up and down and incubated at RT for 2 min. The RNP/cell mixture (20 µL) was electroporated using code CM-137 on the 4D-Nucleofector (Lonza). Electroporations were performed in duplicate. The Tracr was SEQ ID NO: 7808 and the crRNA had the following format with 2'O-Methyl (m) and Phosphorothioate Bond (*) modifications indicated: mN*mN*mN*rNrNrNrNrNrNrNrNrNrNrNrNrNrNrNrNrGrUrUrUrUrArGrArGrCrUrArU*mG*mC*mU (SEQ ID NO: 2341), where N's are the nucleotides of the targeting domain.

In vitro erythropoiesis and FACS analysis for HbF containing erythroid cells. After electroporation, the cells were immediately transferred into pre-warmed medium consisting of EDM and supplements. During days 0–7 of culture, EDM was further supplemented with 1 µM hydrocortisone (Sigma H8672), 100 ng/mL human SCF (Life Technologies, Cat. #PHC2113), and 5 ng/mL human IL-3 (Peprotech #10779-598). During days 7–11 of culture, EDM was supplemented with 100 ng/mL of human SCF only. During days 11–21 of culture, EDM had no additional supplements. Cell cultures were initiated at 2.6x10^4 cells per ml on day 0, adjusted to 4.0x10^4 cells per ml on day 7, and adjusted to 1.0x10^6 cells per ml on day 11. On days 14 and 19, the media was replenished. Viable cells were counted at 1, 4, 7, 11, 14 and 21 days post-RNP delivery. All viable cell counts were determined by flow cytometry using AccuCheck Counting Beads (ThermoFisher cat. No. PCB100) with inviable cells discriminated by DAPI (4',6-Diamidino-2-Phenylindole) staining. On days 7, 16 and 21 of the culture, the cells (1 x 10^5) were analyzed by intracellular staining for HbF expression. On days 16 and 21 intracellular staining for HbF expression did not include anti-CD71 and anti-CD235a antibodies, and % of HbF positive cells (F-cells) in the entire viable cell population was reported. On day 21 LIVE/DEAD® Fixable Near-IR Dead Cell Stain (ThermoFisher L34975) was used as the viability dye.

Genomic DNA preparation and next generation sequencing (NGS). Genomic DNA was prepared from edited and unedited HSPC at 7 days post-electroporation using Quick Extract DNA Extraction Solution (Epicentre Cat # QE09050).

Results:

Without being bound by theory, it is believed that targeted genetic disruption of the HPFH region will relieve repression of γ-globin expression, allowing production of the red blood cells containing elevated HbF protein, (cells expressing fetal hemoglobin are sometimes referred to herein as "F-cells"). The elevated HbF prevents sickling of the red blood cells under deoxygenated conditions and will be therapeutic/curative for the patients of both β-thalassemia and SCD. Autologous hematopoietic stem cell transplantation (HSCT) with *ex vivo* genome edited HSC from SCD patients was also combined with stem cell expansion enhancing technology, e.g., an aryl hydrocarbon receptor (AHR) inhibitor, e.g., as described in WO2010/059401 (the contents of which are incorporated by reference in their entirety), e.g., Compound 4 to improve ex vivo expansion and increase the dose of gene modified HSC delivered.

For efficient genome editing via programmable nuclease, Cas9, the successful delivery of guide RNA (gRNA) and Cas9 protein into target cells and tissues is essential. Recent reports demonstrated that Cas9 ribonucleoprotein (RNP) complexes when delivered into target cells by electroporation can accomplish efficient and specific genome editing in several different cell types. Cas9-RNP complexes cleave chromosomal DNA almost immediately after delivery and are degraded rapidly in cells, reducing off-target effects. In contrast, use of plasmid and viral vector systems used to deliver Cas9 results in prolonged expression of the enzyme aggravating off-target effects associated with the system. Additionally, delivery of RNPs into the target cells requires no additional tools which would greatly facilitate translation of genome editing for therapeutic purposes in the clinic. Purified recombinant Cas9 protein and gRNA complexes (RNPs) were delivered into cultured HSPC and an overview experiments used are shown in Figure 17.

Recombinant Cas9 protein was purified from Escherichia coli and complexed with synthetic dual gRNAs (dgRNA) that consist of crRNA and tracr to generate ribonucleoprotein (RNP) complexes. The list of gRNAs used in the study are shown in Table 20. The RNP complexes were electroporated into CD34+ HSPC via electroporation as described under materials and methods. The cells were expanded prior to the delivery of RNP complexes. Actively dividing cells may facilitate uptake of RNP complexes delivered by electroporation.

Table 20. Relative viable cell proliferation in the current study. Individual electroporation replicates are shown. All gRNA molecules were tested in the dgRNA format using the tracr SEQ ID NO: 7808, and the crRNA had the following format with 2'O-Methyl (m) and Phosphorothioate Bond (*) modifications indicated: mN*mN*mN*rNrNrNrNrNrNrNrNrNrNrNrNrNrNrNrNrGrUrUrUrUrArGrArGrCrUrArU*mG*mC*mU (SEQ ID NO: 2342), where N's are the nucleotides of the targeting domain. (n.d. not determined)

Guide RNA targeting domain ID and replicate	Day 0	Day 1	Day 4	Day 7	Day 11	Day 14	Day 21
CR001030 replicate 1	1	0.66	4.3	43.1	627	680	772
CR001030 replicate 2	1	0.65	4.0	38.4	651	694	880
CR001028 replicate 1	1	0.61	4.0	33.2	588	509	742
CR001028 replicate 2	1	0.77	6.1	44.9	724	759	838
CR001095 replicate 1	1	0.66	4.0	40.7	665	503	835
CR001095 replicate 2	1	0.96	5.2	42.2	651	777	n.d.
CR001212 replicate 1	1	0.58	3.4	33.6	465	414	495
CR001212 replicate 2	1	0.74	3.6	32.4	490	519	572
g8 replicate 1	1	0.61	4.4	31.8	221	341	91
g8 replicate 2	1	0.60	5.2	33.2	269	270	103
None/control replicate 1	1	0.79	7.6	58.5	741	862	707
None/control replicate 2	1	0.71	8.2	51.4	923	1204	1075

The genome edited and unedited HSPC were analyzed for proliferation in a three-stage erythroid differentiation cell culture protocol. Percent cell recovery at 1 day after electroporation ranged from 58% to 96% and was similar across conditions, including the unedited but electroporated control (Table 20). Proliferation was suppressed in the cells edited by dgRNA including the targeting domain of g8 targeting exon 2 of BCL11A (10-12% of unedited control at day 21, Table 20), but proliferation of cells edited with the included HPFH region targeting dgRNAs was similar to control (47-99% of unedited control at day 21, Table 20).

Table 21. HbF induction in the current study. Individual electroporation replicates are shown. All gRNA molecules were tested in the dgRNA format. All gRNA molecules were tested in the dgRNA format using the tracr SEQ ID NO: 7808, and the crRNA had the following format with 2'O-Methyl (m) and Phosphorothioate Bond (*) modifications indicated: mN*mN*mN*rNrNrNrNrNrNrNrNrNrNrNrNrNrNrNrGrUrUrUrUrArGrArGrCrUrArU*mG*mC*mU (SEQ ID NO: 2343), where N's are the nucleotides of the targeting domain. (n.d. not determined)

Guide RNA targeting domain ID and replicate	% edited, Day 7	% CD71+, Day 7	% HbF+ (F cells), Day 7	% HbF+ (F cells), Day 16	% HbF+ (F cells), Day 21
CR001030 replicate 1	90.7	91.2	61.0	45.4	53.7
CR001030 replicate 2	90.1	91.1	63.9	44.3	55.9
CR001028 replicate 1	91.9	90.0	61.6	40.9	52.0
CR001028 replicate 2	87.6	90.7	56.3	46.6	45.8
CR001095 replicate 1	25.7	91.4	51.3	36.8	43.7
CR001095 replicate 2	30.5	91.1	52.5	42.7	n.d.
CR001212 replicate 1	86.2	90.8	57.5	38.7	45.2
CR001212 replicate 2	80.9	90.4	54.7	36.5	42.7
g8 replicate 1	95.3	84.6	70.7	71.9	63.4
g8 replicate 2	94.3	82.6	70.0	72.6	54.8
None/control replicate 1	n/a	94.0	27.1	24.4	22.8
None/control replicate 2	n/a	93.8	26.2	25.7	21.1

The genome edited and unedited HSPC were analyzed by flow cytometry for expression levels of fetal globin and two erythroid cell surface markers, transferrin receptor (CD71) and glycophorin A (CD235a) using antibodies conjugated to fluorescent dyes. The live cells were identified and gated by exclusion of Live/Dead Fixable Dead Cell Stain. Genome editing did not adversely affect erythroid differentiation as the cultured cells showed percentages of CD71+ cells consistent with erythroblasts similar to uneditied cells at day 7 of differentiation. Cultures treated with the included HPFH region targeting dgRNAs resulted in increased percentage of erythroid cells containing HbF compared to mock electroporated cells throughout the 21 day culture period (Table 21). Induction of HbF positive cells by dgRNA including the targeting domain of g8 targeting exon 2 of BCL11A was also observed in parallel. Genomic PCR products of the HPFH region were also subjected to next generation sequencing (NGS) to determine the percentage of edited alleles in the cell population. Genome editing at the HFPH locus was observed in cell cultures electroporated with RNPs containing Cas9, crRNA of the given targeting domain and Tracr (Table 21), but not in control cells with no targeting domain delivered (RNPs containing only Cas9 and Tracr). An increase in HbF-containing erythrocytes derived from genome edited cells is likely to have therapeutic implications by reduced sickling.

Example 4.4

Methods: Methods are as in Example 4, with the following exceptions.

Human $CD34^+$ cell culture. Human CD34+ cells were expanded for 3 to 6 days prior to RNP delivery in expansion medium, depending on study.

Assembly of Cas9 and guide RNA ribonucleoprotein (RNP) complexes, preparation of HSPC, and electroporation of RNP into HSPC. For some studies, the RNP complexes were delivered using the 4D-Nucleofector (Lonza). In those studies, the HSPC collected by centrifugation were resuspended in P3 Primary Cell Solution (Lonza cat. No. PBP3-00675) at a cell density of 2.2 x 10^6/mL to 6.4 x 10^6/mL, depending on study. The RNP was mixed with 20 µL of cells by pipetting up and down and incubated at RT for 2 min. The RNP/cell mixture (20 µL) was electroporated using code CM-137 on the 4D-Nucleofector (Lonza). Electroporations were performed in duplicate. The dgRNA format varied between studies and is indicated in Table 22 by the following notation. Form A is the dgRNA format described above in Example 1, with the targeting domain sequence indicated. Form B is a dgRNA format using a crRNA of rNrNrNrNrNrNrNrNrNrNrNrNrNrNrNrNrNrNrGrUrUrUrUrArGrArGrCrUrArUrGrCrU (SEQ ID NO: 2344), where r indicates an RNA base and the N's correspond to the indicated targeting domain sequence, and a tracr consisting of SEQ ID NO: 7808. Form C is a dgRNA format using crRNA of the sequence

mN*mN*mN*rNrNrNrNrNrNrNrNrNrNrNrNrNrNrNrNrGrUrUrUrUrArGrArGrCrUrArU*mG*mC*mU (SEQ ID NO: 2345), where r indicates an RNA base, N's corresponds to the indicated targeting domain sequence, m indicates a base with 2'O-Methyl modification, and * indicates a phosphorothioate bond, and the tracr consists of SEQ ID NO: 7808.

In vitro erythropoiesis and FACS analysis for HbF containing erythroid cells. In one study, cell cultures were initiated at $2.6x10^4$ cells per ml on day 0. For those initiated by seeding directly into 250 µl (as described in Example 4), the cell culture was diluted in fresh medium after 1 to 3 days, depending on the study.

Genomic DNA preparation and next generation sequencing (NGS). Genomic DNA was prepared from edited and unedited HSPC at 24 hours to 7 days post-electroporation, depending on the study, using Quick Extract DNA Extraction Solution (Epicentre Cat # QE09050).

Results:

Without being bound by theory, it is believed that targeted genetic disruption of the HPFH region will relieve repression of γ-globin expression, allowing production of the red blood cells containing elevated HbF protein, (cells expressing fetal hemoglobin are sometimes referred to herein as "F-cells"). The elevated HbF prevents sickling of the red blood cells under deoxygenated conditions and will be therapeutic/curative for the patients of both β-thalassemia and SCD. Autologous hematopoietic stem cell transplantation (HSCT) with *ex vivo* genome edited HSC from SCD patients was also combined with stem cell expansion enhancing technology, e.g., an aryl hydrocarbon receptor (AHR) inhibitor, e.g., as described in WO2010/059401 (the contents of which are incorporated by reference in their entirety), e.g., Compound 4 to improve ex vivo expansion and increase the dose of gene modified HSC delivered.

For efficient genome editing via programmable nuclease, Cas9, the successful delivery of guide RNA (gRNA) and Cas9 protein into target cells and tissues is essential. Recent reports demonstrated that Cas9 ribonucleoprotein (RNP) complexes when delivered into target cells by electroporation can accomplish efficient and specific genome editing in several different cell types. Cas9-RNP complexes cleave chromosomal DNA almost immediately after delivery and are degraded rapidly in cells, reducing off-target effects. In contrast, use of plasmid and viral vector systems used to deliver Cas9 results in prolonged expression of the enzyme aggravating off-target effects associated with the system. Additionally, delivery of RNPs into the target cells requires no additional tools which would greatly facilitate translation of genome editing for therapeutic purposes in the clinic. Purified recombinant Cas9 protein and gRNA complexes (RNPs) were delivered into cultured HSPC and an overview experiments used are shown in Figure 17.

Recombinant Cas9 protein was purified from Escherichia coli and complexed with synthetic dual gRNAs (dgRNA) that consist of crRNA and tracr to generate ribonucleoprotein (RNP) complexes. The list of gRNAs used in the studies are shown in Table 22. The RNP complexes were electroporated into CD34+ HSPC via electroporation as described under materials and methods. The cells were expanded prior to the delivery of RNP complexes. Actively dividing cells may facilitate uptake of RNP complexes delivered by electroporation.

Table 22. Summary data for multiple studies evaluating indicated gRNAs targeting the HPFH region and controls. All gRNA molecules were tested in dgRNA formats. Details of the dgRNA formats in the indicated studies are specified as described above. Note that evaluations 4 and 5 were performed in parallel and thus share control conditions.

Guide RNA targeting domain ID		Evaluation number							
		1	2	3	4	5	6	7	8
CR001028	Format	A	A	B	B	C			C
	Replicates	2	2	2	2	2			2
	% HbF+ (F cells), average of replicates	42.9	39.7	47.4	51.1	55.3			59.0
	% edited, average of replicates	91.7	78.0	87.5	90.9	84.6			89.8
CR001030	Format	A	A	B	B	C	C	C	C
	Replicates	2	2	2	2	2	2	2	2
	% HbF+ (F cells), average of replicates	51.4	48.7	50.9	51.8	58.0	39.7	50.6	62.5
	% edited, average of replicates	84.5	61.8	74.3	75.0	85.6	94.1	85.4	90.4
CR001036	Format	A	A	B					
	Replicates	2	2	2					
	% HbF+ (F cells), average of replicates	42.4	40.8	43.3					
	% edited, average of replicates	84.4	78.3	92.6					
CR001043	Format	A	A	B					
	Replicates	2	2	2					
	% HbF+ (F cells), average of replicates	44.8	33.0	42.9					
	% edited, average of replicates	80.0	42.7	87.7					
CR001080	Format	A	A			C			
	Replicates	2	2			2			
	% HbF+ (F cells), average of replicates	39.2	34.9			49.3			
	% edited, average of replicates	32.4	24.0			41.6			
CR001095	Format	A	A	B	B	C	C	C	C
	Replicates	2	2	1	2	2	2	2	2
	% HbF+ (F cells), average of replicates	49.3	41.5	47	51.8	51.8	32.9	46.8	51.9

	% edited, average of replicates	66.1	49.8	65.1	64.6	64.2	66.8	56.1	28.1
CR001137	Format	A	A				C	C	
	Replicates	2	2				2	2	
	% HbF+ (F cells), average of replicates	34.8	45.6				31.0	40.8	
	% edited, average of replicates	41.5	46.9				69.0	57.9	
CR001142	Format	A	A			C			
	Replicates	2	2			2			
	% HbF+ (F cells), average of replicates	43.4	45.5			48.1			
	% edited, average of replicates	76.9	63.7			89.2			
CR001158	Format	A	A			C			
	Replicates	2	2			2			
	% HbF+ (F cells), average of replicates	41.7	36.9			44.6			
	% edited, average of replicates	72.4	43.9			78.4			
CR001212	Format	A	A	B	B	C	C	C	C
	Replicates	2	2	2	2	2	2	2	2
	% HbF+ (F cells), average of replicates	42.6	46.9	43.8	44.5	53.5	39.4	47.1	56.1
	% edited, average of replicates	81.6	58.1	48.6	47.5	69.2	82.0	67.0	83.6
CR001217	Format	A	A				C	C	
	Replicates	2	2				2	2	
	% HbF+ (F cells), average of replicates	40.1	41.5				29.9	45.9	
	% edited, average of replicates	80.9	50.3				89.0	82.1	
CR001221	Format	A	A	B	B	C			
	Replicates	2	2	1	2	2			
	% HbF+ (F cells), average of replicates	41.8	45.2	44.6	46.2	48.6			
	% edited, average of replicates	83.9	71.1	73.6	70.7	92.1			
g8	Format	C	C	C	C	C		C	C
	Replicates	16	2	2	2	2		2	2
	% HbF+ (F cells), average of replicates	59.2	60.0	66.3	64.7	64.7		55.8	70.4
	% edited, average of replicates	95.1	85.4	94.2	94.6	94.6		91.7	94.8
None/control	Format	n/a	n/a	n/a	n/a	n/a	n/a	n/a	n/a
	Replicates	16	2	2	2	2	2	2	2
	% HbF+ (F cells), average of replicates	21.0	20.3	22.4	22.4	22.4	13.9	24.0	26.7
	% edited, average of replicates	n/a	n/a	n/a	n/a	n/a	n/a	n/a	n/a

The genome edited and unedited HSPC were analyzed by flow cytometry for expression levels of fetal globin and two erythroid cell surface markers, transferrin receptor (CD71) and glycophorin A (CD235a) using antibodies conjugated to fluorescent dyes. The live cells were identified and gated by exclusion of Live Dead Violet. HPFH region targeting resulted in increased percentage of erythroid cells containing HbF compared to mock electroporated cells, a consistent result across multiple evaluations and dgRNA formats (Table 22). In some instances, an increase in %HbF+ cells was associated with a particular dgRNA form, for example Form C for CR001028 (Table 22). Induction of HbF positive cells by dgRNA including the targeting domain of g8 targeting exon 2 of BCL11A was also observed in parallel. Genomic PCR products of the HPFH region were also subjected to next generation sequencing (NGS) to determine the percentage of edited alleles in the cell population. Genome editing at the HFPH locus was observed in cell cultures electroporated with RNPs containing Cas9, crRNA of the given targeting domain and Tracr (Table 22), but not in control cells with no targeting domain delivered (RNPs containing only Cas9 and Tracr).

Finally, the indel pattern as well as frequency of each indel was assessed for each gRNA by NGS. The most frequently occurring indels at each target site are shown in Table 26.

Table 26. 5 most frequent indels at each taget sequence after exposure to RNP comprising the indicated gRNA molecule. Each gRNA was tested in dgRNA format in two separate experiments, and the results are shown seperately for each experiment. Capital letters are the naturally occurring nucleotides at and near the target sequence. Deletions relative to the unmodified target sequence are shown as "-"; insertions are shown as lowercase letters.

Experiment Number	dgRNA targeting domain	Variant Read (Genomic Sequence)	SEQ ID NO:	% of all reads	Indel Length
1	CR001028	TTCTGTCATGTGTGTCTTGACTCAGAAACCCTGTTCTCCTCTA-ATATCTCCCCACCGCATCTCTTTCAGCAGTTGTTTC	2346	13.26%	-1
1	CR001028	TTCTGTCATGTGTGTCTTGACTCAGAAACCCTGTTCTCC----------CCACCGCATCTCTTTCAGCAGTTGTTTC	2347	12.48%	-13
1	CR001028	TTCTGTCATGTGTGTCTTGACTCAGAAACCCTGTTCTCCTCTA----TCTCCCCACCGCATCTCTTTCAGCAGTTGTTTC	2348	6.04%	-4
1	CR001028	TTCTGTCATGTGTGTCTTGACTCAGAAACCCTGTTCTCCTCTA--TATCTCCCCACCGCATCTCTTTCAGCAGTTGTTTC	2349	3.94%	-2
1	CR001028	TTCTGTCATGTGTGTCTTGACTCAGAAACCCTGTTCTCCTC----------ACCGCATCTCTTTCAGCAGTTGTTTC	2350	3.65%	-13
1	CR001028			...	...
2	CR001028	TTCTGTCATGTGTGTCTTGACTCAGAAACCCTGTTCTCC----------CCACCGCATCTCTTTCAGCAGTTGTTTC	2351	14.30%	-13
2	CR001028	TTCTGTCATGTGTGTCTTGACTCAGAAACCCTGTTCTCCTCTA-ATATCTCCCCACCGCATCTCTTTCAGCAGTTGTTTC	2352	11.51%	-1
2	CR001028	TTCTGTCATGTGTGTCTTGACTCAGAAACCCTGTTCTCCTCTA--TATCTCCCCACCGCATCTCTTTCAGCAGTTGTTTC	2353	5.63%	-2
2	CR001028	TTCTGTCATGTGTGTCTTGACTCAGAAACCCTGTTCTCCTCTA----TCTCCCCACCGCATCTCTTTCAGCAGTTGTTTC	2354	4.98%	-4
2	CR001028	TTCTGTCATGTGTGTCTTGACTCAGAAACCCTGTTCTCCTC----------ACCGCATCTCTTTCAGCAGTTGTTTC	2355	4.91%	-13

2	CR001028			...	...
1	CR001030	TCTTGACTCAGAAACCCTGTTCTCCTCTACATATCTC---------- TTTCAGCAGTTGTTTCTAAAAATATCCTCC	2356	9.10%	-13
1	CR001030	TCTTGACTCAGAAACCCTGTTCTCCTCTACATATCTCCCCACC- CATCTCTTTCAGCAGTTGTTTCTAAAAATATCCTCC	2357	4.77%	-1
1	CR001030	TCTTGACTCAGAAACCCTGTTCTCCTCTACATATCTCCCCACC-- ATCTCTTTCAGCAGTTGTTTCTAAAAATATCCTCC	2358	3.54%	-2
1	CR001030	TCTTGACTCAGAAACCCTGTTCTCCTCTACATATCTCCCCACCGgCATCTCTTTCA GCAGTTGTTTCTAAAAATATCCTCC	2359	2.51%	1
1	CR001030	TCTTGACTCAGAAACCCTGTTCTCCTCTACATATCTCCCCA----- TCTCTTTCAGCAGTTGTTTCTAAAAATATCCTCC	2360	2.39%	-5
1	CR001030			...	...
2	CR001030	TCTTGACTCAGAAACCCTGTTCTCCTCTACATATCTC---------- TTTCAGCAGTTGTTTCTAAAAATATCCTCC	2361	9.67%	-13
2	CR001030	TCTTGACTCAGAAACCCTGTTCTCCTCTACATATCTCCCCACC- CATCTCTTTCAGCAGTTGTTTCTAAAAATATCCTCC	2362	4.87%	-1
2	CR001030	TCTTGACTCAGAAACCCTGTTCTCCTCTACATATCTCCCCACC-- ATCTCTTTCAGCAGTTGTTTCTAAAAATATCCTCC	2363	3.33%	-2
2	CR001030	TCTTGACTCAGAAACCCTGTTCTCCTCTACATATCTCCCCACCGgCATCTCTTTCA GCAGTTGTTTCTAAAAATATCCTCC	2364	2.93%	1
2	CR001030	TCTTGACTCAGAAACCCTGTTCTCCTCTACATATCTCCCCAC- GCATCTCTTTCAGCAGTTGTTTCTAAAAATATCCTCC	2365	1.85%	-1
2	CR001030			...	...
1	CR001036	CCTAGTTTCATTTTTGCAGAAGTGTTTTAGGCTAAT- TAGTGGAATGTATCTTAGAGTTTAACTTATTTGTTTCTGTCAC	2366	19.08%	-1
1	CR001036	CCTAGTTTCATTTTTGCAGAAGTGTTTTAGGCTAATA-- GTGGAATGTATCTTAGAGTTTAACTTATTTGTTTCTGTCAC	2367	17.13%	-2
1	CR001036	CCTAGTTTCATTTTTGCAGAAGTGTTTTAG---------- TGGAATGTATCTTAGAGTTTAACTTATTTGTTTCTGTCAC	2368	3.55%	-10
1	CR001036	CCTAGTTTCATTTTTGCAGAAGTGTTTTAGGCTAATAaTAGTGGAATGTATCTTAG AGTTTAACTTATTTGTTTCTGTCAC	2369	2.42%	1
1	CR001036	CCTAGTTTCATTTTTGCAGAAGTGTTTTAGGCTAATA- AGTGGAATGTATCTTAGAGTTTAACTTATTTGTTTCTGTCAC	2370	2.38%	-1
1	CR001036			...	...
2	CR001036	CCTAGTTTCATTTTTGCAGAAGTGTTTTAGGCTAATA-- GTGGAATGTATCTTAGAGTTTAACTTATTTGTTTCTGTCAC	2371	22.26%	-2
2	CR001036	CCTAGTTTCATTTTTGCAGAAGTGTTTTAGGCTAAT- TAGTGGAATGTATCTTAGAGTTTAACTTATTTGTTTCTGTCAC	2372	19.77%	-1
2	CR001036	CCTAGTTTCATTTTTGCAGAAGTGTTTTAG---------- TGGAATGTATCTTAGAGTTTAACTTATTTGTTTCTGTCAC	2373	6.25%	-10
2	CR001036	CCTAGTTTCATTTTTGCAGAAGTGTTTTAGGCTAATA- AGTGGAATGTATCTTAGAGTTTAACTTATTTGTTTCTGTCAC	2374	1.96%	-1
2	CR001036	CCTAGTTTCATTTTTGCAGAAGTGTTTTAGG---------- AATGTATCTTAGAGTTTAACTTATTTGTTTCTGTCAC	2375	1.41%	-12
2	CR001036			...	...
1	CR001043	TAGAGATTTTTGTCTCCAAGGGAATTTTGAGAGGTTG- AATGGACAAATCTATTGCTGCAGTTTAAACTTGCTTGCTTCC	2376	5.28%	-1
1	CR001043	TAGAGATTTTTGTCTCCAAGGGAATTTTGAGAGGTTGGA----- CAAATCTATTGCTGCAGTTTAAACTTGCTTGCTTCC	2377	2.67%	-5
1	CR001043	TAGAGATTTTTGTCTCCAAGGGAATTTTGA--------- ATGGACAAATCTATTGCTGCAGTTTAAACTTGCTTGCTTCC	2378	2.62%	-9
1	CR001043	TAGAGATTTTTGTCTCCAAGGGAATTTTGAGAGG--------- ACAAATCTATTGCTGCAGTTTAAACTTGCTTGCTTCC	2379	2.22%	-9
1	CR001043	TAGAGATTTTTGTCTCCAAGGGAATTTTGAGAGGTTGGgAATGGACAAATCTATTG CTGCAGTTTAAACTTGCTTGCTTCC	2380	2.06%	1
1	CR001043			...	...
2	CR001043	TAGAGATTTTTGTCTCCAAGGGAATTTTGAGAGGTTG- AATGGACAAATCTATTGCTGCAGTTTAAACTTGCTTGCTTCC	2381	5.87%	-1
2	CR001043	TAGAGATTTTTGTCTCCAAGGGAATTTTGAGAGG--------- ACAAATCTATTGCTGCAGTTTAAACTTGCTTGCTTCC	2382	3.11%	-9
2	CR001043	TAGAGATTTTTGTCTCCAAGGGAATTTTGAGAGGTTGGA----- CAAATCTATTGCTGCAGTTTAAACTTGCTTGCTTCC	2383	2.42%	-5
2	CR001043	TAGAGATTTTTGTCTCCAAGGGAATTTTGAGAGGTTGGgAATGGACAAATCTATTG	2384	1.90%	1

		CTGCAGTTTAAACTTGCTTGCTTCC			
2	CR001043	TAGAGATTTTTGTCTCCAAGGGAATTTTGA--------- ATGGACAAATCTATTGCTGCAGTTTAAACTTGCTTGCTTCC	2385	1.72%	-9
2	CR001043			...	...
1	CR001080	GAGAAAGGAAGGAAGGAAGAGGGGAAGAGAGAGGATG- AAGGGATGGAGGAGAAGAAGGAAAAATAAATAATGGAGAGGA	2386	2.72%	-1
1	CR001080	GAGAAAGGAAGGAAGGAAGAGGGGAAGAGAGAGGATGGA--------- GGAGAAGAAGGAAAAATAAATAATGGAGAGGA	2387	2.22%	-9
1	CR001080	GAGAAAGGAAGGAAGGAAGAGGGGAAGAGAGAGG-------- GATGGAGGAGAAGAAGGAAAAATAAATAATGGAGAGGA	2388	1.44%	-8
1	CR001080	GAGAAAGGAAGGAAGGAAGAGGGGAAGAGAGAGGATGGgAAGGGATGGAGGAGAAG AAGGAAAAATAAATAATGGAGAGGA	2389	1.41%	1
1	CR001080	GAGAAAGGAAGGAAGGAAGAGGGGAAGAGAGAGGA---- AGGGATGGAGGAGAAGAAGGAAAAATAAATAATGGAGAGGA	2390	1.11%	-4
1	CR001080			...	...
2	CR001080	GAGAAAGGAAGGAAGGAAGAGGGGAAGAGAGAGGATGGA--------- GGAGAAGAAGGAAAAATAAATAATGGAGAGGA	2391	3.43%	-9
2	CR001080	GAGAAAGGAAGGAAGGAAGAGGGGAAGAGAGAGGATG- AAGGGATGGAGGAGAAGAAGGAAAAATAAATAATGGAGAGGA	2392	3.17%	-1
2	CR001080	GAGAAAGGAAGGAAGGAAGAGGGGAAGAGA--------- AGGGATGGAGGAGAAGAAGGAAAAATAAATAATGGAGAGGA	2393	1.61%	-9
2	CR001080	GAGAAAGGAAGGAAGGAAGAGGGGAAGAGAGAGGA---- AGGGATGGAGGAGAAGAAGGAAAAATAAATAATGGAGAGGA	2394	1.28%	-4
2	CR001080	GAGAAAGGAAGGAAGGAAGAGGGGAAGAGAGAGG-------- GATGGAGGAGAAGAAGGAAAAATAAATAATGGAGAGGA	2395	1.16%	-8
2	CR001080			...	...
1	CR001095	GAGAAAGAGAAAGGGAAGGGAAGAGAGGAAAGAAGA-- AGAGGAGAGAAAAGAAACGAAGAGAGGGGAAGGGAAGGAAAA	2396	5.94%	-2
1	CR001095	GAGAAAGAGAAAGGGAAGGGAAGAGAGGAAAGAAGAG----- GAGAGAAAAGAAACGAAGAGAGGGGAAGGGAAGGAAAA	2397	5.54%	-5
1	CR001095	GAGAAAGAGAAAGGGAAGGGAAGAGAGGA---------- GAGAAAAGAAACGAAGAGAGGGGAAGGGAAGGAAAA	2398	4.02%	-15
1	CR001095	GAGAAAGAGAAAGGGAAGGGAAGAGAGGAAAGAA---------- ACGAAGAGAGGGGAAGGGAAGGAAAA	2399	3.23%	-20
1	CR001095	GAGAAAGAGAAAGGGAAGGGAAGAGAGGAAAGA-------- GGAGAGAAAAGAAACGAAGAGAGGGGAAGGGAAGGAAAA	2400	2.49%	-8
1	CR001095			...	...
2	CR001095	GAGAAAGAGAAAGGGAAGGGAAGAGAGGAAAGAAGAG----- GAGAGAAAAGAAACGAAGAGAGGGGAAGGGAAGGAAAA	2401	7.89%	-5
2	CR001095	GAGAAAGAGAAAGGGAAGGGAAGAGAGGAAAGAAGA-- AGAGGAGAGAAAAGAAACGAAGAGAGGGGAAGGGAAGGAAAA	2402	6.18%	-2
2	CR001095	GAGAAAGAGAAAGGGAAGGGAAGAGAGGA---------- GAGAAAAGAAACGAAGAGAGGGGAAGGGAAGGAAAA	2403	4.16%	-15
2	CR001095	GAGAAAGAGAAAGGGAAGGGAAGAGAGGAAAGAAGAGgAAGAGGAGAGAAAAGAAA CGAAGAGAGGGGAAGGGAAGGAAAA	2404	2.77%	1
2	CR001095	GAGAAAGAGAAAGGGAAGGGA---------- GGAGAGAAAAGAAACGAAGAGAGGGGAAGGGAAGGAAAA	2405	1.98%	-20
2	CR001095			...	...
1	CR001137	AAATGCTTATGACAGCAATAATCATAAAAACCTCAAACC------- ACTTAAATGCTTACCAACAGTAGAATTGATAAAT	2406	6.73%	-7
1	CR001137	AAATGCTTATGACAGCAATAATCATAAAAACCTCAAACCGGTAGgCCACTTAAATG CTTACCAACAGTAGAATTGATAAAT	2407	4.02%	1
1	CR001137	AAATGCTTATGACAGCAATAATCATAAAAACCTCAAACCGGTAaGCCACTTAAATG CTTACCAACAGTAGAATTGATAAAT	2408	2.87%	1
1	CR001137	AAATGCTTATGACAGCAATAATCATAAAAACCTCA-------- GCCACTTAAATGCTTACCAACAGTAGAATTGATAAAT	2409	1.71%	-8
1	CR001137	AAATGCTTATGACAGCAATAATCATAAAAACC---------- ACTTAAATGCTTACCAACAGTAGAATTGATAAAT	2410	0.95%	-14
1	CR001137			...	...
2	CR001137	AAATGCTTATGACAGCAATAATCATAAAAACCTCAAACC------- ACTTAAATGCTTACCAACAGTAGAATTGATAAAT	2411	7.25%	-7
2	CR001137	AAATGCTTATGACAGCAATAATCATAAAAACCTCAAACCGGTAGgCCACTTAAATG CTTACCAACAGTAGAATTGATAAAT	2412	3.44%	1

2	CR001137	AAATGCTTATGACAGCAATAATCATAAAAACCTCAAACCGGTAaGCCACTTAAATG CTTACCAACAGTAGAATTGATAAAT	2413	2.50%	1
2	CR001137	AAATGCTTATGACAGCAATAATCATAAAAACCTCAAACCGGTA-------- AATGCTTACCAACAGTAGAATTGATAAAT	2414	1.37%	-8
2	CR001137	AAATGCTTATGACAGCAATAATCATAAAAACCTCAAACCGGT------- TAAATGCTTACCAACAGTAGAATTGATAAAT	2415	1.11%	-7
2	CR001137			...	...
1	CR001142	AAATGCATTTTACAGCATTTGGTTGATTAAAAGTAACCcAGAGGTGAGTTCAAACT ATATGACTTTATTTGTATATAGAAA	2416	8.00%	1
1	CR001142	AAATGCATTTTACAGCATTTGGTTGATTAAAAG------- AGGTGAGTTCAAACTATATGACTTTATTTGTATATAGAAA	2417	6.63%	-7
1	CR001142	AAATGCATTTTACAGCATTTGGTTGATTAAAAGTAAC- AGAGGTGAGTTCAAACTATATGACTTTATTTGTATATAGAAA	2418	2.86%	-1
1	CR001142	AAATGCATTTTACAGCATTTGGTTGATTAAAAG--------- GTGAGTTCAAACTATATGACTTTATTTGTATATAGAAA	2419	2.03%	-9
1	CR001142	AAATGCATTTTACAGCATTTGGTTGA-------------------- GTTCAAACTATATGACTTTATTTGTATATAGAAA	2420	1.71%	-20
1	CR001142			...	...
2	CR001142	AAATGCATTTTACAGCATTTGGTTGATTAAAAGTAACCcAGAGGTGAGTTCAAACT ATATGACTTTATTTGTATATAGAAA	2421	9.94%	1
2	CR001142	AAATGCATTTTACAGCATTTGGTTGATTAAAAG------- AGGTGAGTTCAAACTATATGACTTTATTTGTATATAGAAA	2422	5.81%	-7
2	CR001142	AAATGCATTTTACAGCATTTGGTTGATTAAAAGTAAC- AGAGGTGAGTTCAAACTATATGACTTTATTTGTATATAGAAA	2423	4.19%	-1
2	CR001142	AAATGCATTTTACAGCATTTGGTTGATTAAAAG--------- GTGAGTTCAAACTATATGACTTTATTTGTATATAGAAA	2424	2.59%	-9
2	CR001142	AAATGCATTTTACAGCATTTGGTTGA-------------------- GTTCAAACTATATGACTTTATTTGTATATAGAAA	2425	2.26%	-20
2	CR001142			...	...
1	CR001158	CCTGGAAGCCAACGAAAGATATTGAATAATTCAAGAAAaGGTGGTGGCATGGTTTG ATTTGTGTCTTTAAAAGATTATTCT	2426	10.94%	1
1	CR001158	CCTGGAAGCCAACGAAAGATATTGAATAATTCAAG---- GTGGTGGCATGGTTTGATTTGTGTCTTTAAAAGATTATTCT	2427	10.03%	-4
1	CR001158	CCTGGAAGCCAACGAAAGATATTGAATAATTCAAGAA- GGTGGTGGCATGGTTTGATTTGTGTCTTTAAAAGATTATTCT	2428	3.80%	-1
1	CR001158	CCTGGAAGCCAACGAAAGATATTGAATAATTCAAGA-- GGTGGTGGCATGGTTTGATTTGTGTCTTTAAAAGATTATTCT	2429	1.19%	-2
1	CR001158	CCTGGAAGCCAACGAAAGATATTGAATAATTCA----- GGTGGTGGCATGGTTTGATTTGTGTCTTTAAAAGATTATTCT	2430	0.78%	-5
1	CR001158			...	...
2	CR001158	CCTGGAAGCCAACGAAAGATATTGAATAATTCAAGAAAaGGTGGTGGCATGGTTTG ATTTGTGTCTTTAAAAGATTATTCT	2431	11.89%	1
2	CR001158	CCTGGAAGCCAACGAAAGATATTGAATAATTCAAG---- GTGGTGGCATGGTTTGATTTGTGTCTTTAAAAGATTATTCT	2432	9.97%	-4
2	CR001158	CCTGGAAGCCAACGAAAGATATTGAATAATTCAAGAA- GGTGGTGGCATGGTTTGATTTGTGTCTTTAAAAGATTATTCT	2433	3.45%	-1
2	CR001158	CCTGGAAGCCAACGAAAGATATTGAATAATTCAAGA-- GGTGGTGGCATGGTTTGATTTGTGTCTTTAAAAGATTATTCT	2434	0.86%	-2
2	CR001158	CCTGGAAGCCAACGAAAGATATTGAATAATTCAAGAAcaAGGTGGTGGCATGGTTT GATTTGTGTCTTTAAAAGATTATTCT	2435	0.49%	2
2	CR001158			...	...
1	CR001212	CCTTGGCCTCCCAAAGTGCTGGGTTTACAAGCCTGAGCCA-------------- GGATAAGGTCTAAAAGTGGAAAGAATA	2436	11.38%	-13
1	CR001212	CCTTGGCCTCCCAAAGTGCTGGGTTTACAAGCCTGAGCCACC- CATCCAGCCAGGATAAGGTCTAAAAGTGGAAAGAATA	2437	3.98%	-1
1	CR001212	CCTTGGCCTCCCAAAGTGCTGGGTTTACAAGCCTGAGCCA----- TCCAGCCAGGATAAGGTCTAAAAGTGGAAAGAATA	2438	3.05%	-5
1	CR001212	CCTTGGCCTCCCAAAGTGCTGGGTTTACAAGCCTGAGCCACCG- ATCCAGCCAGGATAAGGTCTAAAAGTGGAAAGAATA	2439	2.94%	-1
1	CR001212	CCTTGGCCTCCCAAAGTGCTGGGTTTACAAGCCTGAGCCACC------ AGCCAGGATAAGGTCTAAAAGTGGAAAGAATA	2440	2.82%	-6
1	CR001212			...	...
2	CR001212	CCTTGGCCTCCCAAAGTGCTGGGTTTACAAGCCTGAGCCA--------------	2441	11.42%	-13

		GGATAAGGTCTAAAAGTGGAAAGAATA			
2	CR001212	CCTTGGCCTCCCAAAGTGCTGGGTTTACAAGCCTGAGCCACC- CATCCAGCCAGGATAAGGTCTAAAAGTGGAAAGAATA	2442	6.41%	-1
2	CR001212	CCTTGGCCTCCCAAAGTGCTGGGTTTACAAGCCTGAGCCACCG- ATCCAGCCAGGATAAGGTCTAAAAGTGGAAAGAATA	2443	5.61%	-1
2	CR001212	CCTTGGCCTCCCAAAGTGCTGGGTTTACAAGCCTGAGCCACCG-- TCCAGCCAGGATAAGGTCTAAAAGTGGAAAGAATA	2444	2.85%	-2
2	CR001212	CCTTGGCCTCCCAAAGTGCTGGGTTTACAAGCCTGAGCCACC------ AGCCAGGATAAGGTCTAAAAGTGGAAAGAATA	2445	1.96%	-6
2	CR001212			...	...
1	CR001217	AAGTGCTGGGTTTACAAGCCTGAGCCACCGCATCCAGCCAGG------ TCTAAAAGTGGAAAGAATAGCATCTACTCTTG	2446	17.75%	-6
1	CR001217	AAGTGCTGGGTTTACAAGCCTGAGCCACCGCATCCAGCCAGGATtAAGGTCTAAAA GTGGAAAGAATAGCATCTACTCTTG	2447	4.06%	1
1	CR001217	AAGTGCTGGGTTTACAAGCCTGAGCCACCGCATCCAGCCAGGAaTAAGGTCTAAAA GTGGAAAGAATAGCATCTACTCTTG	2448	2.38%	1
1	CR001217	AAGTGCTGGGTTTACAAGCCTGAGCCACCGCATCCAGCCAGGA- AAGGTCTAAAAGTGGAAAGAATAGCATCTACTCTTG	2449	1.35%	-1
1	CR001217	AAGTGCTGGGTTTACAAGCCTGAGCCACCGCATCCAGCCAGGAT----- CTAAAAGTGGAAAGAATAGCATCTACTCTTG	2450	1.10%	-5
1	CR001217			...	...
2	CR001217	AAGTGCTGGGTTTACAAGCCTGAGCCACCGCATCCAGCCAGG------ TCTAAAAGTGGAAAGAATAGCATCTACTCTTG	2451	18.91%	-6
2	CR001217	AAGTGCTGGGTTTACAAGCCTGAGCCACCGCATCCAGCCAGGATtAAGGTCTAAAA GTGGAAAGAATAGCATCTACTCTTG	2452	5.59%	1
2	CR001217	AAGTGCTGGGTTTACAAGCCTGAGCCACCGCATCCAGCCAGGAaTAAGGTCTAAAA GTGGAAAGAATAGCATCTACTCTTG	2453	1.42%	1
2	CR001217	AAGTGCTGGGTTTACAAGCCTGAGCCACCGCATCCAGCCAGGA- AAGGTCTAAAAGTGGAAAGAATAGCATCTACTCTTG	2454	1.38%	-1
2	CR001217	AAGTGCTGGGTTTACAAGCCTGAGCCACCGCATCCAGCCAGGAT----- CTAAAAGTGGAAAGAATAGCATCTACTCTTG	2455	1.26%	-5
2	CR001217			...	...
1	CR001221	TAGCATCTACTCTTGTTCAGGAAACAATGAGGACCTG---- GGCAGTAAGAGTGGTGATTAATAGATAGGGACAAATTGA	2456	28.78%	-4
1	CR001221	TAGCATCTACTCTTGTTCAGGAAACAATGAGGACCT- ACTGGGCAGTAAGAGTGGTGATTAATAGATAGGGACAAATTGA	2457	9.51%	-1
1	CR001221	TAGCATCTACTCTTGTTCAGGAAACAATGAGGAC----- TGGGCAGTAAGAGTGGTGATTAATAGATAGGGACAAATTGA	2458	4.35%	-5
1	CR001221	TAGCATCTACTCTTGTTCAGGAAACAATGAGG---------- CAGTAAGAGTGGTGATTAATAGATAGGGACAAATTGA	2459	1.87%	-11
1	CR001221	TAGCATCTACTCTTGTTCAGGAAACAATG---------- GGCAGTAAGAGTGGTGATTAATAGATAGGGACAAATTGA	2460	1.71%	-12
1	CR001221			...	...
2	CR001221	TAGCATCTACTCTTGTTCAGGAAACAATGAGGACCTG---- GGCAGTAAGAGTGGTGATTAATAGATAGGGACAAATTGA	2461	29.12%	-4
2	CR001221	TAGCATCTACTCTTGTTCAGGAAACAATGAGGACCT- ACTGGGCAGTAAGAGTGGTGATTAATAGATAGGGACAAATTGA	2462	10.32%	-1
2	CR001221	TAGCATCTACTCTTGTTCAGGAAACAATGAGGAC----- TGGGCAGTAAGAGTGGTGATTAATAGATAGGGACAAATTGA	2463	4.26%	-5
2	CR001221	TAGCATCTACTCTTGTTCAGGAAACAATGAGGAC---------- AGTAAGAGTGGTGATTAATAGATAGGGACAAATTGA	2464	1.89%	-10
2	CR001221	TAGCATCTACTCTTGTTCAGGAAACAATGAGG---------- CAGTAAGAGTGGTGATTAATAGATAGGGACAAATTGA	2465	1.67%	-11
2	CR001221			...	...

Although in some cases, the relative abundance of the most frequent indels varied from experiment to experiment, the top indels were largely the same across both experiments for any given gRNA. This indicates that for these dgRNAs, the indel pattern created in HSC cells was consistent. As well, these results support the surprising finding from earlier expeirments that small indels (e.g., in this case,

indels from 1-20 nucelotides) in the HPFH regions targeted by these gRNAs could result in significant upregulation of fetal hemoglobin. An increase in HbF-containing erythrocytes derived from genome edited cells is likely to have therapeutic implications by reduced sickling.

Example 4.5

Methods: Methods are as in sub-example 4.1, with the following exceptions.

Human $CD34^+$ cell culture. Human CD34+ cells were derived from bone marrow (Hemacare Corporation, Cat. No. BM34C-3). CD34+ cells were thawed and expanded in expansion medium for 1 day prior to RNP delivery. After RNP delivery, cells were immediatedly transferred back into 200 µl expansion medium and allowed to recover overnight. The following day, the cultures were counted and adjusted to $2.0x10^5$ viable cells per ml. Percent recovery was calculated as the viable cell count 1 day after RNP delivery as a percentage of the viable cells electroporated. After an additional 7 days in expansion medium (8 days following RNP delivery), the viable cell count was again determined. Fold proliferation was calculated as the viable cell count after 7 days in expansion medium divided by $2.0x10^5$ cells per ml. All viable cell counts were measured by flow cytometry using AccuCheck Counting Beads (ThermoFisher cat. No. PCB100) with inviable cells discriminated by DAPI (4',6-Diamidino-2-Phenylindole) staining. After an additional 1 day in expansion medium (9 days following RNP delivery), the cell cultures were phenotyped by flow cytometry as described under Cell phenotyping.

Assembly of Cas9 and guide RNA ribonucleoprotein (RNP) complexes, preparation of HSPC, and electroporation of RNP into HSPC. The HSPC collected by centrifugation were resuspended in P3 Primary Cell Solution (Lonza cat. No. PBP3-00675) at a cell density of 5.4 x 10^6/mL. The RNP was mixed with 20 µL of cells by pipetting up and down and incubated at RT for 2 min. The RNP/cell mixture (20 µL) was electroporated using code CM-137 on the 4D-Nucleofector (Lonza). Electroporations were performed in duplicate. The crRNAs used were of the sequence mN*mN*mN*rNrNrNrNrNrNrNrNrNrNrNrNrNrNrNrNrGrUrUrUrUrArGrArGrCrUrArU*mG*mC*mU (SEQ ID NO: 2466), where r indicates an RNA base, m indicates a base with 2'O-Methyl modification, and * indicates a Phosphorothioate Bond. N's indicate the residues of the indicated targeting domain. The tracr sequence used was SEQ ID NO: 7808.

Colony forming unit cell assay. The day following RNP delivery, viable cells were counted as described in Human CD34+ cell culture. For the granulocyte/macrophage progenitor colony forming unit (CFU) assay, 227 cells per 1 mL Methocult H4035 methylcellulose medium (StemCell Technologies) was plated in duplicate. 1x antibiotic/antimycotic (Gibco, Cat. #10378-016) was added into the Methocult. The culture dishes were incubated in a humidified incubator at 37°C. Colonies

containing at least 50 cells were counted at day 15 post-plating. Colony number per ml of Methocult was divided by 227 and multiplied by 1000 to obtain the CFU frequency per 1000 cells.

Cell phenotyping. Cells were analyzed for surface marker expression after staining with the following antibody panels. Panel 1: Antibodies specific for CD38 (FITC-conjugate, BD Biosciences #340926, clone HB7), CD133 epitope 1 (PE-conjugate, Miltenyi #130-080-801, clone AC133), CD34 (PerCP-conjugate, BD Biosciences #340666, clone 8G12), CD90 (APC-conjugate, BD Biosciences #598695, clone E10), CD45RA (Pe-Cy7-conjugate, eBioscience #25-0458-42, clone HI100). Panel 2: CD34 (PerCP-conjugate, BD Biosciences #340666, clone 8G12), CD33 (PE-Cy7-conjugate, BD Biosciences #333946, clone P67.6), CD14 (APC-H7-conjugate, BD Biosciences #560270, clone MφP9), CD15 (PE-conjugate, Biolegend #301905, clone HI98). Panel 3: CD34 (PerCP-conjugate, BD Biosciences #340666, clone 8G12), CD41a (APC-H7-conjugate, BD Biosciences #561422, clone HIP8), CD71 (FITC-conjugate, BD Biosciences #555536, clone M-A712), CD19 (PE-conjugate, BD Biosciences #340720, clone SJ25C1), CD56 (APC-conjugate, Biolegend #318310, clone HCD56). Correspoding isotype control antibody panels were used to stain cultures in parallel, except that anti-CD45RA was included instead of its isotype control. Inviable cells were discriminated by DAPI (4',6-Diamidino-2-Phenylindole) staining. Stained samples were analyzed on an LSRFortessa flow cytometer (BD Biosciences) for cell surface protein expression. The results were analyzed using Flowjo, and data were presented as % of the DAPI negative viable cell population.

Genomic DNA preparation and next generation sequencing (NGS). Genomic DNA was prepared from edited and unedited HSPC at 1 and 8 days post-electroporation using Quick Extract DNA Extraction Solution (Epicentre Cat # QE09050).

Results:

Without being bound by theory, it is believed that targeted genetic disruption of the HPFH or BCL11A erythroid enhancer region will relieve repression of γ-globin expression, allowing production of the red blood cells containing elevated HbF protein, (cells expressing fetal hemoglobin are sometimes referred to herein as "F-cells"). The elevated HbF prevents sickling of the red blood cells under deoxygenated conditions and will be therapeutic/curative for the patients of both β-thalassemia and SCD. Autologous hematopoietic stem cell transplantation (HSCT) with *ex vivo* genome edited HSC from SCD patients was also combined with stem cell expansion enhancing technology, e.g., an aryl hydrocarbon receptor (AHR) inhibitor, e.g., as described in WO2010/059401 (the contents of which are incorporated by reference in their entirety), e.g., Compound 4 to improve ex vivo expansion and increase the dose of gene modified HSC delivered.

For efficient genome editing via programmable nuclease, Cas9, the successful delivery of guide RNA (gRNA) and Cas9 protein into target cells and tissues is essential. Recent reports demonstrated that

Cas9 ribonucleoprotein (RNP) complexes when delivered into target cells by electroporation can accomplish efficient and specific genome editing in several different cell types. Cas9-RNP complexes cleave chromosomal DNA almost immediately after delivery and are degraded rapidly in cells, reducing off-target effects. In contrast, use of plasmid and viral vector systems used to deliver Cas9 results in prolonged expression of the enzyme aggravating off-target effects associated with the system. Additionally, delivery of RNPs into the target cells requires no additional tools which would greatly facilitate translation of genome editing for therapeutic purposes in the clinic. Purified recombinant Cas9 protein and gRNA complexes (RNPs) were delivered into cultured HSPC and an overview experiments used are shown in Figure 17.

Recombinant Cas9 protein was purified from Escherichia coli and complexed with synthetic dual gRNAs (dgRNA) that consist of crRNA and tracr to generate ribonucleoprotein (RNP) complexes. The list of gRNAs used in the study are shown in Table 23. The RNP complexes were electroporated into CD34+ HSPC via electroporation as described under materials and methods. The cells were expanded prior to the delivery of RNP complexes. Actively dividing cells may facilitate uptake of RNP complexes delivered by electroporation.

Table 23. Relative viable cell recovery, proliferation in CD34+ medium, and granulocyte/macrophage progenitor colony forming unit (CFU) frequency for edited and unedited cell cultures in the current study. Percent recovery, Fold proliferation and CFU frequency were calculated as described in Materials and Methods. Individual electroporation replicates are shown. All gRNA molecules were tested in the dgRNA format. The Tracr sequence was SEQ ID NO: 7808, and the crRNA had the following format with 2'O-Methyl (m) and Phosphorothioate Bond (*) modifications indicated: mN*mN*mN*rNrNrNrNrNrNrNrNrNrNrNrNrNrNrNrNrGrUrUrUrUrArGrArGrCrUrArU*mG*mC*mU (SEQ ID NO: 2467), where N's are the residues of the indicated targeting domain.

Guide RNA targeting domain ID and replicate	% recovery	Fold proliferation (7 days)	CFU (per 1000 cells)
CR001030 replicate 1	77.7	7.1	117
CR001030 replicate 2	87.9	4.8	95
CR001028 replicate 1	85.3	10.6	176
CR001028 replicate 2	82.1	10.9	141
CR001095 replicate 1	72.5	7.3	121
CR001095 replicate 2	73.3	7.3	126
CR001212 replicate 1	75.6	7.7	123
CR001212 replicate 2	75.5	8.2	97
CR000312 replicate 1	77.7	12.2	145
CR000312 replicate 2	81.0	9.0	143
g8 replicate 1	80.0	16.6	145
g8 replicate 2	84.6	17.3	145
None/control replicate 1	89.8	19.3	185
None/control replicate 2	81.2	20.5	154

Percent cell recovery at 1 day after electroporation ranged from 72.5% to 89.8% and was similar across conditions, including the unedited but electroporated control (Table 23). The genome edited and unedited HSPC were analyzed for proliferation in CD34+ cell expansion medium. Proliferation ranged from 4.8-fold to 17.3-fold over 7 days for edited cell cultures, and ranged from 19.3 to 20.5-fold for unedited cells (Table 22). Editing by dgRNAs in this study targeting the HPFH or BCL11A erythroid enhancer regions did not alter the composition of cell types in the culture compared to unedited control, as determined by surface marker expression, indicating that targeting these sites does not alter HSPC fate under these conditions (Figure 26A-B). In contrast, editing with dgRNA targeting g8 in the BCL11A exon resulted in a modest reduction in proliferation but a marked shift in cell composition, specifically a decrease in the percentage of all CD34+ HSPC sub-types as well as of the CD71+ erythroid population and an increase in the percentage of CD14+ monocyte and CD15+ granulocyte poplulations (Table 23 and Figure 26A-B). The frequency of granulocyte/macrophage progenitor colony forming units (CFU) was similar across edited cultures, with only a modest CFU reduction in edited cultures (ranging from 95 to 145 CFU per 1000 cells) compared with unedited cultures (154 to 185 CFU per 1000 cells), suggesting that granulocyte/macrophage progenitor function is not grossly altered by targeting these sites (Table 23).

Example 4.6

Methods: Methods are as in Example 4, with the following exceptions.

Assembly of Cas9 and guide RNA ribonucleoprotein (RNP) complexes, preparation of HSPC, and electroporation of RNP into HSPC. In some instances, crRNAs containing two different targeting domains were delivered into the same cell culture. In these instances, the total RNP delivered to cells contained 6 µg of Cas9, 3 µg of crRNA and 3 µg of Tracr, as in sub-example 4.1; however, the two crRNAs containing 1.5 µg each were independently complexed Tracr/CAS9 mixtures containing 1.5 µg Tracr and 3 µg Cas9 and only combined when added to the cells. The HSPC collected by centrifugation were resuspended in P3 Primary Cell Solution (Lonza cat. No. PBP3-00675) at a cell density of 2.5 x 10^6/mL. The RNP was mixed with 20 µL of cells by pipetting up and down and incubated at RT for 2 min. The RNP/cell mixture (20 µL) was electroporated using code CM-137 on the 4D-Nucleofector (Lonza). Electroporations were performed in duplicate. The dgRNA format used a tracr having SEQ ID NO: 7808, and a crRNA of the sequence mN*mN*mN*rNrNrNrNrNrNrNrNrNrNrNrNrNrNrNrNrGrUrUrUrUrArGrArGrCrUrArU*mG*mC*mU (SEQ ID NO: 2468), where r indicates an RNA base, m indicates a base with 2'O-Methyl modification, and * indicates a Phosphorothioate Bond, and N's indicate the residues of the indicated targeting domain.

In vitro erythropoiesis and FACS analysis for HbF containing erythroid cells. The cell culture was diluted in fresh medium after 3 days.

Genomic DNA preparation and next generation sequencing (NGS). Genomic DNA was prepared from edited and unedited HSPC at 3 days post-electroporation using Quick Extract DNA Extraction Solution (Epicentre Cat # QE09050).

Results:

Without being bound by theory, it is believed that targeted genetic disruption of the HPFH or BCL11A erythroid enhancer region will relieve repression of γ-globin expression, allowing production of the red blood cells containing elevated HbF protein, (cells expressing fetal hemoglobin are sometimes referred to herein as "F-cells"). The elevated HbF prevents sickling of the red blood cells under deoxygenated conditions and will be therapeutic/curative for the patients of both β-thalassemia and SCD. Autologous hematopoietic stem cell transplantation (HSCT) with *ex vivo* genome edited HSC from SCD patients was also combined with stem cell expansion enhancing technology, e.g., an aryl hydrocarbon receptor (AHR) inhibitor, e.g., as described in WO2010/059401 (the contents of which are incorporated by reference in their entirety), e.g., Compound 4 to improve ex vivo expansion and increase the dose of gene modified HSC delivered.

For efficient genome editing via programmable nuclease, Cas9, the successful delivery of guide RNA (gRNA) and Cas9 protein into target cells and tissues is essential. Recent reports demonstrated that Cas9 ribonucleoprotein (RNP) complexes when delivered into target cells by electroporation can accomplish efficient and specific genome editing in several different cell types. Cas9-RNP complexes cleave chromosomal DNA almost immediately after delivery and are degraded rapidly in cells, reducing off-target effects. In contrast, use of plasmid and viral vector systems used to deliver Cas9 results in prolonged expression of the enzyme aggravating off-target effects associated with the system. Additionally, delivery of RNPs into the target cells requires no additional tools which would greatly facilitate translation of genome editing for therapeutic purposes in the clinic. Purified recombinant Cas9 protein and gRNA complexes (RNPs) were delivered into cultured HSPC and an overview experiments used are shown in Figure 17.

Recombinant Cas9 protein was purified from Escherichia coli and complexed with synthetic dual gRNAs (dgRNA) that consist of crRNA and tracr to generate ribonucleoprotein (RNP) complexes. The list of gRNAs used in the study are shown in Table 24. The RNP complexes were electroporated into CD34+ HSPC via electroporation as described under materials and methods. The cells were expanded prior to the delivery of RNP complexes. Actively dividing cells may facilitate uptake of RNP complexes delivered by electroporation.

Table 24. HbF induction by simultaneous targeting of both the BCL11A erythroid enhancer and HPFH regions. All gRNA molecules were tested in the dgRNA format in duplicate. The tracr used has the sequence of SEQ ID NO: 7808, and the crRNA had the following format with 2'O-Methyl (m) and Phosphorothioate Bond (*) modifications indicated:

mN*mN*mN*rNrNrNrNrNrNrNrNrNrNrNrNrNrNrNrNrGrUrUrUrUrArGrArGrCrUrArU*mG*mC*mU (SEQ ID NO: 2469), where N's are the residues of the indicated targeting domain.

Guide RNA targeting domain ID #1	Guide RNA targeting domain ID #2	% HbF+ (F cells), average of replicates	% edited at targeting site #1, average of replicates	% edited at targeting site #2, average of replicates
CR000312	n/a	41.3	91.3	n/a
CR001128_EH15	n/a	43.7	77.5	n/a
n/a	CR001030	58.0	n/a	85.6
n/a	CR001221	48.6	n/a	92.1
CR000312	CR001030	66.8	58.3	81.2
CR000312	CR001221	60.6	64.2	85.0
CR001128_EH15	CR001030	69.1	49.8	82.9
CR001128_EH15	CR001221	62.7	58.5	84.8
g8	n/a	64.7	94.6	n/a
None/control	n/a	23.8	n/a	n/a

The genome edited and unedited HSPC were analyzed by flow cytometry for expression levels of fetal globin and two erythroid cell surface markers, transferrin receptor (CD71) and glycophorin A (CD235a) using antibodies conjugated to fluorescent dyes. The live cells were identified and gated by exclusion of Live Dead Violet. HPFH region or BCL11A erythroid enhancer targeting resulted in increased percentage of erythroid cells containing HbF compared to mock electroporated cells (Table 24). Induction of HbF positive cells by dgRNA including the targeting domain of g8 targeting exon 2 of BCL11A was also observed in parallel. When the HPFH region and BCL11A erythroid enhancer were targeted simultaneously in the same cell population, the percentage of HbF containing cells was increased beyond that of targeting either region independently (Table 24). Thus, an increase in HbF-containing erythrocytes derived from edited cells can be achieved by targeting either the HPFH region or BCL11A erythroid enhancer, as well as to a greater extent by simultaneous targeting of both regions.

Genomic PCR products of both regions were independently subjected to next generation sequencing (NGS) to determine the percentage of edited alleles in the cell population. Genome editing was observed in cell cultures electroporated with RNPs containing Cas9, crRNA of the given targeting domain and Tracr (Table 24), but not in control cells with no targeting domain delivered (RNPs containing only Cas9 and Tracr). When RNPs targeting two sites were delivered into the same cell population, editing at both sites was observed (Table 24). In some instances, the percent edited cells at a given site was modestly reduced when two RNPs were delivered compared with when only one RNP was delivered (Table 24), possibly due to the lower RNP concentration targeting a given site in the former instance. Higher editing percentages and potentially higher percentages of HbF containing cells may be achieved by increasing the each individual RNP concentration when two RNPs are

delivered simultaneously. An increase in HbF-containing erythrocytes derived from genome edited cells is likely to have therapeutic implications by reduced sickling.

Example 4.7

Methods: Methods are as in Example 4, with the following exceptions.

Human CD34+ cell culture. Human CD34+ cells were derived from bone marrow (Lonza, Cat. No. 2M-101D). CD34+ cells were thawed and expanded for 2 days in expansion medium prior to RNP delivery.

Assembly of Cas9 and guide RNA ribonucleoprotein (RNP) complexes, preparation of HSPC, and electroporation of RNP into HSPC. For formation of RNP using single guide RNAs (sgRNAs), 6 µg of sgRNA was added to 6 µg of CAS9 protein (in 0.8 to 1 µL) and 0.5 µL of 5 x CCE buffer (20 mM HEPES, 100 mM KCL, 5 mM MgCL2, 5% Glycerol and freshly added 1 mM DTT) in a total volume of 5 µL and incubated for 5 min at 37oC. The HSPC were collected by centrifugation were resuspended in P3 Primary Cell Solution (Lonza cat. No. PBP3-00675) at a cell density of 6.4 x 106/mL. The RNP was mixed with 20 µL of cells by pipetting up and down and incubated at RT for 2 min. The RNP/cell mixture (20 µL) was electroporated using code CM-137 on the 4D-Nucleofector (Lonza). Electroporations were performed in duplicate. For dgRNA, dgRNA-PS and dgRNA-OMePS the Tracr was SEQ ID NO: 6660, with the exception of g8 which was used with Tracr SEQ ID NO: 7808. The formats for all gRNAs used in this experiment are shown in Table 36, with the exception of the dgRNA g8 OMePS, which included a crRNA having the sequence mC*mA*mC*AAACGGAAACAAUGCAAGUUUUAGAGCUAU*mG*mC*mU (SEQ ID NO: 2470). and a tracr having the sequence of SEQ ID NO: 7808.

In vitro erythropoiesis and FACS analysis for HbF containing erythroid cells. After RNP delivery, cells were maintained as per Protocol 1 or Protocol 2. For Protocol 1, the cells were immediately transferred into pre-warmed medium consisting of EDM and supplements. During days 0–7 of culture, EDM was further supplemented with 1 µM hydrocortisone (Sigma H8672), 100 ng/mL human SCF (Life Technologies, Cat. #PHC2113), and 5 ng/mL human IL-3 (Peprotech #10779-598). During days 7–11 of culture, EDM was supplemented with 100 ng/mL of human SCF only. During days 11–21 of culture, EDM had no additional supplements. Cell cultures were adjusted to $4.0x10^4$ cells per ml on day 7. On days 11, 14 and 19, the media was replenished. For Protocol 2, cells were immediatedly transferred back into 200 µl expansion medium and allowed to expand for an additional 2 days. The cultures were counted at 2 days after RNP delivery. The cells were then pelleted and resuspended in pre-warmed medium consisting of EDM and supplements. During days 0–7 of EDM culture, EDM was further supplemented with 1 µM hydrocortisone (Sigma H8672), 100 ng/mL human SCF (Life Technologies, Cat. #PHC2113), and 5 ng/mL human IL-3 (Peprotech #10779-598).

During days 7–11 of culture, EDM was supplemented with 100 ng/mL of human SCF only. During days 11–21 of culture, EDM had no additional supplements. Cell cultures were initiated at $4.0x10^4$ cells per ml on day 0, diluted 4-fold with fresh medium on day 4, and adjusted to $2.0x10^5$ cells per ml on day 7. On days 11, 14 and 19, the media was replenished. Viable cells were counted at 7, 18 and 21 days in EDM culture. All viable cell counts were determined by flow cytometry using AccuCheck Counting Beads (ThermoFisher cat. No. PCB100) with inviable cells discriminated by DAPI (4',6-Diamidino-2-Phenylindole) staining. For both protocols, on days 7, 14 and 21 of the erythroid differentiation culture, the cells were analyzed by intracellular staining for HbF expression. On days 14 and 21 intracellular staining for HbF expression did not include anti-CD71 and anti-CD235a antibodies, and % of HbF positive cells (F-cells) in the entire viable cell population was reported. LIVE/DEAD® Fixable Near-IR Dead Cell Stain (ThermoFisher L34975) was used as the viability dye.

Genomic DNA preparation and next generation sequencing (NGS). Genomic DNA was prepared at 2 and 6 days post-electroporation from edited and unedited HSPC cultured by Protocol 2 using Quick Extract DNA Extraction Solution (Epicentre Cat # QE09050).

Results:

Without being bound by theory, it is believed that targeted genetic disruption of the HPFH region will relieve repression of γ-globin expression, allowing production of the red blood cells containing elevated HbF protein, (cells expressing fetal hemoglobin are sometimes referred to herein as "F-cells"). The elevated HbF prevents sickling of the red blood cells under deoxygenated conditions and will be therapeutic/curative for the patients of both β-thalassemia and SCD. Autologous hematopoietic stem cell transplantation (HSCT) with *ex vivo* genome edited HSC from SCD patients was also combined with stem cell expansion enhancing technology, e.g., an aryl hydrocarbon receptor (AHR) inhibitor, e.g., as described in WO2010/059401 (the contents of which are incorporated by reference in their entirety), e.g., Compound 4 to improve ex vivo expansion and increase the dose of gene modified HSC delivered.

For efficient genome editing via programmable nuclease, Cas9, the successful delivery of guide RNA (gRNA) and Cas9 protein into target cells and tissues is essential. Recent reports demonstrated that Cas9 ribonucleoprotein (RNP) complexes when delivered into target cells by electroporation can accomplish efficient and specific genome editing in several different cell types. Cas9-RNP complexes cleave chromosomal DNA almost immediately after delivery and are degraded rapidly in cells, reducing off-target effects. In contrast, use of plasmid and viral vector systems used to deliver Cas9 results in prolonged expression of the enzyme aggravating off-target effects associated with the system. Additionally, delivery of RNPs into the target cells requires no additional tools which would greatly facilitate translation of genome editing for therapeutic purposes in the clinic. Purified

recombinant Cas9 protein and gRNA complexes (RNPs) were delivered into cultured HSPC and an overview experiments used are shown in Figure 17.

Recombinant Cas9 protein was purified from Escherichia coli and complexed with synthetic single gRNAs (sgRNA) or dual gRNAs (dgRNA) that consist of crRNA and tracr to generate ribonucleoprotein (RNP) complexes. The formats of gRNAs used in the study are shown in Table 36. The RNP complexes were electroporated into CD34+ HSPC via electroporation as described under materials and methods. The cells were expanded prior to the delivery of RNP complexes and, in some cases (Protocol 2) also after electroporation. Actively dividing cells may facilitate uptake of RNP complexes delivered by electroporation.

Genomic PCR products of the HPFH region were subjected to next generation sequencing (NGS) to determine the percentage of edited alleles in the cell population. Genome editing at the HFPH locus was observed in cell cultures electroporated with RNPs containing Cas9, crRNA of the given targeting domain and Tracr (Figure 43), but not in control cells with no targeting domain delivered (RNPs containing only Cas9 and Tracr). In some instances, editing was greater at a given target site usind modified sgRNAs relative to the other gRNA formats (Figure 43). Finally, the indel pattern as well as frequency of each indel was assessed for each gRNA by NGS. Indel pattern across multiple replicates using the same gRNA/Cas9 were similar. Representative most frequently occurring indels at each target site are shown in Table 37.

Table 36. gRNA sequences used in the experiments described in this sub-example. N indicates the residues of the indicated targeting domain; mN indicates a 2'-OMe-modified nucleic acid; * indicates a phosphorothioate modification.

Label	Format	Sequence
CRxxxxxx sg	sgRNA	NNNNNNNNNNNNNNNNNNNGUUUUAGAGCUAGAAAUAGCAAGUUAAAAUAAGGCUAGUCCGUUAUCAACUUGAAAAAGUGGCACCGAGUCGGUGCUUUU (SEQ ID NO: 2471)
CRxxxxxx OMePS sg or CRxxxxxx sg OMePS	sgRNA	mN*mN*mN*NNNNNNNNNNNNNNNNNNGUUUUAGAGCUAGAAAUAGCAAGUUAAAAUAAGGCUAGUCCGUUAUCAACUUGAAAAAGUGGCACCGAGUCGGUGCmU*mU*mU*U (SEQ ID NO: 2472)
CRxxxxxx PS sg or CRxxxxxx sg PS	sgRNA	N*N*N*NNNNNNNNNNNNNNNNNNGUUUUAGAGCUAGAAAUAGCAAGUUAAAAUAAGGCUAGUCCGUUAUCAACUUGAAAAAGUGGCACCGAGUCGGUGCU*U*U*U (SEQ ID NO: 2473)
CRxxxxxx	dgRNA	NNNNNNNNNNNNNNNNNNNGUUUUAGAGCUAUGCUGUUUUG (SEQ ID NO: 2474) and AACAGCAUAGCAAGUUAAAAUAAGGCUAGUCCGUUAUCAACUUGAAAAAGUGGCACCGAGUCGGUGCUUUUUUU (SEQ ID NO: 6660)
CRxxxxxx OMePS	dgRNA	mN*mN*mN*NNNNNNNNNNNNNNNNNNGUUUUAGAGCUAUGCUGUU*mU*mU*mG (SEQ ID NO: 2475)

		and AACAGCAUAGCAAGUUAAAAUAAGGCUAGUCCGUUAUCAACUUG AAAAAGUGGCACCGAGUCGGUGCUUUUUUU (SEQ ID NO: 6660)
CRxxxxxx PS	dgRNA	N*N*N*NNNNNNNNNNNNNNNNGUUUUAGAGCUAUGCUGUU*U* U*G (SEQ ID NO: 2476) and AACAGCAUAGCAAGUUAAAAUAAGGCUAGUCCGUUAUCAACUUG AAAAAGUGGCACCGAGUCGGUGCUUUUUUU (SEQ ID NO: 6660)

Table 37. Top indels observed for each gRNA (targeting domain and format) from NGS sequencing at Day 6 post-RNP introduction. gRNA sequences are as indicated in Table 36. Capital letters are the naturally occurring nucleotides at and near the target sequence. Deletions relative to the unmodified target sequence are shown as "-"; insertions are shown as lowercase letters.

gRNA targeting domain ID and format	Variant Read (Genomic Sequence)	SEQ ID NO:	% of all reads	Indel length
g8 dgRNA OMePS	ACATTCTTATTTTTATCGAGCACAAACGGAAACAATG-----GCAGCCTCTGCTTAGAAAAAGCTGTGGATAAGCCACCT	2477	47.57%	-5
g8 dgRNA OMePS	ACATTCTTATTTTTATCGAGCACAAACGGAAACAATG-AATGGCAGCCTCTGCTTAGAAAAAGCTGTGGATAAGCCACCT	2478	13.92%	-1
g8 dgRNA OMePS	ACATTCTTATTTTTATCGAGCACAAACGGAAACAATG--ATGGCAGCCTCTGCTTAGAAAAAGCTGTGGATAAGCCACCT	2479	2.89%	-2
g8 dgRNA OMePS	ACATTCTTATTTTTATCGAGCACAAACGGAAACAATGCA-----GCCTCTGCTTAGAAAAAGCTGTGGATAAGCCACCT	2480	2.01%	-6
g8 dgRNA OMePS	ACATTCTTATTTTTATCGAGCACAAACGGAAACAAT-CAATGGCAGCCTCTGCTTAGAAAAAGCTGTGGATAAGCCACCT	2481	1.65%	-1
g8 dgRNA OMePS	ACATTCTTATTTTTATCGAGCACAAACGGAAACAAaTGCAATGGCAGCCTCTGCTTAGAAAAAGCTGTGGATAAGCCACCT	2482	1.53%	1
CR001028	TTCTGTCATGTGTGTCTTGACTCAGAAACCCTGTTCTCC----------CCACCGCATCTCTTTCAGCAGTTGTTTC	2483	14.45%	-13
CR001028	TTCTGTCATGTGTGTCTTGACTCAGAAACCCTGTTCTCCTCTgCATATCTCCCCACCGCATCTCTTTCAGCAGTTGTTTC	2484	7.55%	0
CR001028	TTCTGTCATGTGTGTCTTGACTCAGAAACCCTGTTCTCCTCTA-ATATCTCCCCACCGCATCTCTTTCAGCAGTTGTTTC	2485	7.49%	-1
CR001028	TTCTGTCATGTGTGTCTTGACTCAGAAACCCTGTTCTCCTC----------ACCGCATCTCTTTCAGCAGTTGTTTC	2486	4.94%	-13
CR001028	TTCTGTCATGTGTGTCTTGACTCAGAAACCCTGTTCTCCTCTA----TCTCCCCACCGCATCTCTTTCAGCAGTTGTTTC	2487	4.33%	-4
CR001028	TTCTGTCATGTGTGTCTTGACTCAGAAACCCTGTTCTCCTCTA--TATCTCCCCACCGCATCTCTTTCAGCAGTTGTTTC	2488	2.83%	-2
CR001028 OMePS sg	TTCTGTCATGTGTGTCTTGACTCAGAAACCCTGTTCTCC----------CCACCGCATCTCTTTCAGCAGTTGTTTC	2489	19.29%	-13

CR001028 OMePS sg	TTCTGTCATGTGTGTCTTGACTCAGAAACCCTGTTCTCCTC TgCATATCTCCCCACCGCATCTCTTTCAGCAGTTGTTTC	2490	7.11%	0
CR001028 OMePS sg	TTCTGTCATGTGTGTCTTGACTCAGAAACCCTGTTCTCCTC ----------ACCGCATCTCTTTCAGCAGTTGTTTC	2491	6.26%	-13
CR001028 OMePS sg	TTCTGTCATGTGTGTCTTGACTCAGAAACCCTGTTCTCCTC TA-ATATCTCCCCACCGCATCTCTTTCAGCAGTTGTTTC	2492	6.19%	-1
CR001028 OMePS sg	TTCTGTCATGTGTGTCTTGACTCAGAAACCCTGTTCTCCTC TA----TCTCCCCACCGCATCTCTTTCAGCAGTTGTTTC	2493	5.44%	-4
CR001028 OMePS sg	TTCTGTCATGTGTGTCTTGACTCAGAAACCCTGTTCTCCTC TA--TATCTCCCCACCGCATCTCTTTCAGCAGTTGTTTC	2494	2.89%	-2
CR001028 OMePS	TTCTGTCATGTGTGTCTTGACTCAGAAACCCTGTTCTCC---- ---------CCACCGCATCTCTTTCAGCAGTTGTTTC	2495	15.91%	-13
CR001028 OMePS	TTCTGTCATGTGTGTCTTGACTCAGAAACCCTGTTCTCCTC TgCATATCTCCCCACCGCATCTCTTTCAGCAGTTGTTTC	2496	8.91%	0
CR001028 OMePS	TTCTGTCATGTGTGTCTTGACTCAGAAACCCTGTTCTCCTC TA----TCTCCCCACCGCATCTCTTTCAGCAGTTGTTTC	2497	4.80%	-4
CR001028 OMePS	TTCTGTCATGTGTGTCTTGACTCAGAAACCCTGTTCTCCTC ----------ACCGCATCTCTTTCAGCAGTTGTTTC	2498	4.59%	-13
CR001028 OMePS	TTCTGTCATGTGTGTCTTGACTCAGAAACCCTGTTCTCCTC TA-ATATCTCCCCACCGCATCTCTTTCAGCAGTTGTTTC	2499	2.92%	-1
CR001028 OMePS	TTCTGTCATGTGTGTCTTGACTCAGAAACCtTGTTCTCCTC TACATATCTCCCCACCGCATCTCTTTCAGCAGTTGTTTC	2500	1.75%	0
CR001028 PS	TTCTGTCATGTGTGTCTTGACTCAGAAACCCTGTTCTCC---- ---------CCACCGCATCTCTTTCAGCAGTTGTTTC	2501	13.02%	-13
CR001028 PS	TTCTGTCATGTGTGTCTTGACTCAGAAACCCTGTTCTCCTC TgCATATCTCCCCACCGCATCTCTTTCAGCAGTTGTTTC	2502	8.11%	0
CR001028 PS	TTCTGTCATGTGTGTCTTGACTCAGAAACCCTGTTCTCCTC TA-ATATCTCCCCACCGCATCTCTTTCAGCAGTTGTTTC	2503	6.08%	-1
CR001028 PS	TTCTGTCATGTGTGTCTTGACTCAGAAACCCTGTTCTCCTC ----------ACCGCATCTCTTTCAGCAGTTGTTTC	2504	4.43%	-13
CR001028 PS	TTCTGTCATGTGTGTCTTGACTCAGAAACCCTGTTCTCCTC TA----TCTCCCCACCGCATCTCTTTCAGCAGTTGTTTC	2505	3.86%	-4
CR001028 PS	TTCTGTCATGTGTGTCTTGACTCAGAAACCCTGTTCTCCTC TA--TATCTCCCCACCGCATCTCTTTCAGCAGTTGTTTC	2506	2.96%	-2
CR001028 PS sg	TTCTGTCATGTGTGTCTTGACTCAGAAACCCTGTTCTCC---- ---------CCACCGCATCTCTTTCAGCAGTTGTTTC	2507	17.48%	-13
CR001028 PS sg	TTCTGTCATGTGTGTCTTGACTCAGAAACCCTGTTCTCCTC ----------ACCGCATCTCTTTCAGCAGTTGTTTC	2508	7.01%	-13
CR001028 PS sg	TTCTGTCATGTGTGTCTTGACTCAGAAACCCTGTTCTCCTC TgCATATCTCCCCACCGCATCTCTTTCAGCAGTTGTTTC	2509	6.84%	0
CR001028 PS sg	TTCTGTCATGTGTGTCTTGACTCAGAAACCCTGTTCTCCTC TA----TCTCCCCACCGCATCTCTTTCAGCAGTTGTTTC	2510	6.05%	-4
CR001028 PS sg	TTCTGTCATGTGTGTCTTGACTCAGAAACCCTGTTCTCCTC TA--TATCTCCCCACCGCATCTCTTTCAGCAGTTGTTTC	2511	4.59%	-2
CR001028 PS sg	TTCTGTCATGTGTGTCTTGACTCAGAAACCCTGTTCTCCTC TA-ATATCTCCCCACCGCATCTCTTTCAGCAGTTGTTTC	2512	3.53%	-1
CR001028 sg	TTCTGTCATGTGTGTCTTGACTCAGAAACCCTGTTCTCC---- ---------CCACCGCATCTCTTTCAGCAGTTGTTTC	2513	10.58%	-13
CR001028	TTCTGTCATGTGTGTCTTGACTCAGAAACCCTGTTCTCCTC	2514	9.11%	0

sg	TgCATATCTCCCCACCGCATCTCTTTCAGCAGTTGTTTC			
CR001028 sg	TTCTGTCATGTGTGTCTTGACTCAGAAACCCTGTTCTCCTC TA-ATATCTCCCCACCGCATCTCTTTCAGCAGTTGTTTC	2515	6.47%	-1
CR001028 sg	TTCTGTCATGTGTGTCTTGACTCAGAAACCCTGTTCTCCTC TA--TATCTCCCCACCGCATCTCTTTCAGCAGTTGTTTC	2516	4.78%	-2
CR001028 sg	TTCTGTCATGTGTGTCTTGACTCAGAAACCCTGTTCTCCTC ----------ACCGCATCTCTTTCAGCAGTTGTTTC	2517	4.06%	-13
CR001028 sg	TTCTGTCATGTGTGTCTTGACTCAGAAACCCTGTTCTCCTC TA----TCTCCCCACCGCATCTCTTTCAGCAGTTGTTTC	2518	3.41%	-4
CR001030	TCTTGACTCAGAAACCCTGTTCTCCTCTACATATCTC-------- -----TTTCAGCAGTTGTTTCTAAAAATATCCTCC	2519	8.30%	-13
CR001030	TCTTGACTCAGAAACCCTGTTCTCCTCTgCATATCTCCCCA CCGCATCTCTTTCAGCAGTTGTTTCTAAAAATATCCTCC	2520	4.39%	0
CR001030	TCTTGACTCAGAAACCCTGTTCTCCTCTACATATCTCCCC A-----TCTCTTTCAGCAGTTGTTTCTAAAAATATCCTCC	2521	2.61%	-5
CR001030	TCTTGACTCAGAAACCCTGTTCTCCTCTACATATCTCCCC ACC-CATCTCTTTCAGCAGTTGTTTCTAAAAATATCCTCC	2522	2.18%	-1
CR001030	TCTTGACTCAGAAACCtTGTTCTCCTCTACATATCTCCCCA CCGCATCTCTTTCAGCAGTTGTTTCTAAAAATATCCTCC	2523	2.12%	0
CR001030	TCTTGACTCAGAAACCCTGTTCTCCTCTACATATCTCCCC ACC--ATCTCTTTCAGCAGTTGTTTCTAAAAATATCCTCC	2524	2.10%	-2
CR001030 IDT	TCTTGACTCAGAAACCCTGTTCTCCTCTACATATCTC-------- -----TTTCAGCAGTTGTTTCTAAAAATATCCTCC	2525	10.40%	-13
CR001030 IDT	TCTTGACTCAGAAACCCTGTTCTCCTCTACATATCTCCCC ACCGgCATCTCTTTCAGCAGTTGTTTCTAAAAATATCCTCC	2526	4.56%	1
CR001030 IDT	TCTTGACTCAGAAACCCTGTTCTCCTCTACATATCTCCCC AC-GCATCTCTTTCAGCAGTTGTTTCTAAAAATATCCTCC	2527	3.83%	-1
CR001030 IDT	TCTTGACTCAGAAACCCTGTTCTCCTCTACATATCTCCCC ACC--ATCTCTTTCAGCAGTTGTTTCTAAAAATATCCTCC	2528	3.68%	-2
CR001030 IDT	TCTTGACTCAGAAACCCTGTTCTCCTCTACATATCTCCCC A-----TCTCTTTCAGCAGTTGTTTCTAAAAATATCCTCC	2529	2.87%	-5
CR001030 IDT	TCTTGACTCAGAAACCCTGTTCTCCTCTACATATCT---------- -----TTCAGCAGTTGTTTCTAAAAATATCCTCC	2530	2.54%	-15
CR001030	TCTTGACTCAGAAACCCTGTTCTCCTCTACATATCTC-------- -----TTTCAGCAGTTGTTTCTAAAAATATCCTCC	2531	9.90%	-13
CR001030	TCTTGACTCAGAAACCCTGTTCTCCTCTACATATCTCCCC ACCGgCATCTCTTTCAGCAGTTGTTTCTAAAAATATCCTCC	2532	4.63%	1
CR001030	TCTTGACTCAGAAACCCTGTTCTCCTCTACATATCTCCCC ACC-CATCTCTTTCAGCAGTTGTTTCTAAAAATATCCTCC	2533	3.71%	-1
CR001030	TCTTGACTCAGAAACCCTGTTCTCCTCTACATATCTCCCC ACC--ATCTCTTTCAGCAGTTGTTTCTAAAAATATCCTCC	2534	2.39%	-2
CR001030	TCTTGACTCAGAAACCCTGTTCTCCTCTgCATATCTCCCCA CCGCATCTCTTTCAGCAGTTGTTTCTAAAAATATCCTCC	2535	2.03%	0
CR001030	TCTTGACTCAGAAACCCTGTTCTCCTCTACATATCTCCCC A-----TCTCTTTCAGCAGTTGTTTCTAAAAATATCCTCC	2536	1.95%	-5
CR001030 OMePS sg	TCTTGACTCAGAAACCCTGTTCTCCTCTACATATCTC-------- -----TTTCAGCAGTTGTTTCTAAAAATATCCTCC	2537	19.91%	-13
CR001030	TCTTGACTCAGAAACCCTGTTCTCCTCTACATATCTCCCC	2538	5.76%	-1

OMePS sg	ACC-CATCTCTTTCAGCAGTTGTTTCTAAAAATATCCTCC			
CR001030 OMePS sg	TCTTGACTCAGAAACCCTGTTCTCCTCTACATATCTCCCC ACCGgCATCTCTTTCAGCAGTTGTTTCTAAAAATATCCTCC	2539	3.09%	1
CR001030 OMePS sg	TCTTGACTCAGAAACCCTGTTCTCCTCTACATATCTCCCC ACCG----TCTTTCAGCAGTTGTTTCTAAAAATATCCTCC	2540	3.03%	-4
CR001030 OMePS sg	TCTTGACTCAGAAACCCTGTTCTCCTCTACATATCTCCCC AC------TCTTTCAGCAGTTGTTTCTAAAAATATCCTCC	2541	2.98%	-6
CR001030 OMePS sg	TCTTGACTCAGAAACCCTGTTCTCCTCTgCATATCT---------- -----TTCAGCAGTTGTTTCTAAAAATATCCTCC	2542	2.81%	-15
CR001030 OMePS	TCTTGACTCAGAAACCCTGTTCTCCTCTACATATCTC-------- -----TTTCAGCAGTTGTTTCTAAAAATATCCTCC	2543	8.52%	-13
CR001030 OMePS	TCTTGACTCAGAAACCCTGTTCTCCTCTgCATATCTCCCCA CCGCATCTCTTTCAGCAGTTGTTTCTAAAAATATCCTCC	2544	5.21%	0
CR001030 OMePS	TCTTGACTCAGAAACCCTGTTCTCCTCTACATATCTCCCC ACCGgCATCTCTTTCAGCAGTTGTTTCTAAAAATATCCTCC	2545	2.63%	1
CR001030 OMePS	TCTTGACTCAGAAACCCTGTTCTCCTCTACATATCTCCCC AC-GCATCTCTTTCAGCAGTTGTTTCTAAAAATATCCTCC	2546	2.25%	-1
CR001030 OMePS	TCTTGACTCAGAAACCCTGTTCTCCTCTACATATCTCCCC A-----TCTCTTTCAGCAGTTGTTTCTAAAAATATCCTCC	2547	1.81%	-5
CR001030 OMePS	TCTTGACTCAGAAACCCTGTTCTCCTCTACATATCTCCCC ACC-CATCTCTTTCAGCAGTTGTTTCTAAAAATATCCTCC	2548	1.77%	-1
CR001030 PS	TCTTGACTCAGAAACCCTGTTCTCCTCTACATATCTC-------- -----TTTCAGCAGTTGTTTCTAAAAATATCCTCC	2549	5.99%	-13
CR001030 PS	TCTTGACTCAGAAACCCTGTTCTCCTCTgCATATCTCCCCA CCGCATCTCTTTCAGCAGTTGTTTCTAAAAATATCCTCC	2550	4.09%	0
CR001030 PS	TCTTGACTCAGAAACCCTGTTCTCCTCTACATATCTCCCC ACCGgCATCTCTTTCAGCAGTTGTTTCTAAAAATATCCTCC	2551	3.90%	1
CR001030 PS	TCTTGACTCAGAAACCCTGTTCTCCTCTACATATCTCCCC A-----TCTCTTTCAGCAGTTGTTTCTAAAAATATCCTCC	2552	3.59%	-5
CR001030 PS	TCTTGACTCAGAAACCCTGTTCTCCTCTACATATCTCCCC ACC-CATCTCTTTCAGCAGTTGTTTCTAAAAATATCCTCC	2553	2.86%	-1
CR001030 PS	TCTTGACTCAGAAACCCTGTTCTCCTCTACATATCTCCCC ACC--ATCTCTTTCAGCAGTTGTTTCTAAAAATATCCTCC	2554	2.39%	-2
CR001030 PS sg	TCTTGACTCAGAAACCCTGTTCTCCTCTACATATCTC-------- -----TTTCAGCAGTTGTTTCTAAAAATATCCTCC	2555	11.86%	-13
CR001030 PS sg	TCTTGACTCAGAAACCCTGTTCTCCTCTACATATCTCCCC ACC-CATCTCTTTCAGCAGTTGTTTCTAAAAATATCCTCC	2556	5.20%	-1
CR001030 PS sg	TCTTGACTCAGAAACCCTGTTCTCCTCTACATATCTCCCC ACCGgCATCTCTTTCAGCAGTTGTTTCTAAAAATATCCTCC	2557	3.65%	1
CR001030 PS sg	TCTTGACTCAGAAACCCTGTTCTCCTCTACATATCTCCCC ACC--ATCTCTTTCAGCAGTTGTTTCTAAAAATATCCTCC	2558	3.33%	-2
CR001030 PS sg	TCTTGACTCAGAAACCCTGTTCTCCTCTACATATCTCCCC A-----TCTCTTTCAGCAGTTGTTTCTAAAAATATCCTCC	2559	2.92%	-5
CR001030 PS sg	TCTTGACTCAGAAACCCTGTTCTCCTCTACAT---------- CTCTTTCAGCAGTTGTTTCTAAAAATATCCTCC	2560	2.14%	-15
CR001030 PS sg	TCTTGACTCAGAAACCCTGTTCTC---------- TTTCAGCAGTTGTTTCTAAAAATATCCTCC	2561	2.08%	-26

CR001030 sg	TCTTGACTCAGAAACCCTGTTCTCCTCTACATATCTC----------TTTCAGCAGTTGTTTCTAAAAATATCCTCC	2562	11.22%	-13
CR001030 sg	TCTTGACTCAGAAACCCTGTTCTCCTCTACATATCTCCCCACC-CATCTCTTTCAGCAGTTGTTTCTAAAAATATCCTCC	2563	4.64%	-1
CR001030 sg	TCTTGACTCAGAAACCCTGTTCTCCTCTACATATCTCCCCACCGgCATCTCTTTCAGCAGTTGTTTCTAAAAATATCCTCC	2564	2.78%	1
CR001030 sg	TCTTGACTCAGAAACCCTGTTCTCCTCTACATATCTCCCCA-----TCTCTTTCAGCAGTTGTTTCTAAAAATATCCTCC	2565	2.73%	-5
CR001030 sg	TCTTGACTCAGAAACCCTGTTCTCCTCTACATATCTCCCCAC-GCATCTCTTTCAGCAGTTGTTTCTAAAAATATCCTCC	2566	2.34%	-1
CR001030 sg	TCTTGACTCAGAAACCCTGTTCTCCTCTACATATCTCCCCAC------TCTTTCAGCAGTTGTTTCTAAAAATATCCTCC	2567	2.29%	-6
CR001137	AAATGCTTATGACAGCAATAATCATAAAAACCTCAAACCGGTAGgCCACTTAAATGCTTACCAACAGTAGAATTGATAAAT	2568	4.26%	1
CR001137	AAATGCTTATGACAGCAATAATCATAAAAACCTCAAACC------ACTTAAATGCTTACCAACAGTAGAATTGATAAAT	2569	3.80%	-7
CR001137	AAATGCTTATGACAGCAATAATCATAAAAACCTCAAACCGGTAaGCCACTTAAATGCTTACCAACAGTAGAATTGATAAAT	2570	1.32%	1
CR001137	AAATGCTTATGACAGCAATAATCATAAAAACCTCAAACCGGTA--------AATGCTTACCAACAGTAGAATTGATAAAT	2571	0.98%	-8
CR001137	AAATGCTTATGACAGCAATAATCATAAAAACCTCAAACCGGT-------TAAATGCTTACCAACAGTAGAATTGATAAAT	2572	0.97%	-7
CR001137	AAATGCTTATGACAGCAATAATCATAAAAACCTCAAA-----GCCACTTAAATGCTTACCAACAGTAGAATTGATAAAT	2573	0.85%	-6
CR001137	AAATGCTTATGACAGCAATAATCATAAAAACCTCAAACCGGT-GCCACTTAAATGCTTACCAACAGTAGAATTGATAAAT	2574	0.73%	-1
CR001137 OMePS sg	AAATGCTTATGACAGCAATAATCATAAAAACCTCAAACCGGTAGgCCACTTAAATGCTTACCAACAGTAGAATTGATAAAT	2575	19.40%	1
CR001137 OMePS sg	AAATGCTTATGACAGCAATAATCATAAAAACCTCAAACC------ACTTAAATGCTTACCAACAGTAGAATTGATAAAT	2576	7.73%	-7
CR001137 OMePS sg	AAATGCTTATGACAGCAATAATCATAAAAACCTCAA-------GCCACTTAAATGCTTACCAACAGTAGAATTGATAAAT	2577	2.97%	-7
CR001137 OMePS sg	AAATGCTTATGACAGCAATAATCATAAAAACCTCAAACCGGTA--------AATGCTTACCAACAGTAGAATTGATAAAT	2578	2.78%	-8
CR001137 OMePS sg	AAATGCTTATGACAGCAATAATCATAAAAACCTCAAACCGGTAaGCCACTTAAATGCTTACCAACAGTAGAATTGATAAAT	2579	2.27%	1
CR001137 OMePS sg	AAATGCTTATGACAGCAATAAT----------TACCAACAGTAGAATTGATAAAT	2580	2.06%	-35
CR001137 OMePS sg	AAATGCTTATGACAGCAATAATCATAAAAACCTCAAA----------TGCTTACCAACAGTAGAATTGATAAAT	2581	2.04%	-16
CR001137 OMePS	AAATGCTTATGACAGCAATAATCATAAAAACCTCAAACCGGTAGgCCACTTAAATGCTTACCAACAGTAGAATTGATAAAT	2582	5.27%	1
CR001137 OMePS	AAATGCTTATGACAGCAATAATCATAAAAACCTCAAACC------ACTTAAATGCTTACCAACAGTAGAATTGATAAAT	2583	4.66%	-7

CR001137 OMePS	AAATGCTTATGACAGCAATAATCATAAAAACCTCAAACC GGTA--------AATGCTTACCAACAGTAGAATTGATAAAT	2584	2.38%	-8
CR001137 OMePS	AAATGCTTATGACAGCAATAATCATAAAAACCTCAAACC GGT-------TAAATGCTTACCAACAGTAGAATTGATAAAT	2585	1.91%	-7
CR001137 OMePS	AAATGCTTATGACAGCAATAATCATAAAAACCTCAAACC GGTAaGCCACTTAAATGCTTACCAACAGTAGAATTGATAA AT	2586	1.72%	1
CR001137 OMePS	AAATGCTTATGACAGCAATAATCATAAAAACCTCAA------- GCCACTTAAATGCTTACCAACAGTAGAATTGATAAAT	2587	1.03%	-7
CR001137 OMePS	AAATGCTTATGACAGCAATAATCATAAAAACCTCA-------- GCCACTTAAATGCTTACCAACAGTAGAATTGATAAAT	2588	0.82%	-8
CR001137 PS	AAATGCTTATGACAGCAATAATCATAAAAACCTCAAACC- ------ACTTAAATGCTTACCAACAGTAGAATTGATAAAT	2589	7.49%	-7
CR001137 PS	AAATGCTTATGACAGCAATAATCATAAAAACCTCAAACC GGTAGgCCACTTAAATGCTTACCAACAGTAGAATTGATAA AT	2590	6.85%	1
CR001137 PS	AAATGCTTATGACAGCAATAATCATAAAAACCTCAAACC GGTA--------AATGCTTACCAACAGTAGAATTGATAAAT	2591	2.64%	-8
CR001137 PS	AAATGCTTATGACAGCAATAATCATAAAAACCTCAAACC GGTAaGCCACTTAAATGCTTACCAACAGTAGAATTGATAA AT	2592	2.11%	1
CR001137 PS	AAATGCTTATGACAGCAATAATCATAAAAACCTCAAACC GG---CCACTTAAATGCTTACCAACAGTAGAATTGATAAAT	2593	1.91%	-3
CR001137 PS	AAATGCTTATGACAGCAATAATCATAAAAACCTCAAAC--- -------TTAAATGCTTACCAACAGTAGAATTGATAAAT	2594	1.81%	-10
CR001137 PS	AAATGCTTATGACAGCAATAATCATAAAAACCTCAAACC GGT-------TAAATGCTTACCAACAGTAGAATTGATAAAT	2595	1.28%	-7
CR001137 PS sg	AAATGCTTATGACAGCAATAATCATAAAAACCTCAAACC GGTAGgCCACTTAAATGCTTACCAACAGTAGAATTGATAA AT	2596	11.90%	1
CR001137 PS sg	AAATGCTTATGACAGCAATAATCATAAAAACCTCAAACC- ------ACTTAAATGCTTACCAACAGTAGAATTGATAAAT	2597	7.45%	-7
CR001137 PS sg	AAATGCTTATGACAGCAATAATCATAAAAACCTCAAACC GGTAG----------AATTGATAAAT	2598	4.87%	-25
CR001137 PS sg	AAATGCTTATGACAGCAATAATCATAAAAACCTCAAACC GGT- GCCACTTAAATGCTTACCAACAGTAGAATTGATAAAT	2599	3.82%	-1
CR001137 PS sg	AAATGCTTATGACAGCAATAATCATAAAAACCTCAAACC GGTAaGCCACTTAAATGCTTACCAACAGTAGAATTGATAA AT	2600	3.57%	1
CR001137 PS sg	AAATGCTTATGACAGCAATAATCATAAAAACCTCAAACC GGTA- CCACTTAAATGCTTACCAACAGTAGAATTGATAAAT	2601	2.81%	-1
CR001137 PS sg	AAATGCTTATGACAGCAATAATCATAAAAACCTCAAACC GGTA---ACTTAAATGCTTACCAACAGTAGAATTGATAAAT	2602	2.35%	-3
CR001137 sg	AAATGCTTATGACAGCAATAATCATAAAAACCTCAAACC- ------ACTTAAATGCTTACCAACAGTAGAATTGATAAAT	2603	6.84%	-7
CR001137 sg	AAATGCTTATGACAGCAATAATCATAAAAACCTCAAACC GGTAGgCCACTTAAATGCTTACCAACAGTAGAATTGATAA	2604	4.54%	1

	AT			
CR001137 sg	AAATGCTTATGACAGCAATAATCATAAAAACCTCAAACC GGTAaGCCACTTAAATGCTTACCAACAGTAGAATTGATAA AT	2605	2.46%	1
CR001137 sg	AAATGCTTATGACAGCAATAATCATAAAAACCTCAAACC GGT-------TAAATGCTTACCAACAGTAGAATTGATAAAT	2606	1.83%	-7
CR001137 sg	AAATGCTTATGACAGCAATAATCATAAAAACCTCAAACC GGTA--------AATGCTTACCAACAGTAGAATTGATAAAT	2607	1.11%	-8
CR001137 sg	AAATGCTTATGACAGCAATAATCATAAAAACCTCAAACC GGTA----CTTAAATGCTTACCAACAGTAGAATTGATAAAT	2608	0.78%	-4
CR001137 sg	AAATGCTTATGACAGCAATAATCATAAAAACCTCAAACC GGTAtGCCACTTAAATGCTTACCAACAGTAGAATTGATAA AT	2609	0.72%	1
CR001221	TAGCATCTACTCTTGTTCAGGAAACAATGAGGACCTG---- GGCAGTAAGAGTGGTGATTAATAGATAGGGACAAATTGA	2610	29.13%	-4
CR001221	TAGCATCTACTCTTGTTCAGGAAACAATGAGGACCT-ACTGGGCAGTAAGAGTGGTGATTAATAGATAGGGACAAATTGA	2611	4.65%	-1
CR001221	TAGCATCTACTCTTGTTCAGGAAACAATGAGGAC----- TGGGCAGTAAGAGTGGTGATTAATAGATAGGGACAAATTGA	2612	4.27%	-5
CR001221	TAGCATCTACTCTTGTTCAGGAAACAATGAGG---------- GCAGTAAGAGTGGTGATTAATAGATAGGGACAAATTGA	2613	1.47%	-10
CR001221	TAGCATCTACTCTTGTTCAGGAAACAATGAGGAC---------- AGTAAGAGTGGTGATTAATAGATAGGGACAAATTGA	2614	1.14%	-10
CR001221	TAGCATCTACTCTTGTTCAGG------------------------ TAAGAGTGGTGATTAATAGATAGGGACAAATTGA	2615	1.04%	-25
CR001221	TAGCATCTACTCTTGTTCAGGAAACAATGAGGACCTtACT GGGCAGTAAGAGTGGTGATTAATAGATAGGGACAAATTG A	2616	0.86%	0
CR001221 OMePS sg	TAGCATCTACTCTTGTTCAGGAAACAATGAGGACCTG---- GGCAGTAAGAGTGGTGATTAATAGATAGGGACAAATTGA	2617	26.33%	-4
CR001221 OMePS sg	TAGCATCTACTCTTGTTCAGGAAACAATGAGGACCT-ACTGGGCAGTAAGAGTGGTGATTAATAGATAGGGACAAATTGA	2618	15.83%	-1
CR001221 OMePS sg	TAGCATCTACTCTTGTTCAGGAAACAATGAGGAC----- TGGGCAGTAAGAGTGGTGATTAATAGATAGGGACAAATTGA	2619	6.26%	-5
CR001221 OMePS sg	TAGCATCTACTCTTGTTCAGGAAACAATGAGGACCTG-- TGGGCAGTAAGAGTGGTGATTAATAGATAGGGACAAATTGA	2620	3.75%	-2
CR001221 OMePS sg	TAGCATCTACTCTTGTTCAGGAAACAATGAGGACCTGtAC TGGGCAGTAAGAGTGGTGATTAATAGATAGGGACAAATTGA	2621	2.61%	1
CR001221 OMePS sg	TAGCATCTACTCTTGTTCAGGAAACAATGAGGAC---------- AGTAAGAGTGGTGATTAATAGATAGGGACAAATTGA	2622	2.15%	-10
CR001221 OMePS sg	TAGCATCTACTCTTGTTCAGGAAACAATGAGGACCTGAaC TGGGCAGTAAGAGTGGTGATTAATAGATAGGGACAAATTGA	2623	1.82%	1

CR001221 OMePS	TAGCATCTACTCTTGTTCAGGAAACAATGAGGACCTG----GGCAGTAAGAGTGGTGATTAATAGATAGGGACAAATTGA	2624	32.73%	-4
CR001221 OMePS	TAGCATCTACTCTTGTTCAGGAAACAATGAGGACCT-ACTGGGCAGTAAGAGTGGTGATTAATAGATAGGGACAAATTGA	2625	6.46%	-1
CR001221 OMePS	TAGCATCTACTCTTGTTCAGGAAACAATGAGGAC-----TGGGCAGTAAGAGTGGTGATTAATAGATAGGGACAAATTGA	2626	5.49%	-5
CR001221 OMePS	TAGCATCTACTCTTGTTCAGGAAACAATGAGG----------CAGTAAGAGTGGTGATTAATAGATAGGGACAAATTGA	2627	3.16%	-11
CR001221 OMePS	TAGCATCTACTCTTGTTCAGGAAACAATGAGG----------GCAGTAAGAGTGGTGATTAATAGATAGGGACAAATTGA	2628	2.03%	-10
CR001221 OMePS	TAGCATCTACTCTTGTTCAGGAAACAATGAGGACCTGtACTGGGCAGTAAGAGTGGTGATTAATAGATAGGGACAAATTGA	2629	1.53%	1
CR001221 OMePS	TAGCATCTACTCTTGTTCAGGAAACAATG----------GGCAGTAAGAGTGGTGATTAATAGATAGGGACAAATTGA	2630	1.05%	-12
CR001221 PS	TAGCATCTACTCTTGTTCAGGAAACAATGAGGACCTG----GGCAGTAAGAGTGGTGATTAATAGATAGGGACAAATTGA	2631	33.94%	-4
CR001221 PS	TAGCATCTACTCTTGTTCAGGAAACAATGAGGACCT-ACTGGGCAGTAAGAGTGGTGATTAATAGATAGGGACAAATTGA	2632	7.39%	-1
CR001221 PS	TAGCATCTACTCTTGTTCAGGAAACAATGAGGAC-----TGGGCAGTAAGAGTGGTGATTAATAGATAGGGACAAATTGA	2633	5.05%	-5
CR001221 PS	TAGCATCTACTCTTGTTCAGGAAACAATGAGGAC----------AGTAAGAGTGGTGATTAATAGATAGGGACAAATTGA	2634	4.03%	-10
CR001221 PS	TAGCATCTACTCTTGTTCAGGAAACAATGAGGACCTGtACTGGGCAGTAAGAGTGGTGATTAATAGATAGGGACAAATTGA	2635	1.52%	1
CR001221 PS	TAGCATCTACTCTTGTTCAGGAAACAATG----------GGCAGTAAGAGTGGTGATTAATAGATAGGGACAAATTGA	2636	1.48%	-12
CR001221 PS	TAGCATCTACTCTTGTTCAGGAAACAATGAGG----------CAGTAAGAGTGGTGATTAATAGATAGGGACAAATTGA	2637	1.43%	-11
CR001221 PS sg	TAGCATCTACTCTTGTTCAGGAAACAATGAGGACCTG----GGCAGTAAGAGTGGTGATTAATAGATAGGGACAAATTGA	2638	27.00%	-4
CR001221 PS sg	TAGCATCTACTCTTGTTCAGGAAACAATGAGGACCT-ACTGGGCAGTAAGAGTGGTGATTAATAGATAGGGACAAATTGA	2639	13.43%	-1
CR001221 PS sg	TAGCATCTACTCTTGTTCAGGAAACAATGAGGAC-----TGGGCAGTAAGAGTGGTGATTAATAGATAGGGACAAATTGA	2640	6.57%	-5
CR001221 PS sg	TAGCATCTACTCTTGTTCAGGAAACAATGAGGACCTGtACTGGGCAGTAAGAGTGGTGATTAATAGATAGGGACAAATTGA	2641	4.28%	1
CR001221 PS sg	TAGCATCTACTCTTGTTCAGGAAACAATGAGGACC--ACTGGGCAGTAAGAGTGGTGATTAATAGATAGGGACAAATTGA	2642	3.13%	-2
CR001221 PS sg	TAGCATCTACTCTTGTTCAGGAAACAATGAGGAC----------AGTAAGAGTGGTGATTAATAGATAGGGACAAATTGA	2643	2.40%	-10

CR001221 PS sg	TAGCATCTACTCTTGTTCAGGAAACAATGAGGACCTG------GTAAGAGTGGTGATTAATAGATAGGGACAAATTGA	2644	2.13%	-8
CR001221 sg	TAGCATCTACTCTTGTTCAGGAAACAATGAGGACCTG----GGCAGTAAGAGTGGTGATTAATAGATAGGGACAAATTGA	2645	26.35%	-4
CR001221 sg	TAGCATCTACTCTTGTTCAGGAAACAATGAGGACCT-ACTGGGCAGTAAGAGTGGTGATTAATAGATAGGGACAAATTGA	2646	8.55%	-1
CR001221 sg	TAGCATCTACTCTTGTTCAGGAAACAATGAGGAC-----TGGGCAGTAAGAGTGGTGATTAATAGATAGGGACAAATTGA	2647	7.25%	-5
CR001221 sg	TAGCATCTACTCTTGTTCAGGAAACAATGAGGAC----------AGTAAGAGTGGTGATTAATAGATAGGGACAAATTGA	2648	2.41%	-10
CR001221 sg	TAGCATCTACTCTTGTTCAGGAAACAATGAGG----------CAGTAAGAGTGGTGATTAATAGATAGGGACAAATTGA	2649	1.90%	-11
CR001221 sg	TAGCATCTACTCTTGTTCAGGAAACAATGAGGACCTG------TAAGAGTGGTGATTAATAGATAGGGACAAATTGA	2650	1.82%	-9
CR001221 sg	TAGCATCTACTCTTGTTCAGGAAACAATG----------GGCAGTAAGAGTGGTGATTAATAGATAGGGACAAATTGA	2651	1.81%	-12
CR003035	CTGGAAGAGAAACAGTTTTAGTATAACAAGTGAAATACCCATG---AGTCTGAGGTGCCTATAGGACATCTATATAAATA	2652	12.23%	-3
CR003035	CTGGAAGAGAAAtAGTTTTAGTATAACAAGTGAAATACCCATGCTGAGTCTGAGGTGCCTATAGGACATCTATATAAATA	2653	8.25%	0
CR003035	CTGGAAGAGAAAtAGTTTTAGTATAACAAGTGAAATACCCATG---AGTCTGAGGTGCCTATAGGACATCTATATAAATA	2654	4.47%	-3
CR003035	CTGGAAGAGAAACAGTTTTAGTATAACAAGTGAAATACCCAT-CTGAGTCTGAGGTGCCTATAGGACATCTATATAAATA	2655	3.60%	-1
CR003035	CTGGAAGAGAAACAGTTTTAGTATAACAAGTGA----------GTCTGAGGTGCCTATAGGACATCTATATAAATA	2656	2.79%	-14
CR003035	CTGGAAGAGAAACAGTTTTAGTATAACAAGTGAAATACCCATG--GAGTCTGAGGTGCCTATAGGACATCTATATAAATA	2657	2.55%	-2
CR003035	CTGGAAGAGAAACAGTTTTAGTATAACAAGTGAAATAC------TGAGTCTGAGGTGCCTATAGGACATCTATATAAATA	2658	1.68%	-6
CR003035 OMePS sg	CTGGAAGAGAAACAGTTTTAGTATAACAAGTGAAATACCCATG---AGTCTGAGGTGCCTATAGGACATCTATATAAATA	2659	13.59%	-3
CR003035 OMePS sg	CTGGAAGAGAAACAGTTTTAGTATAACAAGTGAAATACCCA--CTGAGTCTGAGGTGCCTATAGGACATCTATATAAATA	2660	5.56%	-2
CR003035 OMePS sg	CTGGAAGAGAAACAGTTTTAGTATAACAAGTGAAATACCCAT-CTGAGTCTGAGGTGCCTATAGGACATCTATATAAATA	2661	5.34%	-1
CR003035 OMePS sg	CTGGAAGAGAAACAGTTTTAGTATAACAAGTGAAATACCCATG--GAGTCTGAGGTGCCTATAGGACATCTATATAAATA	2662	5.30%	-2
CR003035 OMePS sg	CTGGAAGAGAAACAGTTTTAGTATAACAAGTGA----------GTCTGAGGTGCCTATAGGACATCTATATAAATA	2663	4.70%	-14
CR003035 OMePS sg	CTGGAAGAGAAAtAGTTTTAGTATAACAAGTGAAATACCCATG---AGTCTGAGGTGCCTATAGGACATCTATATAAATA	2664	4.44%	-3

CR003035 OMePS sg	CTGGAAGAGAAACAGTTTTAGTATAACAAGTGAAATACC CATG- TGAGTCTGAGGTGCCTATAGGACATCTATATAAATA	2665	2.05%	-1
CR003035 OMePS	CTGGAAGAGAAACAGTTTTAGTATAACAAGTGAAATACC CATG---AGTCTGAGGTGCCTATAGGACATCTATATAAATA	2666	9.22%	-3
CR003035 OMePS	CTGGAAGAGAAAtAGTTTTAGTATAACAAGTGAAATACCC ATGCTGAGTCTGAGGTGCCTATAGGACATCTATATAAATA	2667	7.81%	0
CR003035 OMePS	CTGGAAGAGAAAtAGTTTTAGTATAACAAGTGAAATACCC ATG---AGTCTGAGGTGCCTATAGGACATCTATATAAATA	2668	3.79%	-3
CR003035 OMePS	CTGGAAGAGAAACAGTTTTAGTATAACAAGTGAAATACC CAT- CTGAGTCTGAGGTGCCTATAGGACATCTATATAAATA	2669	2.63%	-1
CR003035 OMePS	CTGGAAGAGAAACAGTTTTAGTATAACAAGTGAAATACC CA--CTGAGTCTGAGGTGCCTATAGGACATCTATATAAATA	2670	2.00%	-2
CR003035 OMePS	CTGGAAGAGAAACAGTTTTAGTATAACAAGTGA---------- -GTCTGAGGTGCCTATAGGACATCTATATAAATA	2671	1.92%	-14
CR003035 OMePS	CTGGAAGAGAAACAGTTTTAGTATAACAAGTGAAATACC- ----TGAGTCTGAGGTGCCTATAGGACATCTATATAAATA	2672	1.69%	-5
CR003035 PS	CTGGAAGAGAAACAGTTTTAGTATAACAAGTGAAATACC CATG---AGTCTGAGGTGCCTATAGGACATCTATATAAATA	2673	13.91%	-3
CR003035 PS	CTGGAAGAGAAAtAGTTTTAGTATAACAAGTGAAATACCC ATG---AGTCTGAGGTGCCTATAGGACATCTATATAAATA	2674	6.11%	-3
CR003035 PS	CTGGAAGAGAAAtAGTTTTAGTATAACAAGTGAAATACCC ATGCTGAGTCTGAGGTGCCTATAGGACATCTATATAAATA	2675	3.77%	0
CR003035 PS	CTGGAAGAGAAACAGTTTTAGTATAACAAGTGAAATACC CAT- CTGAGTCTGAGGTGCCTATAGGACATCTATATAAATA	2676	3.64%	-1
CR003035 PS	CTGGAAGAGAAACAGTTTTAGTATAACAAGTGAAATACC CATG-- GAGTCTGAGGTGCCTATAGGACATCTATATAAATA	2677	2.39%	-2
CR003035 PS	CTGGAAGAGAAACAGTTTTAGTATAACAAGTGAAATACC CA--CTGAGTCTGAGGTGCCTATAGGACATCTATATAAATA	2678	2.16%	-2
CR003035 PS	CTGGAAGAGAAAtAGTTTTAGTATAACAAGTGAAATACCC AT-CTGAGTCTGAGGTGCCTATAGGACATCTATATAAATA	2679	1.87%	-1
CR003035 PS sg	CTGGAAGAGAAACAGTTTTAGTATAACAAGTGAAATACC CAT- CTGAGTCTGAGGTGCCTATAGGACATCTATATAAATA	2680	8.32%	-1
CR003035 PS sg	CTGGAAGAGAAACAGTTTTAGTATAACAAGTGAAATACC CATG---AGTCTGAGGTGCCTATAGGACATCTATATAAATA	2681	6.41%	-3
CR003035 PS sg	CTGGAAGAGAAACAGTTTTAGTATAACAAGTGAAATACC CATG-- GAGTCTGAGGTGCCTATAGGACATCTATATAAATA	2682	4.19%	-2
CR003035 PS sg	CTGGAAGAGAAACAGTTTTAGTATAACAAGTGAAATACC CA--CTGAGTCTGAGGTGCCTATAGGACATCTATATAAATA	2683	4.08%	-2
CR003035 PS sg	CTGGAAGAGAAAtAGTTTTAGTATAACAAGTGAAATACCC AT-CTGAGTCTGAGGTGCCTATAGGACATCTATATAAATA	2684	3.31%	-1

CR003035 PS sg	CTGGAAGAGAAACAGTTTTAGTATAACAAGTGAAATACC C----TGAGTCTGAGGTGCCTATAGGACATCTATATAAATA	2685	2.99%	-4
CR003035 PS sg	CTGGAAGAGAAACAGTTTTAGTATAACAAGTGAAATACC- ----TGAGTCTGAGGTGCCTATAGGACATCTATATAAATA	2686	2.23%	-5
CR003035 sg	CTGGAAGAGAAACAGTTTTAGTATAACAAGTGAAATACC CATG---AGTCTGAGGTGCCTATAGGACATCTATATAAATA	2687	10.92%	-3
CR003035 sg	CTGGAAGAGAAAtAGTTTTAGTATAACAAGTGAAATACCC ATG---AGTCTGAGGTGCCTATAGGACATCTATATAAATA	2688	6.05%	-3
CR003035 sg	CTGGAAGAGAAACAGTTTTAGTATAACAAGTGAAATACC CAT- CTGAGTCTGAGGTGCCTATAGGACATCTATATAAATA	2689	5.42%	-1
CR003035 sg	CTGGAAGAGAAAtAGTTTTAGTATAACAAGTGAAATACCC ATGCTGAGTCTGAGGTGCCTATAGGACATCTATATAAATA	2690	4.55%	0
CR003035 sg	CTGGAAGAGAAACAGTTTTAGTATAACAAGTGAAATACC CA--CTGAGTCTGAGGTGCCTATAGGACATCTATATAAATA	2691	4.53%	-2
CR003035 sg	CTGGAAGAGAAACAGTTTTAGTATAACAAGTGAAATACC CATG-- GAGTCTGAGGTGCCTATAGGACATCTATATAAATA	2692	3.59%	-2
CR003035 sg	CTGGAAGAGAAACAGTTTTAGTATAACAAGTGAAATACC C----TGAGTCTGAGGTGCCTATAGGACATCTATATAAATA	2693	2.30%	-4
CR001128	GTCTAGTGCAAGCTAACAGTTGCTTTTATCACAGGCTCCA GGA-GGGTTTGGCCTCTGATTAGGGTGGGGGCGTGGGTGG	2694	10.38%	-1
CR001128	GTCTAGTGCAAGCTAACAGTTGCTTTTATCACAGGCTCCA GG----GTTTGGCCTCTGATTAGGGTGGGGGCGTGGGTGG	2695	5.87%	-4
CR001128	GTCTAGTGCAAGCTAACAGTTGCTTTTATCACAGGCTCCA GGAAaGGGTTTGGCCTCTGATTAGGGTGGGGGCGTGGGT GG	2696	5.50%	1
CR001128	GTCTAGTGCAAGCTAACAGTTGCTTTTATCACAGGCTCCA GG-----TTTGGCCTCTGATTAGGGTGGGGGCGTGGGTGG	2697	4.87%	-5
CR001128	GTCTAGTGCAAGCTAACAGTTGCTTTTATCACAGGC-------- ----------GTGGGTGG	2698	4.61%	-36
CR001128	GTCTAGTGCAAGCTAACAaC---------- ATCACAGGCTCCAGGATAGGGGGCGTGGGTGG	2699	2.38%	-28
CR001128	GTCTAGTGCAAGCTAACAGTTGCTTTTATCACAGGCTCCA GGA--GGTTTGGCCTCTGATTAGGGTGGGGGCGTGGGTGG	2700	2.00%	-2
CR001128 OMePS	GTCTAGTGCAAGCTAACAGTTGCTTTTATCACAGGCTCCA GG----------TGGGGGCGTGGGTGG	2701	7.56%	-23
CR001128 OMePS	GTCTAGTGCAAGCTAACAGTTGCTTTTATCACAGGCTCCA GG----GTTTGGCCTCTGATTAGGGTGGGGGCGTGGGTGG	2702	6.53%	-4
CR001128 OMePS	GTCTAGTGCAAGCTAACAGTTGCTTTTATCACAGGCTCCA GG-----TTTGGCCTCTGATTAGGGTGGGGGCGTGGGTGG	2703	6.18%	-5
CR001128 OMePS	GTCTAGTGCAAGCTAACAGTTGCTTTTATCACAGGCTCCA GGA-GGGTTTGGCCTCTGATTAGGGTGGGGGCGTGGGTGG	2704	6.06%	-1
CR001128 OMePS	GTCTAGTGCAAGCTAACAGTTGCTTTTATCACAGGCTCCA GGAAaGGGTTTGGCCTCTGATTAGGGTGGGGGCGTGGGT GG	2705	3.92%	1
CR001128 OMePS	GTCTAGTGCAAGCTAACAGTTGCTTTTATCACAGGCTCCA GG----------CCTCTGATTAGGGTGGGGGCGTGGGTGG	2706	2.55%	-10

CR001128 sg	GTCTAGTGCAAGCTAACAGTTGCTTTTATCACAGGCTCCA GGA-GGGTTTGGCCTCTGATTAGGGTGGGGGCGTGGGTGG	2707	10.12%	-1
CR001128 sg	GTCTAGTGCAAGCTAACAGTTGCTTTTATCACAGGCTCCA GG-----TTTGGCCTCTGATTAGGGTGGGGGCGTGGGTGG	2708	7.05%	-5
CR001128 sg	GTCTAGTGCAAGCTAACAGTTGCTTTTATCACAGGCTCCA GG----GTTTGGCCTCTGATTAGGGTGGGGGCGTGGGTGG	2709	4.59%	-4
CR001128 sg	GTCTAGTGCAAGCTAACAGTTGCTTTTATCACAGGCTCCA GGAAaGGGTTTGGCCTCTGATTAGGGTGGGGGCGTGGGT GG	2710	4.24%	1
CR001128 sg	GTCTAGTGCAAGCTAACAGTTGCTTTTATCACAGGCTCCA GG----------GGCGTGGGTGG	2711	2.21%	-27
CR001128 sg	GTCTAGTGCAAGCTAACAGTTGCTTTTATCACAGGCTCCA G----------CGTGGGTGG	2712	1.66%	-30
CR001128 sg	GTCTAGTGCAAGCTAACAGTTGCTTTTATCACAGGC-------- ---------CTCTGATTAGGGTGGGGGCGTGGGTGG	2713	1.48%	-17
CR001128 sg OMePS	GTCTAGTGCAAGCTAACAGTTGCTTTTATCACAGGCTCCA GG-----TTTGGCCTCTGATTAGGGTGGGGGCGTGGGTGG	2714	10.59%	-5
CR001128 sg OMePS	GTCTAGTGCAAGCTAACAGTTGCTTTTATCACAGGCTCCA GG----GTTTGGCCTCTGATTAGGGTGGGGGCGTGGGTGG	2715	7.59%	-4
CR001128 sg OMePS	GTCTAGTGCAAGCTAACAGTTGCTTTTATCACAGGCTCCA GGA-GGGTTTGGCCTCTGATTAGGGTGGGGGCGTGGGTGG	2716	5.92%	-1
CR001128 sg OMePS	GTCTAGTGCAAGCTAACAGTTGCTTTTATCACAGGCTCCA GGAAaGGGTTTGGCCTCTGATTAGGGTGGGGGCGTGGGT GG	2717	3.38%	1
CR001128 sg OMePS	GTCTAGTGCAAGCTAACAGTTGCTTTTATCACAGGCTCCA GGAAGagGGTTTGGCCTCTGATTAGGGTGGGGGCGTGGGT GG	2718	2.49%	2
CR001128 sg OMePS	GTCTAGTGCAAGCTAACAGTTGCTTTTATCACAGGCTCCA GGA----------TTAGGGTGGGGGCGTGGGTGG	2719	1.95%	-16
CR001128 sg OMePS	GTCTAGTGCAAGCTAACAGTTGCTTTTATCACAGGCTCCA GGA--GGTTTGGCCTCTGATTAGGGTGGGGGCGTGGGTGG	2720	1.85%	-2
CR000312	TATCACAGGCTCCAGGAAGGGTTTGGCCTCTGATTAGG- TGGGGGCGTGGGTGGGGTAGAAGAGGACTGGCAGACCTC TC	2721	11.83%	-1
CR000312	TATCACAGGCTCCAGGAAGGGTTTGG---------- GGGCGTGGGTGGGGTAGAAGAGGACTGGCAGACCTCTC	2722	5.11%	-16
CR000312	TATCACAGGCTCCAGGAAGGGTTTGGC---------- GTGGGTGGGGTAGAAGAGGACTGGCAGACCTCTC	2723	4.33%	-19
CR000312	TATCACAGGCTCCAGGAAGGGTTTGGCCTCTGATT-- GGTGGGGGCGTGGGTGGGGTAGAAGAGGACTGGCAGAC CTCTC	2724	3.63%	-2
CR000312	TATCACAGGCTCCAGGAAGGG---------- GCGTGGGTGGGGTAGAAGAGGACTGGCAGACCTCTC	2725	2.50%	-23
CR000312	TATCACAGGCTCCAGGAAGGGTTTGGCCTCTG------ GTGGGGGCGTGGGTGGGGTAGAAGAGGACTGGCAGACCT CTC	2726	2.47%	-6
CR000312	TATCACAGGCTCCAGGAAGGGTTTGGCCTCTG--------- GGGGCGTGGGTGGGGTAGAAGAGGACTGGCAGACCTCTC	2727	2.35%	-9
CR000312 OMePS	TATCACAGGCTCCAGGAAGGGTTTGGCCTCTGATTAGG- TGGGGGCGTGGGTGGGGTAGAAGAGGACTGGCAGACCTC	2728	12.06%	-1

	TC			
CR000312 OMePS	TATCACAGGCTCCAGGAAGGGTTTGG----------TGGGGGCGTGGGTGGGGTAGAAGAGGACTGGCAGACCTCTC	2729	4.75%	-13
CR000312 OMePS	TATCACAGGCTCCAGGAAGGGTTTGGCCTCTGATT--GGTGGGGGCGTGGGTGGGGTAGAAGAGGACTGGCAGACCTCTC	2730	4.32%	-2
CR000312 OMePS	TATCACAGGCTCCAGGAAGGGTTTGGC----------GTGGGTGGGGTAGAAGAGGACTGGCAGACCTCTC	2731	3.97%	-19
CR000312 OMePS	TATCACAGGCTCCAGGAAGGGTTTGG----------GGGCGTGGGTGGGGTAGAAGAGGACTGGCAGACCTCTC	2732	3.28%	-16
CR000312 OMePS	TATCACAGGCTCCAGGAAGGGTTTGGCCTCTGATTAGaGGTGGGGGCGTGGGTGGGGTAGAAGAGGACTGGCAGACCTCTC	2733	3.25%	1
CR000312 OMePS	TATCACAGGCTCCAGGAAGGGTTTGGCCTCTGATTAG--TGGGGGCGTGGGTGGGGTAGAAGAGGACTGGCAGACCTCTC	2734	1.91%	-2
CR000312 sg	TATCACAGGCTCCAGGAAGGGTTTGGCCTCTGATTAG--TGGGGGCGTGGGTGGGGTAGAAGAGGACTGGCAGACCTCTC	2735	6.69%	-2
CR000312 sg	TATCACAGGCTCCAGGAAGGGTTTGGCCTCTGATTAGG-TGGGGGCGTGGGTGGGGTAGAAGAGGACTGGCAGACCTCTC	2736	6.28%	-1
CR000312 sg	TATCACAGGCTCCAGGAAGGGTTTGGCCTCTGA----------AGGACTGGCAGACCTCTC	2737	4.58%	-29
CR000312 sg	TATCACAGGCTCCAGGAAGGGTTTGGCCTCTGATTAGaGGTGGGGGCGTGGGTGGGGTAGAAGAGGACTGGCAGACCTCTC	2738	3.83%	1
CR000312 sg	TATCACAGGCTCCAGGAAGGGTTTGG----------GGGCGTGGGTGGGGTAGAAGAGGACTGGCAGACCTCTC	2739	3.74%	-16
CR000312 sg	TATCACAGGCTCCAGGAAGGGTTTGGCCTCTG---------GGGGCGTGGGTGGGGTAGAAGAGGACTGGCAGACCTCTC	2740	3.66%	-9
CR000312 sg	TATCACAGGCTCCAGGAAGGGTTTGGCCTCTGATTAGGG-----CGTGGGTGGGGTAGAAGAGGACTGGCAGACCTCTC	2741	3.19%	-6
CR000312 sg	TATCACAGGCTCCAGGAAGGGTTTGG----------TGGGGGCGTGGGTGGGGTAGAAGAGGACTGGCAGACCTCTC	2742	3.18%	-13
CR000312 sg OMePS	TATCACAGGCTCCAGGAAGGGTTTGGCCTCTGATTAGG-TGGGGGCGTGGGTGGGGTAGAAGAGGACTGGCAGACCTCTC	2743	12.59%	-1
CR000312 sg OMePS	TATCACAGGCTCCAGGAAGGGTTTGGCCTCTGATT--GGTGGGGGCGTGGGTGGGGTAGAAGAGGACTGGCAGACCTCTC	2744	7.73%	-2
CR000312 sg OMePS	TATCACAGGCTCCAGGAAGGGTTTGGCCTCTG---------GGGGCGTGGGTGGGGTAGAAGAGGACTGGCAGACCTCTC	2745	6.49%	-9
CR000312 sg OMePS	TATCACAGGCTCCAGGAAGGGTTTGG----------GGGCGTGGGTGGGGTAGAAGAGGACTGGCAGACCTCTC	2746	5.32%	-16
CR000312 sg OMePS	TATCACAGGCTCCAGGAAGGGTTTGGC----------GTGGGTGGGGTAGAAGAGGACTGGCAGACCTCTC	2747	3.89%	-19
CR000312	TATCACAGGCTCCAGGAAGGG----------	2748	2.50%	-22

sg OMePS	GGCGTGGGTGGGGTAGAAGAGGACTGGCAGACCTCTC			
CR000312 sg OMePS	TATCACAGGCTCCAGGAAGGGTTTGG----------TGGGGGCGTGGGTGGGGTAGAAGAGGACTGGCAGACCTCTC	2749	2.50%	-13
CR000312 sg OMePS	TATCACAGGCTCCAGGAAGGGTTTGGCCTCTGATTAG--TGGGGGCGTGGGTGGGGTAGAAGAGGACTGGCAGACCTCTC	2750	2.25%	-2
CR003085	ATGTAAGGAGGATGAGCCACATGGTATGGGAGG----------ACTCTAGGGTCAGAGAAATATGGGTTATATCCTTCTA	2751	12.51%	-10
CR003085	ATGTAAGGAGGATGAGCCACATGGTATGGGAGGTAT-CTAAGGACTCTAGGGTCAGAGAAATATGGGTTATATCCTTCTA	2752	8.89%	-1
CR003085	ATGTAAGGAGGATGAGCCACATGGTATGGGAGGTATAaCTAAGGACTCTAGGGTCAGAGAAATATGGGTTATATCCTTCTA	2753	7.30%	1
CR003085	ATGTAAGGAGGATGAGCCACATGGTATGGGA----------CTCTAGGGTCAGAGAAATATGGGTTATATCCTTCTA	2754	6.20%	-13
CR003085	ATGTAAGGAGGATGAGCCACATGGTA----------AGGACTCTAGGGTCAGAGAAATATGGGTTATATCCTTCTA	2755	3.50%	-14
CR003085	ATGTAAGGAGGATGAGCCACATGGTATGGGAGGTA-----AGGACTCTAGGGTCAGAGAAATATGGGTTATATCCTTCTA	2756	3.09%	-5
CR003085	ATGTAAGGAGGATGAGCCACATGGTATGGGAGGTATA---AGGACTCTAGGGTCAGAGAAATATGGGTTATATCCTTCTA	2757	2.29%	-3
CR003085	ATGTAAGGAGGATGAGCCACATGGTATGGGAGGTATA-TAAGGACTCTAGGGTCAGAGAAATATGGGTTATATCCTTCTA	2758	1.64%	-1
CR003085	ATGTAAGGAGGATGAGCCACATGGTATGG---------TAAGGACTCTAGGGTCAGAGAAATATGGGTTATATCCTTCTA	2759	1.43%	-9
CR003085	ATGTAAGGAGGATGAGCCACATGGTATGGGAGGTATA--AAGGACTCTAGGGTCAGAGAAATATGGGTTATATCCTTCTA	2760	1.39%	-2
CR003085 OMePS sg	ATGTAAGGAGGATGAGCCACATGGTATGGGAGGTATAaCTAAGGACTCTAGGGTCAGAGAAATATGGGTTATATCCTTCTA	2761	13.65%	1
CR003085 OMePS sg	ATGTAAGGAGGATGAGCCACATGGTATGGGAGG----------ACTCTAGGGTCAGAGAAATATGGGTTATATCCTTCTA	2762	10.96%	-10
CR003085 OMePS sg	ATGTAAGGAGGATGAGCCACATGGTATGGGA----------CTCTAGGGTCAGAGAAATATGGGTTATATCCTTCTA	2763	8.21%	-13
CR003085 OMePS sg	ATGTAAGGAGGATGAGCCACATGGTATGGGAGGTAT-CTAAGGACTCTAGGGTCAGAGAAATATGGGTTATATCCTTCTA	2764	8.15%	-1
CR003085 OMePS sg	ATGTAAGGAGGATGAGCCACATGGTA----------AGGACTCTAGGGTCAGAGAAATATGGGTTATATCCTTCTA	2765	6.29%	-14
CR003085 OMePS sg	ATGTAAGGAGGATGAGCCACATGGTATGGGAGGTA-----AGGACTCTAGGGTCAGAGAAATATGGGTTATATCCTTCTA	2766	4.53%	-5
CR003085 OMePS sg	ATGTAAGGAGGATGAGCCACATGGTATGGGAGGTATA---AGGACTCTAGGGTCAGAGAAATATGGGTTATATCCTTCTA	2767	3.60%	-3
CR003085 OMePS sg	ATGTAAGGAGGATGAGCCACATGGTATGGGAGGTA--CTAAGGACTCTAGGGTCAGAGAAATATGGGTTATATCCTTCTA	2768	3.47%	-2

CR003085 OMePS sg	ATGTAAGGAGGATGAGCCACATGGTATGGGAGGTATA-TAAGGACTCTAGGGTCAGAGAAATATGGGTTATATCCTTCTA	2769	1.30%	-1
CR003085 OMePS sg	ATGTAAGGAGGATGAGCCACATGGTATGGG----------TTATATCCTTCTA	2770	1.00%	-37
CR003085 OMePS	ATGTAAGGAGGATGAGCCACATGGTATGGGAGGTATAaCTAAGGACTCTAGGGTCAGAGAAATATGGGTTATATCCTTCTA	2771	10.09%	1
CR003085 OMePS	ATGTAAGGAGGATGAGCCACATGGTATGGGAGG----------ACTCTAGGGTCAGAGAAATATGGGTTATATCCTTCTA	2772	9.05%	-10
CR003085 OMePS	ATGTAAGGAGGATGAGCCACATGGTATGGGAGGTAT-CTAAGGACTCTAGGGTCAGAGAAATATGGGTTATATCCTTCTA	2773	6.52%	-1
CR003085 OMePS	ATGTAAGGAGGATGAGCCACATGGTATGGGA----------CTCTAGGGTCAGAGAAATATGGGTTATATCCTTCTA	2774	4.94%	-13
CR003085 OMePS	ATGTAAGGAGGATGAGCCACATGGTA----------AGGACTCTAGGGTCAGAGAAATATGGGTTATATCCTTCTA	2775	4.55%	-14
CR003085 OMePS	ATGTAAGGAGGATGAGCCACATGGTATGGGAGGTA-----AGGACTCTAGGGTCAGAGAAATATGGGTTATATCCTTCTA	2776	2.40%	-5
CR003085 OMePS	ATGTAAGGAGGATGAGCCACATGGTATGGGAGGTA--CTAAGGACTCTAGGGTCAGAGAAATATGGGTTATATCCTTCTA	2777	2.00%	-2
CR003085 OMePS	ATGTAAGGAGGATGAGCCACATGGTATGGGAGGTATA---AGGACTCTAGGGTCAGAGAAATATGGGTTATATCCTTCTA	2778	1.82%	-3
CR003085 OMePS	ATGTAAGGAGGATGAGCCACATGGTATGGGAGGTATA-TAAGGACTCTAGGGTCAGAGAAATATGGGTTATATCCTTCTA	2779	1.57%	-1
CR003085 OMePS	ATGTAAGGAGGATGAGCCACATGGTATGGGAGGT----------TATATCCTTCTA	2780	1.16%	-34
CR003085 PS	ATGTAAGGAGGATGAGCCACATGGTATGGGAGG----------ACTCTAGGGTCAGAGAAATATGGGTTATATCCTTCTA	2781	15.06%	-10
CR003085 PS	ATGTAAGGAGGATGAGCCACATGGTATGGGAGGTAT-CTAAGGACTCTAGGGTCAGAGAAATATGGGTTATATCCTTCTA	2782	11.15%	-1
CR003085 PS	ATGTAAGGAGGATGAGCCACATGGTATGGGAGGTATAaCTAAGGACTCTAGGGTCAGAGAAATATGGGTTATATCCTTCTA	2783	8.37%	1
CR003085 PS	ATGTAAGGAGGATGAGCCACATGGTATGGGA----------CTCTAGGGTCAGAGAAATATGGGTTATATCCTTCTA	2784	7.44%	-13
CR003085 PS	ATGTAAGGAGGATGAGCCACATGGTA----------AGGACTCTAGGGTCAGAGAAATATGGGTTATATCCTTCTA	2785	5.33%	-14
CR003085 PS	ATGTAAGGAGGATGAGCCACATGGTATGGGAGGTA-----AGGACTCTAGGGTCAGAGAAATATGGGTTATATCCTTCTA	2786	3.58%	-5
CR003085 PS	ATGTAAGGAGGATGAGCCACATGGTATGGGAGGTATA---AGGACTCTAGGGTCAGAGAAATATGGGTTATATCCTTCTA	2787	3.50%	-3
CR003085 PS	ATGTAAGGAGGATGAGCCACATGGTATGGGAGGTA--CTAAGGACTCTAGGGTCAGAGAAATATGGGTTATATCCTTCTA	2788	2.05%	-2
CR003085 PS	ATGTAAGGAGGATGAGCCACATGGTATGG----------ACTCTAGGGTCAGAGAAATATGGGTTATATCCTTCTA	2789	1.39%	-14

CR003085 PS	ATGTAAGGAGGATGAGCCACATGGTATGGGAGGTATA-TAAGGACTCTAGGGTCAGAGAAATATGGGTTATATCCTTCTA	2790	0.86%	-1
CR003085 PS sg	ATGTAAGGAGGATGAGCCACATGGTATGGGAGGTAT-CTAAGGACTCTAGGGTCAGAGAAATATGGGTTATATCCTTCTA	2791	12.62%	-1
CR003085 PS sg	ATGTAAGGAGGATGAGCCACATGGTATGGGAGGTATAaCTAAGGACTCTAGGGTCAGAGAAATATGGGTTATATCCTTCTA	2792	11.73%	1
CR003085 PS sg	ATGTAAGGAGGATGAGCCACATGGTATGGGAGG----------ACTCTAGGGTCAGAGAAATATGGGTTATATCCTTCTA	2793	8.86%	-10
CR003085 PS sg	ATGTAAGGAGGATGAGCCACATGGTATGGGA----------CTCTAGGGTCAGAGAAATATGGGTTATATCCTTCTA	2794	6.59%	-13
CR003085 PS sg	ATGTAAGGAGGATGAGCCACATGGTA----------AGGACTCTAGGGTCAGAGAAATATGGGTTATATCCTTCTA	2795	4.88%	-14
CR003085 PS sg	ATGTAAGGAGGATGAGCCACATGGTATGGGAGGTATA---AGGACTCTAGGGTCAGAGAAATATGGGTTATATCCTTCTA	2796	3.68%	-3
CR003085 PS sg	ATGTAAGGAGGATGAGCCACATGGTATGGGAGGTA--CTAAGGACTCTAGGGTCAGAGAAATATGGGTTATATCCTTCTA	2797	3.62%	-2
CR003085 PS sg	ATGTAAGGAGGATGAGCCACATGGTATGGGAGGTATA-TAAGGACTCTAGGGTCAGAGAAATATGGGTTATATCCTTCTA	2798	3.48%	-1
CR003085 PS sg	ATGTAAGGAGGATGAGCCACATGGTATGGGAGGTA-----AGGACTCTAGGGTCAGAGAAATATGGGTTATATCCTTCTA	2799	2.90%	-5
CR003085 PS sg	ATGTAAGGAGGATGAGCCACATGGTAT----------AAGGACTCTAGGGTCAGAGAAATATGGGTTATATCCTTCTA	2800	1.10%	-12
CR003085 sg	ATGTAAGGAGGATGAGCCACATGGTATGGGAGG----------ACTCTAGGGTCAGAGAAATATGGGTTATATCCTTCTA	2801	11.79%	-10
CR003085 sg	ATGTAAGGAGGATGAGCCACATGGTATGGGAGGTAT-CTAAGGACTCTAGGGTCAGAGAAATATGGGTTATATCCTTCTA	2802	9.21%	-1
CR003085 sg	ATGTAAGGAGGATGAGCCACATGGTATGGGAGGTATAaCTAAGGACTCTAGGGTCAGAGAAATATGGGTTATATCCTTCTA	2803	6.84%	1
CR003085 sg	ATGTAAGGAGGATGAGCCACATGGTATGGGA----------CTCTAGGGTCAGAGAAATATGGGTTATATCCTTCTA	2804	6.44%	-13
CR003085 sg	ATGTAAGGAGGATGAGCCACATGGTA----------AGGACTCTAGGGTCAGAGAAATATGGGTTATATCCTTCTA	2805	4.12%	-14
CR003085 sg	ATGTAAGGAGGATGAGCCACATGGTATGGGAGGTA-----AGGACTCTAGGGTCAGAGAAATATGGGTTATATCCTTCTA	2806	3.46%	-5
CR003085 sg	ATGTAAGGAGGATGAGCCACATGGTATGGGAGGTATA---AGGACTCTAGGGTCAGAGAAATATGGGTTATATCCTTCTA	2807	3.22%	-3
CR003085 sg	ATGTAAGGAGGATGAGCCACATGGTATGGGAGGTA--CTAAGGACTCTAGGGTCAGAGAAATATGGGTTATATCCTTCTA	2808	1.65%	-2
CR003085 sg	ATGTAAGGAGGATGAGCCACATGGTATGGGAGGTATA-TAAGGACTCTAGGGTCAGAGAAATATGGGTTATATCCTTCTA	2809	1.07%	-1
CR003085	ATGTAAGGAGGATGAGCCACATGGTATGG----------	2810	0.95%	-14

sg	ACTCTAGGGTCAGAGAAATATGGGTTATATCCTTCTA			

The genome edited and unedited HSPC were analyzed for proliferation and HbF upregulation in a three-stage erythroid differentiation cell culture protocol. The genome edited and unedited HSPC were analyzed by flow cytometry for expression levels of fetal globin and at day 7 for two erythroid cell surface markers, transferrin receptor (CD71) and glycophorin A (CD235a) using antibodies conjugated to fluorescent dyes. The live cells were identified and gated by exclusion of Live/Dead Fixable Dead Cell Stain. Genome editing with the included HPFH region targeting and BCL11A erythroid enhancer targeting gRNAs did not adversely affect erythroid differentiation as the cultured cells showed percentages of CD71+ cells consistent with erythroblasts similar to unedited cells at day 7 of differentiation, although Protocol 1 and Protocol 2 differed in percentages of CD71+ across conditions (Figure 44). Cultures treated with the included HPFH region targeting and BCL11A erythroid enhancer targeting gRNAs resulted in similar patterns of relative changes in the percentage of erythroid cells containing HbF compared to mock electroporated cells throughout the 21 day culture period and between the two protocols (Figures 45, Figure 46 and Figure 47). HbF was induced in cells exposed ot RNPs and maintined in either Protocol 1 or Protocol 2, however, the percentage of cells that were HbF positive tended to be lower across conditions and timepoints with Protocol 2 (Figures 45, Figure 46 and Figure 47). Induction of HbF was most pronounced with gRNAs consisting of target domains CR001030, CR00312 and CR001128, particularly at the later timepoints (Figures 45, Figure 46 and Figure 47). Across targeting domains, sgRNAs trended to higher induction of HbF than dgRNAs, particularly OMePS modified sgRNAs (Figures 45, Figure 46 and Figure 47). Relatively low induction of HbF with targeting domain CR001137 may be explained by the lower level of editing at this target site (Figures 43, Figure 45-Figure 47). Induction of HbF positive cells by dgRNA including the targeting domain of g8 targeting exon 2 of BCL11A was also observed in parallel (Figure 45-Figure 47). An increase in HbF-containing erythrocytes derived from genome edited cells is likely to have therapeutic implications by reduced sickling. Edited cells were capable of proliferating in erythroid differentiation conditions (9 to 53-fold at day 7 and 36 to 143-fold at day 21, Figure 48), however, in some cases, proliferation was suppressed relative to unedited control cells (14-83% of unedited control at day 7 and 18-95% of unedited control at day 21) (Figure 48). Lowest proliferation was observed with the cells edited by dgRNA including the targeting domain of g8 targeting exon 2 of BCL11A (30% of unedited control at day 7 and 18% of unedited control at day 21) and with many of the OMePS modified sgRNAs (Figure 48).

Example 5 Excision using two gRNAs to the HPFH region

Primary human CD34+ HSPCs were electroporated with RNP containing two different gRNA moleucles to different sites within the HPFH region. For each RNP, dgRNA molecules as described

above, were used. Briefly, RNP comprising a dgRNA targeting a first site within the French HPFH region and RNP comprising a dgRNA targeting a second site within the French HPFH region were combined, and electroporated into CD34+ HSPCs in the following ratios: 0.5X first dgRNA RNP + 0.5X second dgRNA RNP; 1.0X g2 dgRNA ("g2" = positive control comprising a targeting domain of CR000088, which targets a coding sequence of the BCL11a gene); no RNPs ("control"). Cells were cultured as described above, and differentiated into erythrocytes using the protocol described above (see Figure 17). Fetal hemoglobin expression was assessed. The results are showin in Figure 27 and Table 25. Without being bound by theory, it is believed that simultaneous introduction of RNPs comprising gRNA molecules to two target sequences will cause the deletion (i.e., excision) of the DNA between the two cut sites (e.g., all or most of the DNA between the two cut sites), including any regulatory or coding sequences contained within that region. These results show that RNPs targeting two separate regions within the HPFH region could be delivered simultaneously to CD34+ HSPCs by electroporation and induce fetal hemoglobin expression in edited cells differentiated into erythrocytes.

Table 25.

Guide RNA targeting domain ID 1/Guide RNA targeting domain ID 2	% HbF+ (F cells), average of replicates
CR001016/CR001021	50.9
CR001021/CR001034	53.4
CR001034/CR001037	56.1
CR001037/CR001045	50.6
CR001045/CR001058	45.2
CR001058/CR001065	42.6
CR001065/CR001075	43.3
CR001075/CR001086	40.4
CR001086/CR001096	39.3
CR001096/CR001107	41.6
CR001107/CR001135	45.6
CR001143/CR001151	40.1
CR001151/CR001159	40.9
CR001159/CR001166	42.0
CR001166/CR001173	44.8
CR001173/CR001179	43.1
CR001179/CR001191	41.9
CR001191/CR001199	42.7
CR001199/CR001212	48.3
CR001212/CR001227	45.6
CR001016/CR001034	53.4
CR001034/CR001045	50.0
CR001045/CR001065	44.2
CR001065/CR001086	39.1
CR001086/CR001107	43.4

CR001107/CR001143	44.8
CR001143/CR001159	45.0
CR001159/CR001173	46.6
CR001173/CR001191	44.8
CR001191/CR001212	51.7
CR001021/CR001037	56.9
CR001037/CR001058	48.0
CR001058/CR001075	41.7
CR001075/CR001096	41.5
CR001096/CR001135	44.3
CR001135/CR001151	42.9
CR001151/CR001166	41.9
CR001166/CR001179	40.4
CR001179/CR001199	38.5
CR001199/CR001227	40.0
g2	54.0
ctrl	34.5

Example 6. Potential Off-Target Editing Assessment of gRNAs Targeting the BCL11a Enhancer

An oligo insertion based assay (See, e.g., Tsai et al., *Nature Biotechnology*. **33**, 187–197; 2015) was used to determine potential off-target genomic sites cleaved by Cas9 targeting the BCL11a enhancer. A total of 28 guides (dual guide RNAs comprising the indicated targeting domain) targeting the BCL11a enhancer and 10 gRNAs targeting the HPFH region were screened in the Cas9-expressing HEK293 cells described above, and the results are plotted in Figure 33 (BCL11a enhancer) and Figure 49 (HPFH). Withr repsect to the gRNAs targeting the BCL11a enhancer, the assay identified potential off-target sites for some guides, however targeted deep sequencing was used to determine whether the potential sites were bona fide off-target sites cleaved by Cas9. Using primers that flanked the potential off-target sites, isolated genomic DNA was amplified and the amplicons were sequenced. If the potential off-target site was cleaved by Cas9, indels should be detected at the site. From these follow-on interrogations of the potential off-target sites, no indels were detected at the potential off-target sites for at least three of the guide RNAs: CR000311, CR000312, CR001128. With respect to the gRNAs targeting the BCL11a enhancer, the assay did not identify any potential off-target sites for at least gRNAs CR001137, CR001212, and CR001221. Targeted deep sequencing will be performed to determine whetehr the potential off target sites identified for the other gRNA molecules are bona-fide off target sites cleaved by Cas9.

Example 7: Evaluation of Cas9 Variants

Evaluation in CD34+ hematopoietic stem cells

We evaluated 14 purified *Streptococcus pyogenes* Cas9 (SPyCas9) proteins by measuring their efficiency of knocking out the beta-2-microglobulin (B2M) gene in primary human hematopoietic stem cells (HSCs). These proteins were divided into 3 groups: the first group consisted of SPyCas9 variants with improved selectivity (Slaymaker et al. 2015, Science 351: 84 (e1.0, e1.1 and K855A); Kleinstiver et al. 2016, Nature 529: 490 (HF)). The second group consisted of wild type SPyCas9 with different numbers and/or positions of the SV40 nuclear localization signal (NLS) and the 6xHistidine (His6) or 8xHistidine (His8) tag (SEQ ID NOS 2969 and 2970, respectively) with or without a cleavable TEV site, and a SPyCas9 protein with two cysteine substitutions (C80L, C574E), which have been reported to stabilize Cas9 for structural studies (Nishimasu et al. 2014, Cell 156:935). The third group consisted of the same recombinant SPyCas9 produced by different processes (Fig 60). B2M knockout was determined by FACS and next generation sequencing (NGS).

Methods

Materials

1. Neon electroporation instrument (Invitrogen, MPK5000)
2. Neon electroporation kit (Invitrogen, MPK1025)
3. crRNA (targeting domain sequence of GGCCACGGAGCGAGACAUCU (SEQ ID NO: 2811), complementary to a sequence in the B2M gene, fused to SEQ ID NO: 6607)
4. tracrRNA (SEQ ID NO: 6660)
5. Cas9 storage buffer: 20 mM Tris-Cl, pH 8.0, 200mM KCl, 10mM $MgCl_2$
6. Bone marrow derived CD34+ HSCs (Lonza, 2M-101C)
7. Cell culture media (Stemcell Technologies, StemSpam SFEM II with StemSpam CC-100)
8. FACS wash buffer: 2% FCS in PBS
9. FACS block buffer: per mL PBS, add 0.5 ug mouse IgG, 150 ug Fc block, 20 uL FCS
10. Chelex suspension: 10% Chelex 100 (bioRad, Cat# 142-1253) in H_2O
11. Anti-B2M antibody: Biolegend, cat# 316304

Process

Thaw and grow the cells following Lonza's recommendations, add media every 2-3 days. On day 5, pellet the cells at 200 x g for 15 min, wash once with PBS, resuspend the cells with T-buffer from NEON kit at $2x10^4$/uL, put on ice. Dilute Cas 9 protein with Cas9 storage buffer to 5 mg/ml. Reconstitute crRNA and tracrRNA to 100 uM with H_2O. The ribonucleoprotein (RNP) complex is made by mixing 0.8 uL each of CAS 9 protein, crRNA and tracrRNA with 0.6 uL of Cas9 storage buffer, incubate at room temperature for 10 min. Mix 7 uL of HSCs with RNP complex for two minutes and transfer the entire 10 uL into a Neon pipette tip, electroporate at 1700v, 20 ms and 1 pulse. After electroporation, immediately transfer cells into a well of 24-well plate containing 1 ml

media pre-calibrated at 37°C, 5% CO_2. Harvest cells 72 hrs post-electroproation for FACS and NGS analysis.

FACS: take 250 uL of the cells from each well of 24-well plate, to wells of 96-well U-bottom plate and pellet the cells. Wash once with 2% FCS (fetal calf serum)-PBS. Add 50 uL FACS block buffer to the cells and incubate on ice for 10 minutes, add 1 uL FITC labeled B2M antibody and incubate for 30 minutes. Wash with 150 uL FACS wash buffer once followed by once more with 200 uL FACS wash buffer once. Cells were resuspended in 200 uL FACS buffer FACS analysis.

NGS sample prep: transfer 250 uL of cell suspension from each well of the 24-well plate to a 1.5 ml Eppendorf tube, add 1 mL PBS and pellet the cells. Add 100 uL of Chelex suspension, incubate at 99°C for 8 minutes and vortex 10 seconds followed by incubating at 99°C for 8 minutes, vortex 10 seconds. Pellet down the resin by centrifuging at 10,000 x g for 3 minutes and the supernatant lysate is used for PCR. Take 4 uL lysate and do PCR reaction with the b2m primers (b2mg67F: CAGACAGCAAACTCACCCAGT (SEQ ID NO: 2812), b2mg67R: CTGACGCTTATCGACGCCCT (SEQ ID NO: 2813)) using Titanium kit (Clonetech, cat# 639208) and follow the manufacturer's instruction. The following PCR conditions are used: 5 minutes at 98°C for 1 cycle; 15 seconds at 95°C, 15 seconds at 62°C, and 1 minute at 72°C for 30 cycles; and finally 3 minutes at 72°C for 1 cycle. The PCR product was used for NGS.

Statistics: The percentage of B2M KO cells by FACS and the percentage of indels by NGS are used to evaluate the CAS 9 cleavage efficiency. The experiment was designed with Cas9 as fixed effect. Each experiment is nested within donors, as nested random effects. Therefore, the mixed linear model was applied for the analysis of FACS and NGS data.

Results

In order to normalize the experimental and donor variations, we graphed the relative activity of each protein to iProt105026, the original design with two SV40 NLS flanking the wild type SPyCas9 and the His6 tag (SEQ ID NO: 2969) at the C-terminal of the protein (Fig 34). The statistical analysis shows that compared with the reference Cas9 protein iProt105026, iProt106331, iProt106518, iProt106520 and iProt106521 are not significantly different in knocking out B2M in HSCs, while the other variants tested (PID426303, iProt106519, iProt106522, iProt106545, iProt106658, iProt106745, iProt106746, iProt106747, iProt106884) are highly significantly different from the reference iProt105026 in knocking out B2M in HSCs. We found that moving the His6 tag (SEQ ID NO: 2969) from the C-terminal to N-terminal (iProt106520) did not affect the activity of the protein (Fig. 34). One NLS was sufficient to maintain activity only when it was placed at the C-terminal of the protein (iProt106521 vs. iProt106522, Fig. 34). Proteins purified from process 1 had consistent higher knockout efficiency than those from processes 2 and 3 (iProt106331 vs. iProt106545 & PID426303,

Fig. 34). In general, the SPyCas9 variants with a reported improved selectivity were not as active as the wild type SPyCas9 (iProt106745, iProt106746 and iProt106747, Fig. 34). Interestingly iProt106884 did not cut the targeting site. This is consistent with the report by Kleinstiver et al that this variant failed to cut up to 20% of the legitimate targeting sites in mammalian cells (Kleinstiver et al. 2016, Nature 529: 490). Finally, the Cas9 variant with two cysteine substitutions (iProt106518) maintained high levels of enzymatic activity (Fig. 34).

Next, editing efficiency of RNPs comprising different Cas9 variants were tested with either modified or unmodified gRNAs targeting the +58 enhancer region. sgRNA molecules comprising the targeting domains of cr00312 and cr1128 were tested in either unmodified (CR00312 = SEQ ID NO: 342; CR001128 = SEQ ID NO: 347) or modified (OMePS CR00312 = SEQ ID NO: 1762; OMePS CR001128 = SEQ ID NO: 1763), and were precomplexed with Cas9 variants shown in Table 35.

Table 35. Cas9 variants tested for biological function with +58 enhancer region-targeting gRNA molecules.

iProt Code	**Construct**
iProt106518	NLS-Cas9(C80L/C574E)-NLS-His6
iProt106331	NLS-Cas9-NLS-His6
iProt106745	NLS-Cas9(K855A)-NLS-His6
iProt106884	NLS-Cas9(HF)-NLS-His6

RNP formed as described above were delivered to HSPC cells as described above, and the cells assessed for % editing (by NGS) and % HbF induction upon erythroid differentiation, as described in these Examples. The results are shown in Figure 42A (% editing) and Figure 42B (HbF induction). The results show that varying the Cas9 component between those variants tested did not alter the gene editing efficiency of both unmodified and modified versions of sgRNA CR00312 and CR001128, nor did the Cas9 variants impact the ability of the erythroid-differentiated gene edited cells to produce HbF.

Example 8: Ex Vivo Expansion of Gene Edited HSPCs, and Editing Analysis in HSPC subsets

Expansion of cells prior to gene-editing

Human bone marrow $CD34^+$ cells were purchased from either AllCells (Cat#: ABM017F) or Lonza (Cat#: 2M-101C) and expanded for 2 to 3 days using StemSpan SFEM (StemCell Technologies; Cat

no. 09650) supplemented with 50 ng/mL of thrombopoietin (Tpo, Peprotech; Cat# 300-18), 50 ng/mL of human Flt3 ligand (Flt-3L, Peprotech; Cat# 300-19), 50ng/mL of human stem cell factor (SCF, Peprotech; Cat# 300-07), human interleukin-6 (IL-6, Peprotech; Cat# 200-06), 1% L-glutamine; 2% penicillin/streptomycin, and Compound 4 (0.75 μM).

Electroporation of Cas9 and guide RNA ribonucleoprotein (RNP) complexes into cells

Cas9-guide RNA ribonucleoprotein complexes (RNPs) were prepared immediately prior to electroporation. For formation of RNP using dual guide RNAs, 3 μg of each of crRNA (in 2.24 μL) and tracrRNA (in 1.25 μL) were first denatured at 95°C for 2 min in separate tubes and then cooled to room temperature. For preparation of Cas9 protein, 7.3 μg of CAS9 protein (in 1.21 μL) was mixed with 0.52 μL of 5 x CCE buffer (20 mM HEPES, 100 mM KCL, 5 mM MgCL2, 5% Glycerol and freshly added 1 mM DTT). TracrRNA was first mixed with the Cas9 preparation and incubated at 37°C for 5 min. The CrRNA was then added to TracrRNA/CAS9 complexes and incubated for 5 min at 37°C. The HSPC were collected by centrifugation at 200 x g for 15 min and resuspended in T buffer affiliated with the Neon electroporation kit (Invitrogen; Cat#: MPK1096) at a cell density of 2 x 10^7/mL. RNP was mixed with 12 μL of cells by pipetting up and down 3 times gently. To prepare single guide RNA (sgRNA) and Cas9 complexes, 2.25 μg sgRNA (in 1.5 μL) was mixed with 2.25 μg Cas9 protein (in 3 μL) and incubated at RT for 5 min. The sgRNA/Cas9 complex was then mixed with 10.5 μL of 2 x 10^7 /mL cells by pipetting up and down several times gently and incubated at RT for 2 min. The RNP/cell mixture (10 μL) was transferred into a Neon electroporation probe. Electroporation was performed with Neon transfection system (Invitrogen; MPK5000S) using 1700 volts/20 milliseconds and 1 pulse.

Expansion of cells after gene-editing

After electroporation, the cells were transferred into 0.5 mL pre-warmed StemSpan SFEM medium supplemented with growth factors, cytokines and Compound 4 as described above and cultured at 37°C for 3 days. After a total of 10 days of cell expansion, 3 days before electroporation and 7 days after electroporation, the total cell number increased 2-7 fold relative to the starting cell number (Figure 35).

Genomic DNA preparation

Genomic DNA was prepared from edited and unedited HSPC at 48 hours post-electroporation. Cells were lysed in 10 mM Tris-HCL, pH 8.0; 0.05% SDS and freshly added Protease K of 25 μg/mL and incubated at 37°C for 1 hour followed by additional incubation at 85°C for 15 min to inactivate protease K.

T7E1 assay

To determine editing efficiency of HSPCs, T7E1 assay was performed. PCR was performed using Phusion Hot Start II High-Fidelity kit (Thermo Scientific; Cat#: F-549L) with the following cycling condition: 98°C for 30''; 35 cycles of 98°C for 5'', 68°C for 20', 72°C for 30"; 72°C for 5 min. The following primers were used: forward primer: 5'-AGCTCCAAACTCTCAAACCACAGGG-3' (SEQ ID NO: 2814) and reverse primer: 5'-TACAATTTTGGGAGTCCACACGGCA-3' (SEQ ID NO: 2815). PCR products were denatured and re-annealed using the following condition: 95°C for 5 min, 95-85°C at -2°C/s, 85-25°C at -0.1°C/s, 4°C hold. After annealing, 1 µL of mismatch-sensitive T7 E1 nuclease (NEB, Cat# M0302L) was added into 10 µL of PCR product above and further incubated at 37°C for 15 min for digestion of hetero duplexes, and the resulting DNA fragments were analyzed by agarose gel (2%) electrophoresis. Editing efficiency was quantified using ImageJ software (http://rsb.info.nih.gov/ij/).

PCR Preparation for next generation sequencing (NGS)

To determine editing efficiency more precisely and patterns of insertions and deletions (indels), the PCR products were subjected to next generation sequencing (NGS). The PCR were performed in duplicate using Titanium Taq PCR kit (Clontech Laboratories; Cat#: 639210) with the following cycling condition: 98°C for 5 min; 30 cycles of 95°C for 15 seconds, 68°C for 15 seconds, 72°C 1 min; 72°C for 7 min. The following primers were used: forward primer: 5'-AGCTCCAAACTCTCAAACCACAGGG-3' (SEQ ID NO: 2816) and reverse primer: 5'-TACAATTTTGGGAGTCCACACGGCA-3' (SEQ ID NO: 2817). The PCR products were analyzed by 2% agarose gel electrophoresis and submitted for deep sequencing.

Flow cytometry analysis of editing efficiency in hematopoietic stem and progenitor subpopulations.

Cells were subjected to flow cytometry to characterize editing efficiency in stem and progenitor cell (HSPC) subpopulations. The frequencies of HSPC subsets, including CD34+ cells, CD34+CD90+ cells, CD34+CD90+CD45RA- cells, and CD34+CD90+CD45RA-CD49f+ cells, prior to (48 hours in culture) and after genome editing (10 days in culture; 3 days after genome editing) was determined from sampling aliquots of cell cultures (Figure 36, Figure 37, Figure 38). Cells were incubated with anti-CD34 (BD Biosciences, Cat# 555824), anti-CD38 (BD Biosciences, Cat# 560677), anti-CD90 (BD Biosciences, Cat# 555596), anti-CD45RA (BD Biosciences, Cat# 563963), anti-CD49f (BD Biosciences, Cat# 562582) in modified FACS buffer, containing PBS supplemented with 0.5% BSA, 2mM EDTA pH7.4, at 4°C, in dark for 30 min. Cell viability was determined by 7AAD. Cells were washed with modified FACS buffer and multicolor FACS analysis was performed on a Fortessa (BD Biosciences). Flow cytometry results were analyzed using Flowjo software. Genome edited cells grown in the presence of Compound 4 (alone) exhibited detectible levels of all HSPC subsets assessed, including CD34+, CD34+CD90+, CD34+CD90+CD45RA-, and CD34+CD90+CD45RA-

CD49f+ subsets, indicating that long-term HSC populations persist in cell culture in the presence of Compound 4 (alone) after genome editing (Figure 38).

Four hours after gene editing, aliquots of cell cultures were sampled and cells were sorted into HSPC subsets (CD34+, CD34+CD38+, CD34+CD38-, CD34+CD38-CD45RA-, CD34+CD38-CD45RA-CD90+CD49f-, CD34+CD38-CD45RA-CD90-CD49f-, and CD34+CD38-CD45RA-CD90-CD49f+ cells) and subjected to NGS to measure the editing efficiency (Table 28). It is important to note that all hematopoietic subsets, including the subsets enriched in long-term HSCs, displayed similarly high gene editing efficiencies (>95%). This high gene editing efficiency in long-term HSCs has significant therapeutic impact as these cells are capable of engrafting patients in the long-term and sustain life-long hematopoietic multi-lineage regeneration.

Table 28. Editing efficiency in each HSPC subset measured by NGS.

gRNA	HSPC subsets	Avg(% Indels)
Dg CR00312	Total (singlets)	97.98%
	CD34+CD38-CD45RA-	98.66%
	CD34+CD38-CD45RA-CD90+CD49f-	98.19%
	CD34+CD38-CD45RA-CD90-CD49f-	98.70%
	CD34+CD38-CD45RA-CD90-CD49f+	98.81%
Dg CR001128	Total (singlets)	97.62%
	CD34+CD38-CD45RA-	95.93%
	CD34+CD38-CD45RA-CD90-CD49f-	98.00%
	CD34+CD38-CD45RA-CD90-CD49f+	99.01%

Example 9 Evaluation of Potential Off-Target Editing

HSPC culture and CRISPR/Cas9 genome editing

Methods for RNP generation and cell manipulation are as in Example 4, with the following exceptions. Human $CD34^+$ cell culture. Human CD34+ cells were either isolated from G-CSF mobilized peripheral blood from adult donors (AllCells, Cat. No. mPB025-Reg.E) using immunoselection (Miltenyi) according to the manufacturer's instructions or derived from bone marrow (Hemacare Corporation, Cat. No. BM34C-3). CD34+ cells were thawed and expanded for 2 days or 5 days prior to RNP delivery. After RNP delivery, cells were either cultured for an additional 13 days in expansion medium or cultured in erythroid differentiation medium for 7 or 11 days as follows. During days 0–7 of culture, EDM was further supplemented with 1 μM hydrocortisone (Sigma H8672), 100 ng/mL human SCF (Life Technologies, Cat. #PHC2113), and 5 ng/mL human IL-3 (Peprotech #10779-598). During days 7–11 of culture, EDM was supplemented with 100 ng/mL

of human SCF only. At the conclusion of the culture period, cells were harvested for genomic DNA preparation and analysis.

Assembly of Cas9 and guide RNA ribonucleoprotein (RNP) complexes, preparation of HSPC, and electroporation of RNP into HSPC. The HSPC collected by centrifugation were resuspended in P3 Primary Cell Solution (Lonza cat. No. PBP3-00675). The RNP was mixed with 20 µL of cells by pipetting up and down and incubated at RT for 2 min. The RNP/cell mixture (20 µL) was electroporated using code CM-137 on the 4D-Nucleofector (Lonza). dgRNAs comprising a crRNA having the sequence NNNNNNNNNNNNNNNNNNNGUUUUAGAGCUAUGCUGUUUUG (SEQ ID NO: 2818) (where N indicates a residue of the indicated targeting domain) and a tracr having the sequence of SEQ ID NO: 6660 were used.

Genomic DNA extraction

Genomic DNA was isolated from RNP treated and untreated HSPC using the DNeasy Blood & Tissue Kit (Qiagen, Cat # 69506) following the manufacturer's recommendations.

***In silico* identification of potential gRNA off-target loci**

Potential off-target loci for the BCL11A +58 region gRNAs CR00309, CR00311, CR00312, CR00316, CR001125, CR001126, CR001127, and CR001128, and the HPFH region gRNAs CR001028, CR001030, CR001137, CR001221, CR003035, and CR003085 were identified as follows. For each gRNA, the 20 nucleotide gRNA protospacer sequence was aligned to the human genome reference sequence (build GRCh38) using the BFAST sequence aligner (version 0.6.4f, Homer et al, PLoS One, 2009, 4(11), e7767, PMID: 19907642) using standard parameters allowing up to 5 nucleotide mismatches. Loci identified were filtered to only contain sites that are 5' adjacent to the Cas9 canonical 5'-NGG-3' PAM sequence (i.e. 5'-off-target locus-PAM-3'). Using the BEDTools script (version 2.11.2, Quinlan and Hall, Bioinformatics, 2010 26(6):841-2, PMID: 20110278) sites with 5 nucleotide mismatches were further filtered against RefSeq gene annotations (Pruitt et al, Nucleic Acids Res., 2014 42(Database issue):D756-63, PMID: 24259432) to only contain loci annotated as exons. Counts of the potential off-target loci identified for the BCL11A +58 region and the HPFH region gRNAs are shown in Tables 1 and 2 respectively.

Table 29. Counts of *in silico* off-target loci identified for the BCL11A +58 region gRNAs CR00309, CR00311, CR00312, CR00316, CR001125, CR001126, CR001127, and CR001128 with 0, 1, 2, 3 and 4 nucleotide mismatches and 5 nucleotide mismatches within RefSeq exons are shown.

gRNA targeting	Number of off-targets with N mismatches						
	0	1	2	3	4	5 RefSeq exons	Total sites

domain ID							
CR00309	0	0	2	9	77	52	140
CR00311	0	0	3	13	213	38	267
CR00312	0	0	0	6	126	33	165
CR00316	0	0	0	22	234	90	346
CR001125	0	0	1	16	221	83	321
CR001126	0	0	2	26	235	86	349
CR001127	0	0	1	35	331	157	524
CR001128	0	0	0	9	156	42	207

Table 30. Counts of *in silico* off-target loci identified for the HPFH region gRNAs CR001028, CR001030, CR001137, CR001221, CR003035, and CR003085 with 0, 1, 2, 3 and 4 nucleotide mismatches and 5 nucleotide mismatches within RefSeq exons are shown.

gRNA targeting domain ID	Number of off-targets with N mismatches						
	0	**1**	**2**	**3**	**4**	**5 RefSeq exons**	**Total sites**
CR001028	0	0	1	11	154	67	233
CR001030	0	0	0	14	125	85	224
CR001137	0	0	1	6	85	21	113
CR001221	0	0	2	17	166	44	229
CR003035	0	0	4	10	158	77	249
CR003085	0	0	0	5	75	16	96

PCR primer design for targeted amplification of potential off-target sites

PCR amplicons targeting potential off-target loci (and the on-target locus) identified for the BCL11A +58 region gRNAs (CR00309, CR00311, CR00312, CR00316, CR001125, CR001126, CR001127, and CR001128) and the HPFH region gRNAs (CR001028, CR001030, CR001137, CR001221, CR003035, and CR003085) were design using Primer3 (version 2.3.6, Untergasser et al, Nucleic Acids Res., 2012 40(15):e115, PMID: 22730293) using default parameters aiming for an amplicon size range of approximately 160-300 base pairs in length with the gRNA protospacer sequence located in the center of the amplicon. For gRNA CR001127 PCR primers were only designed for sites with 0-4 nucleotide mismatches, no primers were designed for sites with 5 nucleotide mismatches within RefSeq exons. Resulting PCR primer pairs and amplicon sequences were checked for

uniqueness by BLAST searching (version 2.2.19, Altschul et al, J Mol Biol., 1990, 215(3):403-10, PMID: 2231712) sequences against the human genome reference sequence (build GRCh38). Primer pairs resulting in more than one amplicon sequence were discarded and redesigned. Tables 3 and 5 show counts of successful PCR primer pairs designed for the BCL11A +58 region and the HPFH region gRNAs respectively.

Illumina sequencing library preparation, quantification and sequencing

Genomic DNA from RNP treated (2 replicates per gRNA) and untreated (1 replicate per gRNA) HSPC samples was quantified using the Quant-iT PicoGreen dsDNA kit (Thermo Fisher, Cat # P7581) using manufacture's recommendations. Illumina sequencing libraries targeting individual off-target loci (and the on-target locus) were generated for each sample using two sequential PCR reactions. The first PCR amplified the target locus using target specific PCR primers (designed above) that were tailed with universal Illumina sequencing compatible sequences. The second PCR added additional Illumina sequencing compatible sequences to the first PCR amplicon, including sample barcodes to enable multiplexing during sequencing. PCR 1 was performed in a final volume of 10 µL with each reaction containing 3-6 ng of gDNA (equivalent to approximately 500-1000 cells), PCR 1 primer pairs (Integrated DNA Technologies) at a final concentration of 0.25 µM and 1x final concentration of Q5 Hot Start Master Mix (New England BioLabs, Cat # 102500-140). PCR 1 left primers were 5' tailed (i.e. 5'-tail-target specific left primer-3') with sequence 5'-TCGTCGGCAGCGTCAGATGTGTATAAGAGACAG-3' (SEQ ID NO: 2819) and right primers were 5' tailed (i.e. 5'-tail- target specific right primer-3') with sequence 5'-GTCTCGTGGGCTCGGAGATGTGTATAAGAGACAG-3' (SEQ ID NO: 2820). PCR 1 was performed on a thermocycler using the following cycling conditions: 1 cycle of 98°C for 1 min; 25 cycles of 98°C for 10 sec, 63°C for 20 sec, and 72°C for 30 sec; 1 cycle at 72°C for 2 min. PCR 1 was then diluted 1 in 100 using nuclease free water (Ambion, Cat # AM9932) and used as input into PCR 2. PCR 2 was performed in a final volume of 10 µL with each reaction containing 2 µL of diluted PCR 1 product, PCR 2 primer pairs (Integrated DNA Technologies) at a final concentration of 0.5 µM and 1x final concentration of Q5 Hot Start Master Mix (New England BioLabs, Cat # 102500-140). PCR 2 left primer sequence used was 5'-AATGATACGGCGACCACCGAGATCTACACNNNNNNNNTCGTCGGCAGCGTC-3' (SEQ ID NO: 2821) and PCR 2 right primer sequence used was 5'-CAAGCAGAAGACGGCATACGAGATNNNNNNNNGTCTCGTGGGCTCGG-3' (SEQ ID NO: 2822) where the NNNNNNNN denote an 8 nucleotide barcode sequence used for sample multiplexing as part of the standard Illumina sequencing process. PCR 2 was performed on a thermocycler using the following cycling conditions: 1 cycle of 72°C for 3 min; 1 cycle of 98°C for 2 min; 15 cycles of 98°C for 10 sec, 63°C for 30 sec, and 72°C for 2 min. PCR 2 amplicons, now viable Illumina sequencing libraries, were cleaned up using Agencourt AMPure XP beads (Beckman

Coulter, Cat # A63882) following the manufacture's recommendations. The cleaned Illumina sequencing libraries were then quantified using standard qPCR quantification methods using Power SYBR Green PCR master mix (Life Technologies, Cat # 4367660) and primers specific to the Illumina sequencing library ends (forward primer sequence 5'- CAAGCAGAAGACGGCATACGA-3' (SEQ ID NO: 2823) and reverse primer sequence 5'-AATGATACGGCGACCACCGAGA-3' (SEQ ID NO: 2824)). Illumina sequencing libraries were then pooled equimolar and subjected to Illumina sequencing on a MiSeq instrument (Illumina, Cat # SY-410-1003) with 300 base paired-end reads using a MiSeq Reagent Kit v3 (Illumina, Cat # MS-102-3003) following the manufacture's recommendations. A minimum of 1000-fold sequence coverage was generated for each locus for at least one treated replicate. PCR, cleanup, pooling and sequencing of treated and untreated samples were performed separately to avoid any possibility of cross contamination between treated and untreated samples or PCR amplicons generated therefrom.

Illumina sequencing data QC and variant analysis

Using default parameters, the Illumina MiSeq analysis software (MiSeq reporter, version 2.6.2, Illumina) was used to generate amplicon specific FASTQ sequencing data files (Cock et al, Nucleic Acids Res. 2010, 38(6):1767-71, PMID: 20015970). FASTQ files were then processed through an internally developed variant analysis pipeline consisting of a series of public domain software packages joined together using a standard Perl script wrapper. The workflow used was divided into five stages.

Stage1, PCR primer and on- and off-target sequence QC: For both on- and off- target sites the 20 nucleotide gRNA protospacer sequence plus PAM sequence and target specific PCR primer sequences (left and right without the additional Illumina sequences) were aligned to the human genome reference sequence (build GRCh38) using a BLAST search (version 2.2.29+, Altschul et al, J Mol Biol., 1990, 215(3):403-10, PMID: 2231712). On- and off-target sites with multiple genomic locations were flagged.

Stage 2, sequencer file decompression: Illumina sequencer generated FASTQ.GZ files were decompressed to FASTQ files using the gzip script (version 1.3.12) and number of reads per file was calculated. Files with no reads were excluded from further analysis.

Stage 3, sequence read alignment and quality trimming: Sequencing reads in FASTQ files were aligned to the human genome reference sequence (build GRCh38) using the BWA-MEM aligner (version 0.7.4-r385, Li and Durbin, Bioinformatics, 2009, 25(14):1754-60, PMID: 19451168) using 'hard-clipping' to trim 3' ends of reads of Illumina sequences and low quality bases. Resulting aligned reads, in the BAM file format (Li et al, Bioinformatics, 2009 25(16):2078-9, PMID: 19505943), were converted to FASTQ files using the SAMtools script (version 0.1.19-44428cd, Li et

al, Bioinformatics, 2009 25(16):2078-9, PMID: 19505943). FASTQ files were then aligned again to the human genome reference sequence (build GRCh38) using the BWA-MEM aligner, this time without 'hard-clipping'.

Stage 4, variant (SNP and INDEL) analysis: BAM files of aligned reads were processed using the VarDict variant caller (version 1.0 'Cas9 aware' modified by developer ZhangWu Lia, Lai et al, Nucleic Acids Res., 2016, 44(11):e108, PMID: 27060149) with allele frequency detection limit set at >=0.0001 to identify variants (SNPs and INDELs). The Cas9 aware VarDict caller is based on a public domain package but able to move ambiguous variant calls, generated due to repetitive sequences in the alignment region of the variant events, toward the potential Cas9 nuclease cut site in the gRNA protospacer sequence located 3 bases 5' of the PAM sequence. The SAMtools script was used to calculate read coverage per sample amplicon to determine whether the on- and off-target sites were covered at >1000-fold sequence coverage. Sites with <1000-fold sequence coverage were flagged.

Stage 5, dbSNP filtering and treated/untreated differential analysis: Variants identified were filtered for known variants (SNPs and INDELs) found in dbSNP (build 142, Shery et al, Nucleic Acids Res. 2001, 29(1):308-11, PMID: 11125122). Variants in the treated samples were further filtered to exclude: 1) variants identified in the untreated control samples; 2) variants with a VarDict strand bias of 2:1 (where forward and reverse read counts supporting the reference sequence are balanced but imbalanced for the non-reference variant call); 3) variants located outside a 100bp window around the potential Cas9 cut site; 4) single nucleotide variants within a 100bp window around the potential Cas9 cut site. Finally only sites with a combined INDEL frequency of >2% (editing in more than approximately 10-20 cell) in a 100bp window of the potential Cas9 cut site were considered. Potential active editing sites were further examined at the read alignment level using the Integrative Genome Viewer (IGV version 2.3, Robinson et al, Nat Biotechnol. 2011, 9(1):24-6, PMID: 21221095) that allows for visual inspection of read alignments to the genome reference sequence.

On- and off-target analysis results

On-target sites for the BCL11A +58 region and the HPFH region gRNAs showed robust editing at the intended Cas9 cut site in treated samples with an INDEL frequency greater than 88% for all gRNAs. Tables 3 and 5 show number of off-target sites characterized in at least one biological replicate. Uncharacterized sites failed PCR primer design or PCR amplification and remain under investigation.

BCL11A +58 region *in silico* targeted analysis results

gRNA CR00309: The on-target site for gRNA CR00309 showed robust editing at the intended Cas9 cut site with an average INDEL frequency of approximately 92%. Table 31 shows the number of off-target sites characterized. Uncharacterized sites failed in PCR primer design or PCR amplification and remain under investigation. Characterization of potential off-target sites identified four off-target sites in the 100bp window around the proposed Cas9 cut site in both treated replicates. Site 1 has an average INDEL frequency approximately 18%, has 3 mismatches relative to the on-target gRNA protospacer sequence (5'-CtCaCCtCCACCCTAATCAG-PAM-3', PAM = AGG (SEQ ID NO: 2825)) and is located in intron 1 of the Anoctamin 5 gene (ANO5), on chromosome 11 at base pair position 22,195,800-22,195,819, approximately 2.3kb away from exon 1. Site 2 has an average INDEL frequency of approximately 18%, has 2 mismatches relative to the on-target gRNA protospacer sequence (5'- CACGCCCaCACCtTAATCAG -PAM-3', PAM = GGG (SEQ ID NO: 2826)) and is located in an intergenic region of chromosome 12 at base pair position 3,311,901-3,311,926. Site 3 has an average INDEL frequency approximately 80%, has 2 mismatches relative to the on-target gRNA protospacer sequence (5'-CACGaCCCaACCCTAATCAG-PAM-3', PAM = AGG (SEQ ID NO: 2827)) and is located in a GenBank (Clark et al., Nucleic Acids Res. 2016 Jan 4; 44(Database issue): D67–D72, PMID: 26590407) transcript (BC012501 not annotated in RefSeq) on chromosome 1 at base pair position 236,065,415-236,065,434. Site 4 has an average INDEL frequency of approximately 2%, has 4 mismatches relative to the on-target gRNA protospacer sequence (5'-CtaGCCCCtACCCTAATaAG-PAM-3', PAM = TGG (SEQ ID NO: 2828)) and is located in intron 1 of a GenBank annotated transcript called polyhomeotic 2 protein (not annotated in RefSeq) on chromosome 1 at base pair position 33,412,659-33,412,678.

gRNA CR00311: The on-target site for gRNA CR00311 showed robust editing at the intended Cas9 cut site with an average INDEL frequency of approximately 95%. Table 31 shows the number of off-target sites successfully characterized. Uncharacterized sites failed in PCR primer design or PCR amplification and remain under investigation. To date no significant off-target activity was observed at sites examined.

gRNA CR000312: The on-target site for gRNA CR000312 showed robust editing at the intended Cas9 cut site with an average INDEL frequency of approximately 98%. Table 31 shows the number of off-target sites successfully characterized. Uncharacterized sites failed in PCR primer design or PCR amplification and remain under investigation. To date no significant off-target activity was observed at sites examined.

gRNA CR000316: The on-target site for gRNA CR000316 showed robust editing at the intended Cas9 cut site in with an average INDEL frequency of approximately 91%, however the majority of off-target sites remain to be characterized.

gRNA CR001125: The on-target site for gRNA CR0001125 showed robust editing at the intended Cas9 cut site with an average INDEL frequency of approximately 91%. Table 31 shows the number of off-target sites successfully characterized. Uncharacterized sites failed in PCR primer design or PCR amplification and remain under investigation. To date no significant off-target activity was observed at sites examined.

gRNA CR001126: The on-target site for gRNA CR0001126 showed robust editing at the intended Cas9 cut site with an average INDEL frequency of approximately 92%. Table 31 shows the number of off-target sites successfully characterized. Uncharacterized sites failed in PCR primer design or PCR amplification and remain under investigation. Characterization of potential off-target sites identified two off-target sites to date in the 100bp window around the proposed Cas9 cut site in both treated replicates. The first site has an average INDEL frequency approximately 2%, has 2 mismatches relative to the on-target gRNA protospacer sequence (5'-TTTATaACAGGCTCCAGaAA -PAM-3', PAM = TGG (SEQ ID NO: 2829)) and is located in an intergenic region on chromosome 4 at base pair position 35,881,815-35,881,834, approximately 9.5kb away from the nearest GenBank transcript (not annotated in RefSeq). The second site has an average INDEL frequency of approximately 1.7%, has 4 mismatches relative to the on-target gRNA protospacer sequence (5' caTATCACAGGCcCCAGGAg -PAM-3', PAM = GGG (SEQ ID NO: 2830)) and is located in intron 6 of the Ataxin 1 gene (ATXN1), on chromosome 6 at base pair position 16,519,907-16,519,926, approximately 2.7kb away from exon 6.

gRNA CR001127: The on-target site for gRNA CR0001127 showed robust editing at the intended Cas9 cut site with an average INDEL frequency of approximately 97%. Table 31 shows the number of off-target sites successfully characterized. Uncharacterized sites failed in PCR primer design or PCR amplification and remain under investigation. To date no significant off-target activity was observed at sites examined.

gRNA CR001128: The on-target site for gRNA CR0001128 showed robust editing at the intended Cas9 cut site with an average INDEL frequency of approximately 94%. Table 31 shows the number of off-target sites successfully characterized. Uncharacterized sites failed in PCR primer design or PCR amplification and remain under investigation. To date no significant off-target activity was observed at sites examined.

Manual inspection of all actively edited BCL11 +58 region off-target sites identified showed typical INDEL patterns surrounding the proposed Cas9 cut site typical of Cas9 mediated double stranded break non homologous end joining DNA repair. It is unclear whether editing at the sites identified has any detrimental effect on gene expression or cell viability, further analysis is required.

Table 31. Counts of *in silico* off-target sites identified, sites successfully characterized in at least one treated replicate and sites that show editing for the BCL11A +58 region gRNAs CR00309, CR00311, CR00312, CR00316, CR001125, CR001126, CR001127, and CR001128 are shown. *only sites with 0-4 nucleotide mismatches were examined.

gRNA name	Total number of *in silico* off-target sites	Number of *in silico* off-target sites characterized	Number of active *in silico* off-target sites identified
CR00309	141	140	4
CR00311	267	245	0
CR00312	165	163	0
CR00316	346	TBD	TBD
CR001125	321	319	0
CR001126	349	348	2
CR001127*	367	365	0
CR001128	207	194	0

BCL11A +58 region GUIDE-Seq hit validation results

Potential off-target hits identified by GUIDE-seq (Tsai et al, Nat Biotechnol. 2015, 33(2):187-97, PMID: 25513782) were characterized in RNP treated and untreated HSPC using targeted sequencing methods described above for *in silico* defined sites. GUIDE-seq potential hits were identified for gRNAs CR00312, CR00316, CR001125, CR001126, CR001127 and CR001128. No potential hits were identified for gRNA CR00311 and CR001128. When the potential hits were interrogated in HSPCs using targeted sequencing, none of the potential hits validated in treated HSPC for gRNA CR00312, CR001125 and CR001127. One potential hit validated for gRNA CR001126, the same site that was identified by the *in silico* directed method in intron 6 of ATXN1 (chromosome 6:16,519,907-16,519,926 base pairs).Validation of potential hits for gRNAs CR00309 and CR00316 is still in progress.

HPFH region *in silico* targeted analysis results

gRNA CR001028: The on-target site for gRNA CR0001028 showed robust editing at the intended Cas9 cut site with an average INDEL frequency of approximately 91%. Table 32 shows the number of off-target sites successfully characterized. Uncharacterized sites failed in PCR primer design or PCR amplification and remain under investigation. Characterization of potential off-target sites identified two off-target sites to date in the 100bp window around the proposed Cas9 cut site in both treated replicates. Site 1 has an average INDEL frequency approximately 2.8%, has 2 mismatches relative to

the on-target gRNA protospacer sequence (5'- TGgGGTGGGGAGATATGaAG -PAM-3', PAM = AGG (SEQ ID NO: 2831)) and is located in intron 2 of a non-coding RNA (LF330410, not annotated in RefSeq) located on chromosome 4 at base pair position 58,169,308-58,169,327. Site 2 has an average INDEL frequency approximately 3.5%, has 3 mismatches relative to the on-target gRNA protospacer sequence (5'- gGaGGTGGGGAGAgATGTAG-PAM-3', PAM = AGG (SEQ ID NO: 2832)) and is located in intron 1 of the Butyrophilin subfamily 3 member A2 gene (BTN3A2) located on chromosome 6 at base pair position 26,366,733-26,366,752, approximately 1.3kb from exon 2.

gRNA CR001030: The on-target site for gRNA CR0001030 showed robust editing at the intended Cas9 cut site with an average INDEL frequency of approximately 89%. Table 32 shows the number of off-target sites successfully characterized. Uncharacterized sites failed in PCR primer design or PCR amplification and remain under investigation. Characterization of potential off-target sites identified one off-target sites to date with average INDEL frequency of 57% in the 100bp window around the proposed Cas9 cut site in both treated replicates. The site has 3 mismatches relative to the on-target gRNA protospacer sequence (5'-caTGCgGAAAGAGATGCGGT-PAM-3', PAM = TGG (SEQ ID NO: 2833)) and is located in exon 4 of the Pyruvate Dehydrogenase Kinase 3 gene (PDK3) located on the X chromosome at base pair position 24,503,476-24,503,495.

gRNA CR001137: The on-target site for gRNA CR0001037 showed robust editing at the intended Cas9 cut site with an average INDEL frequency of approximately 84%. Table 32 shows the number of off-target sites successfully characterized. Uncharacterized sites failed in PCR primer design or PCR amplification and remain under investigation. To date no significant off-target activity was observed at sites examined.

gRNA CR001221: The on-target site for gRNA CR0001221 showed robust editing at the intended Cas9 cut site with an average INDEL frequency of approximately 95%. Table 32 shows the number of off-target sites successfully characterized. Uncharacterized sites failed in PCR primer design or PCR amplification and remain under investigation. To date no significant off-target activity was observed at sites examined.

gRNA CR003035: The on-target site for gRNA CR0003035 showed robust editing at the intended Cas9 cut site with an average INDEL frequency of approximately 89%. Table 32 shows the number of off-target sites successfully characterized. Uncharacterized sites failed in PCR primer design or PCR amplification and remain under investigation. Characterization of potential off-target sites identified two off-target sites to date in the 100bp window around the proposed Cas9 cut site in both treated replicates. Site 1 has an average INDEL frequency of approximately 20%, has 2 mismatches relative to the on-target gRNA protospacer sequence (5'- AGGtACCTCAaACTCAGCAT-PAM-3', PAM = AGG (SEQ ID NO: 2834)) and is located in an intergenic region on chromosome 2 at base pair position 66,281,781-66,281,800 and is approximately 7.1kb from the nearest transcript (JD432564,

not annotated in RefSeq). Site 2 has an average INDEL frequency approximately 2.5%, has 3 mismatches relative to the on-target gRNA protospacer sequence (5'-AGagACCcCAGACTCAGCAT-PAM-3', PAM = AGG (SEQ ID NO: 2835)) and is located in an intergenic region on chromosome 10 at base pair position 42,997,289-42,997,308, and is approximately 0.3kb from MicroRNA 5100 (MIR5100).

gRNA CR003085: The on-target site for gRNA CR0003038 showed robust editing at the intended Cas9 cut site with an average INDEL frequency of approximately 94%. Table 32 shows the number of off-target sites successfully characterized. Uncharacterized sites failed in PCR primer design or PCR amplification and remain under investigation. Characterization of potential off-target sites identified one off-target sites to date with average INDEL frequency of approximately 2% in the 100bp window around the proposed Cas9 cut site in both treated replicates. The site has 3 mismatches relative to the on-target gRNA protospacer sequence (5'-ATGGTATGaGAaaTATACTA-PAM-3', PAM = TGG (SEQ ID NO: 2836)) and is located in intron 2 of the Solute Carrier Family 25 Member 12 gene (SLC25A12) located on chromosome 2 at base pair position 171,872,630-171,872,649, and is approximately 3.8kb from exon 3.

Manual inspection of all actively edited HPFH region off-target sites identified showed typical INDEL patterns surrounding the proposed Cas9 cut site typical of Cas9 mediated double stranded break non homologous end joining DNA repair. It is unclear whether editing at the sites identified has any detrimental effect on gene expression or cell viability, further analysis is required.

Table 32. Counts of potential *in silico* off-target sites identified, sites successfully characterized in at least one treated replicate and sites that show editing for the HPFH region gRNAs CR001028, CR001030, CR001137, CR001221, CR003035 and CR003085 are shown.

gRNA name	Total number of *in silico* off-target sites	Number of *in silico* off-target sites characterized	Number of active *in silico* off-target sites identified
CR001028	233	217	2
CR001030	224	219	1
CR001137	113	109	0
CR001221	229	224	0
CR003035	249	243	2
CR003085	96	95	1

HPFH region GUIDE-Seq hit validation results

Potential off-target hits identified using GUIDE-seq (Tsai et al, Nat Biotechnol. 2015, 33(2):187-97, PMID: 25513782) were interrogated in RNP treated and untreated HSPC using the same methods described for *in silico* sites. GUIDE-seq potential off-target hits were identified for gRNA CR001028, CR001030, CR003035 and CR003085 (to date). No hits were identified for gRNAs CR001137 and CR001221 to date. One hit for gRNA CR001028 validated in HSPC, the same site that was identified by the *in silico* directed method on chromosome 4 at base pair position 58,169,308-58,169,327. One hit validated for gRNA CR001030 in HSPC, the same site that was identified by the *in silico* directed method in exon 4 of the PDK3 gene. One hit validated for gRNA CR003035 in HSPC, the same site that was identified by the *in silico* directed method in the intergenic region of chromosome 2 at base pair position 66,281,781-66,281,800. One hit validated for gRNA CR003085 in HSPC, the same site as was identified by the *in silico* directed method on chromosome 2 at base pair position 171,872,630-171,872,649.

On-target analysis for gRNA editing efficiency screening

PCR amplicons targeting the gRNA on-target site were cleaned up using Agencourt AMPure XP beads (Beckman Coulter, Cat # A63882) following the manufacture's recommendations. Samples were quantified using the Quant-iT PicoGreen dsDNA kit (Thermo Fisher, Cat # P7581) using manufacture's recommendations. Amplicons were transformed into Illumina sequencing libraries using the Nextera DNA Library Preparation Kit (Illumina, Cat# FC-121-1031) following the manufacture's recommendations. Resulting sequencing libraries were AMPure bead cleaned up, qPCR quantified, pooled and sequenced with an Illumina MiSeq instrument using 150 base (Illumina, Cat# MS-102-2002) or 250 base (Illumina, Cat# MS-102-2003) paired-end reads as described in the off-target analysis section. For each library a minimum of a 1000-fold sequencing coverage was generated and variants were called using a series of in house scripts. In short, sequencing reads spanning an 80-100 base pair window centered on the gRNA sequence were identified using a string based sequence search, compared to the amplicon sequence, binned by sequence differences and variant frequencies were calculated. Additionally, sequencing reads were aligned to the amplicon sequence using the Illumina MiSeq reporter software (Illumina version 2.6.1) and resulting read alignments were examined using the Integrative Genome Viewer (IGV version 2.3, Robinson et al, Nat Biotechnol. 2011, 9(1):24-6, PMID: 21221095).

Example 10: **Evaluation of RNP Concentration On Gene Editing and HbF Induction**

RNP dilution assay to determine optimal RNP concentration for gene editing

Gene editing was performed using a serial dilution of Cas9 (iProt: 106331) and guide ribonucleotide complexes (RNP) concentrations (Table 33). Various gRNA used, their formats, and modification applied in this assay are listed in Table 34.

Table 33: RNP dilution used to investigate RNP concentration effect on gene editing and HbF induction.

gRNA Format	RNP Components	RNP Conc RNP-1	RNP Conc RNP-2	RNP Conc RNP-3	RNP Conc RNP-4	RNP Conc RNP-5
Single gRNA	**crRNA(ug)**	3	1.5	0.75	0.37	0.18
	Cas9(ug)	3	1.5	0.75	0.37	0.18
	RNP(uM)	1.94	0.97	0.48	0.24	0.12
Dual gRNA	**crRNA(ug)**	3.86	1.93	0.97	0.48	0.24
	tracrRNA(ug)	3.86	1.93	0.97	0.48	0.24
	Cas9(ug)	3.86	1.93	0.97	0.48	0.24
	RNP(uM)	5.89	2.94	1.47	0.74	0.37

Table 34: List of gRNAs, in single or dual guide format, with or without chemical modification used in the RNP dilution assay. "OMePS" modification, with respect to dgRNA format, refers to modified crRNA having the following structure: mN*mN*mN*NNNNNNNNNNNNNNNNNGUUUUAGAGCUAUGCUGUU*mU*mU*mG (SEQ ID NO: 2837) paired with unmodified tracr (i.e., tracrRNA) of SEQ ID NO: 6660; and with respect to sgRNA, refers to a gRNA having the following structure: mN*mN*mN*NNNNNNNNNNNNNNNNNGUUUUAGAGCUAGAAAUAGCAAGUUAAAAUAAGGCUAGUCCGUUAUCAACUUGAAAAAGUGGCACCGAGUCGGUGCmU*mU*mU*U (SEQ ID NO: 2838), where N = a nucleotide of the targeting domain, mN refers to a 2'-OMe-modified nucelotide, and * refers to a phosphorothioate bond. "Unmodified" refers to a gRNA having no RNA modifications: dgRNA consist of NNNNNNNNNNNNNNNNNNGUUUUAGAGCUAUGCUGUUUUG (SEQ ID NO: 2839) paired with SEQ ID NO: 6660; sgRNA refer to NNNNNNNNNNNNNNNNNNGUUUUAGAGCUAGAAAUAGCAAGUUAAAAUAAGGCUAGUCCGUUAUCAACUUGAAAAAGUGGCACCGAGUCGGUGCUUUU (SEQ ID NO: 2840), where N = the nucleotides of the indicated targeting domain.

gRNA Format	Sample ID	gRNA Targeting Domain ID	gRNA Modification
Dual gRNA	1	CR00312	Unmodified

	2	CR001128	Unmodified
	3	CR00312	OMePS
	4	CR001128	OMePS
Single gRNA	5	CR00312	Unmodified
	6	CR001128	Unmodified
	7	CR00312	OMePS
	8	CR001128	OMePS
	9	Mock electroporation control	N/A

CD34+ cells were electroporated as described previously, and subjected to measurement of cell viability, gene editing efficiency, and ability to produce HbF. When assessing cell viability, the results showed that varying RNP concentration had no impact on cell viability upon electroporation, either when single or dual guide format is used (Figure 39A and Figure 39B). Upon gene editing of CD34+ cells, NGS data showed that RNP concentrations down to 1.47 uM achieved maximum % gene editing efficiency for umodified CR00312 and CR001128, and modified CR00312, while maximum % gene editing efficiency for modified CR001228 was achieved at RNP concentrations as low as 2.94 uM (Figure 40A). For sgRNA formats, all gRNAs tested achieved maximum % editigin at RNP concnetrations down to 0.48 uM (Figure 40B). In measuring the ability of gene edited cells to differentiate into erythroid lineage and produce HbF, our data showed that the RNP concentration down to 2.94 uM for dgRNA-containing RNP (Figure 41A) and down to 0.97 uM for sgRNA-containing RNP (Figure 41B) resulted in maximum levels of HbF induction.

This application is being filed with a sequence listing. To the extent there are any discrepancies between the sequence listing and any sequence recited in the specification, the sequence recited in the specification should be considered the correct sequence. Unless otherwise indicated, all genomic locations are according to hg38.

INCORPORATION BY REFERENCE

All publications, patents, and patent applications mentioned herein are hereby incorporated by reference in their entirety as if each individual publication, patent or patent application was

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specifically and individually indicated to be incorporated by reference. In case of conflict, the present application, including any definitions herein, will control.

EQUIVALENTS

Those skilled in the art will recognize, or be able to ascertain using no more than routine experimentation, many equivalents to the specific embodiments of the invention described herein. While this invention has been disclosed with reference to specific aspects, it is apparent that other aspects and variations of this invention may be devised by others skilled in the art without departing from the true spirit and scope of the invention. The appended claims are intended to be construed to include all such aspects and equivalent variations.

The reference in this specification to any prior publication (or information derived from it), or to any matter which is known, is not, and should not be taken as an acknowledgment or admission or any form of suggestion that that prior publication (or information derived from it) or known matter forms part of the common general knowledge in the field of endeavour to which this specification relates.

Throughout this specification and the claims which follow, unless the context requires otherwise, the word "comprise", and variations such as "comprises" and "comprising", will be understood to imply the inclusion of a stated integer or step or group of integers or steps but not the exclusion of any other integer or step or group of integers or steps.

EDITORIAL NOTE

Patent No. 2016381313

Please notionally renumber claims pages 447 to 455

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THE CLAIMS DEFINING THE INVENTION ARE AS FOLLOWS:

1. A gRNA molecule comprising, from 5' to 3', [targeting domain]-SEQ ID NO: 7811, wherein said targeting domain comprises SEQ ID NO: 253.

2. The gRNA molecule of claim 1, wherein the targeting domain and said SEQ ID NO: 7811 are disposed on a single nucleic acid molecule, and wherein said single nucleic acid molecule comprises said targeting domain and said SEQ ID NO: 7811 that is disposed immediately 3' to said targeting domain.

3. The gRNA molecule of claim 1 or 2, wherein said nucleic acid molecule comprises:
(a) three phosphorothioate modifications at the 3' end of said nucleic acid molecule;
(b) three phosphorothioate modifications at the 5' end of said nucleic acid molecule;
(c) three 2'-O-methyl modifications at the 3' end of said nucleic acid molecule;
(d) three 2'-O-methyl modifications at the 5' end of said nucleic acid molecule;
(e) a 2' O-methyl modification at each of the 4th-to-terminal or 3rd-to-terminal 3' residues of said nucleic acid molecule;
(f) a 2' O-methyl modification at each of the 3rd-to-terminal 5' residues of said nucleic acid molecule; or
(g) any combination thereof.

4. The gRNA molecule of any one of claims 1-3, comprising the sequence of cuaacaguugcuuuuaucacguuuuagagcuagaaauagcaaguuaaaauaaggcuaguccguuaucaacuugaaaaaguggcaccgagu cggugcuuuu.

5. The gRNA molecule of any one of claims 1-4, comprising:

5'
csusasACAGUUGCUUUUAUCACGUUUUAGAGCUAGAAAUAGCAAGUUAAAAUAAGGCUAGUCCGUUAUCAACUUGAAAAAGUGGCACCGAGUCGGUGCususU 3',
wherein a, c, g, u are 2'-O-methyl residues; s is phosphorothioate; and A, C, G, U are RNA residues.

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6. A composition comprising:
(a) the gRNA molecule of any one of claims 1-5 and a Cas9 molecule;
(b) the gRNA molecule of any one of claims 1-5 and a polynucleotide comprising a nucleic acid sequence encoding a Cas9 molecule;
(c) a polynucleotide comprising a nucleic acid sequence encoding the gRNA molecule of any one of claims 1-5 and a Cas9 molecule; or
(d) a polynucleotide comprising a nucleic acid sequence encoding the gRNA molecule of any one of claims 1-5 and a polynucleotide comprising a nucleic acid sequence encoding a Cas9 molecule.

7. A composition comprising the gRNA molecule of any one of claims 1-5, further comprising a Cas9 molecule.

8. The composition of claim 6 or 7, wherein the Cas9 molecule is an active or inactive *S. pyogenes* Cas9.

9. The composition of any one of claims 6-8, wherein the Cas9 molecule comprises SEQ ID NO: 6611.

10. The composition of any one of claims 6-9, wherein the Cas9 molecule comprises:
(a) SEQ ID NO: 7821;
(b) SEQ ID NO: 7822;
(c) SEQ ID NO: 7823;
(d) SEQ ID NO: 7824;
(e) SEQ ID NO: 7825;
(f) SEQ ID NO: 7826;
(g) SEQ ID NO: 7827;
(h) SEQ ID NO: 7828;
(i) SEQ ID NO: 7829;
(j) SEQ ID NO: 7830; or
(k) SEQ ID NO: 7831.

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11. The composition of any one of claims 7-10, wherein the gRNA molecule and the Cas9 molecule are present in a ribonuclear protein (RNP) complex.

12. The composition of any one of claims 6-11, formulated in a medium suitable for electroporation.

13. The composition of any one of claims 6-12, wherein said RNP is at a concentration of less than about 10uM.

14. A nucleic acid sequence that encodes the gRNA molecule of any one of claims 1-5.

15. The nucleic acid sequence of claim 14, further comprising a promoter operably linked to the nucleic acid sequence that encodes the gRNA molecule.

16. The nucleic acid sequence of claim 15, wherein the promoter is a promoter recognized by an RNA polymerase II or RNA polymerase III.

17. The nucleic acid sequence of claim 16, wherein the promoter is a U6 promoter or an HI promoter.

18. The nucleic acid sequence of any one of claims 14-17, further comprising a nucleic acid sequence that encodes a Cas9 molecule.

19. The nucleic acid sequence of claim 18, wherein the Cas9 molecule comprises SEQ ID NO: 6611, SEQ ID NO: 7821, SEQ ID NO: 7822, SEQ ID NO: 7823, SEQ ID NO: 7824, SEQ ID NO: 7825, SEQ ID NO: 7826, SEQ ID NO: 7827, SEQ ID NO: 7828, SEQ ID NO: 7829, SEQ ID NO: 7830, or SEQ ID NO: 7831.

20. The nucleic acid sequence of any one of claims 18-19, further comprising a promoter operably linked to the nucleic acid sequence that encodes a Cas9 molecule.

21. The nucleic acid sequence of claim 20, wherein the promoter is an EF-1 promoter, a CMV IE gene promoter, an EF-1α promoter, an ubiquitin C promoter, or a phosphoglycerate kinase (PGK) promoter.

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22. A vector comprising the nucleic acid sequence of any one of claims 14-21.

23. The vector of claim 22, wherein the vector is selected from the group consisting of a lentiviral vector, an adenoviral vector, an adeno-associated viral (AAV) vector, a herpes simplex virus (HSV) vector, a plasmid, a minicircle, a nanoplasmid, and an RNA vector.

24. A method of altering a cell at or near a target sequence within said cell, comprising contacting said cell with:
(a) the gRNA molecule of any one of claims 1-5 and a Cas9 molecule;
(b) the gRNA molecule of any one of claims 1-5 and a polynucleotide comprising a nucleic acid sequence encoding a Cas9 molecule;
(c) a nucleic acid molecule encoding the gRNA molecule of any one of claims 1-5 and a Cas9 molecule;
(d) a nucleic acid molecule encoding the gRNA molecule of any one of claims 1-5 and a polynucleotide comprising a nucleic acid encoding a Cas9 molecule;
(e) the composition of any one of claims 6-13; or
(f) the vector of any one of claims 22-23.

25. The method of claim 24, wherein the gRNA molecule or the nucleic acid molecule encoding the gRNA molecule, and the Cas9 molecule or the polynucleotide comprising a nucleic acid sequence encoding the Cas9 molecule, are formulated in a single composition.

26. The method of claim 25, wherein the gRNA molecule or the nucleic acid molecule encoding the gRNA molecule, and the Cas9 molecule or the polynucleotide comprising a nucleic acid sequence encoding the Cas9 molecule, are formulated in more than one composition.

27. The method of claim 26, wherein the more than one composition are delivered simultaneously or sequentially.

28. The method of claim 27, wherein the cell is a hematopoietic stem or progenitor cell (HSPC), a CD34+ cell, a CD34+CD90+ cell or a cell disposed in a composition comprising a population of cells that has been enriched for CD34+ cells.

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29. The method of any one of claims 24-28, wherein the cell is a CD34+ cell.

30. The method of any one of claims 24-29, wherein the cell has been isolated from bone marrow, mobilized peripheral blood, or umbilical cord blood.

31. The method of any one of claims 24-30, wherein the altering results in an indel at or near a genomic DNA sequence complementary to the targeting domain of the gRNA molecule.

32. The method of claim 31, wherein the indel is an indel shown in SEQ ID NOs: 2040-2046.

33. The method of claim 31 or 32, wherein the method results in a population of cells, wherein at least about 50% of said population of cells have been altered.

34. The method of any one of claims 24-33, wherein the altering results in a cell that is capable of differentiating into a differentiated cell of an erythroid lineage, and wherein said differentiated cell produces at least about 6 picograms fetal hemoglobin per cell.

35. A cell, altered by the method of any one of claims 24-32.

36. A cell, comprising the gRNA molecule of any one of claims 1-5, the composition of any one of claims 6-13, the nucleic acid of any one of claims 14-21, or the vector of claim 22 or 23.

37. The cell of claim 35 or 36, wherein expression of fetal hemoglobin is increased in said cell or its progeny relative to a cell or its progeny of the same cell type that has not been modified to comprise a gRNA molecule.

38. The cell of any one of claims 35-37, wherein the differentiated cell of an erythroid lineage produces at least about 6 picograms fetal hemoglobin per cell.

39. The cell of any one of claims 35-38, wherein the cell has been contacted with a stem cell expander.

40. The cell of claim 39, wherein the stem cell expander is compound 1, compound 2, compound 3, compound 4, or a combination thereof.

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41. The cell of any one of claims 35-40, comprising an indel at or near a genomic DNA sequence complementary to the targeting domain of a gRNA molecule of any one of claims 1-5.

42. The cell of claim 41, wherein the indel is an indel shown in SEQ ID NOs: 2040-2046.

43. The cell of any one of claims 35-42, wherein the cell is an animal cell.

44. The cell of claim 43, wherein the cell is a mammalian, a primate, or a human cell.

45. The cell of any one of claims 35-44, wherein the cell is a hematopoietic stem or progenitor cell (HSPC), a CD34+ cell, a CD34+CD90+ cell, or a cell isolated from bone marrow, mobilized peripheral blood, or umbilical cord blood.

46. The cell of any one of claims 35-45, wherein the cell is a CD34+ cell.

47. A population of cells comprising the cell of any one of claims 35-46.

48. The population of cells of claim 47, wherein at least about 50% of said population of cells are a cell according to any one of claims 35-46.

49. The population of cells of claim 47 or 48, wherein the population of cells is capable of differentiating into a population of differentiated cells of an erythroid lineage, and wherein said population of differentiated cells has an increased fraction of F cells relative to a population of unmodified cells of the same type.

50. The population of cells of claim 49, wherein the F cells of the population of differentiated cells produce an average of at least about 6 picograms fetal hemoglobin per cell.

51. The population of cells of any one of claims 47-50, comprising:
(a) at least 1e6 CD34+ cells per kg body weight of a patient to whom the cells are to be administered;
(b) at least 2e6 CD34+ cells per kg body weight of a patient to whom the cells are to be administered;

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(c) at least 3e6 CD34+ cells per kg body weight of a patient to whom the cells are to be administered;
(d) at least 4e6 CD34+ cells per kg body weight of a patient to whom the cells are to be administered; or
(e) from 2e6 to 10e6 CD34+ cells per kg body weight of a patient to whom the cells are to be administered,
wherein the CD34+ cells are a cell according to any one of claims 35-46.

52. The population of cells of any one of claims 47-51, wherein at least about 40% of said population of cells are CD34+ cells.

53. The population of cells of claim 52, wherein at least about 10% of said population of cells of the population are CD34+CD90+ cells.

54. The population of cells of any one of claims 47-53, wherein the population of cells is isolated from bone marrow, mobilized peripheral blood, or umbilical cord blood.

55. The population of cells of any one of claims 47-54, wherein the population of cells are isolated from a patient that has a hemoglobinopathy.

56. A composition comprising the cell of any one of claims 35-46, or the population of cells of any one of claims 47-55.

57. The composition of claim 56, comprising a pharmaceutically acceptable medium suitable for cryopreservation.

58. A method of treating a hemoglobinopathy, comprising administering to a patient the cell of any one of claims 35-46, the population of cells of any one of claims 47-55, or the composition of claim 56 or 57.

59. The method of claim 58, wherein the hemoglobinopathy is beta-thalassemia or sickle cell disease.

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60. A method of increasing fetal hemoglobin expression in a mammal, comprising administering to a patient the cell of any one of claims 35-46, the population of cells of any one of claims 47-55, or the composition of claim 56 or 57.

61. A method of preparing a population of cells comprising:
(a) providing a population of HSPCs;
(b) culturing said population of HSPCs ex vivo in a cell culture medium comprising a stem cell expander; and
(c) introducing into said population of HSPCs the gRNA molecule of any one of claims 1-5, a nucleic acid molecule encoding the gRNA molecule of any one of claims 1-5, the composition of any one of claims 6-13, the nucleic acid of any one of claims 14-21, or the vector of claim 22 or 23.

62. The method of claim 61, wherein the stem cell expander is compound 1, compound 2, compound 3, compound 4, or a combination thereof.

63. The method of claim 61, wherein the cell culture medium comprises the stem cell expander at a concentration ranging from about 1 nM to about 1 mM.

64. The method of claim 61, wherein the period of culturing before the introducing step (c) is at least 12 hours.

65. The method of any one of claims 61-64, further comprising a period of culturing step after the introducing step (c).

66. The method of claim 65, wherein the period of culturing step after the introducing step (c) is at least 12 hours.

67. The method of any one of claims 61-66, wherein the population of cells is expanded at least 4-fold, relative to cells which are not cultured according to step (b).

68. The method of any one of claims 61-67, wherein the introducing of step (c) comprises an electroporation.

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69. The method of any one of claims 61-68, wherein the population of HSPCs provided in step (a) is a population of human cells.

70. The method of claim 69, wherein the population of HSPCs provided in step (a) is isolated from bone marrow, peripheral blood, umbilical cord blood, or bone marrow of a patient suffering from a hemoglobinopathy.

71. The method of any one of claims 61-70, wherein the population of HSPCs provided in step (a) is enriched for CD34+ cells.

72. The method of any one of claims 61-71, wherein subsequent to the introducing step (c), the population of HSPCs is cryopreserved.

73. The method of any one of claims 61-72, wherein after the introducing step (c), at least about 50%, at least about 60%, at least about 70%, at least about 80%, at least about 90%, at least about 95%, at least about 96%, at least about 97%, at least about 98% or at least about 99% of the cells of the population of cells comprise an indel at or near a genomic DNA sequence complementary to the targeting domain of the gRNA molecule.

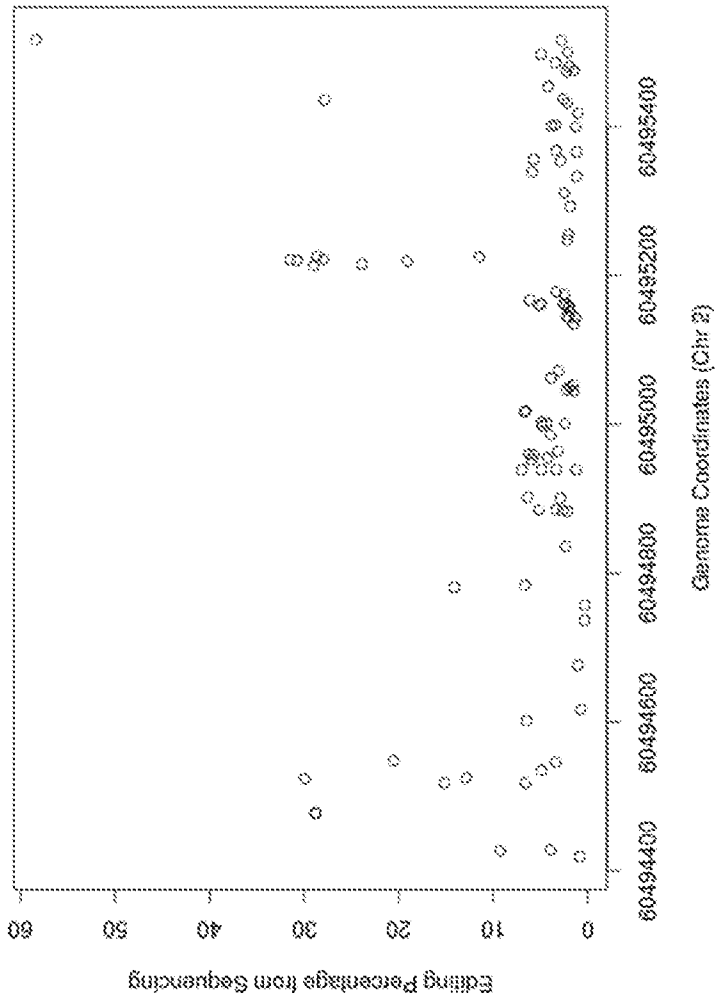
74. The method of claim 73, wherein the indel in each of said cells of the population of cells is an indel shown in SEQ ID NOs: 2040-2046.

75. A cell or a population of cells, prepared by the method of any one of claims 61-74.

76. Use of the gRNA molecule of any one of claims 1-5, the composition of any one of claims 6-13 and 56-57, the nucleic acid of any one of claims 14-21, the vector of claim 22 or 23, the cell of any one of claims 35-46 and 75, or the population of cells of any one of claims 47-55, in the manufacture of a medicament for the treatment of a hemoglobinopathy.

77. The use of claim 76, wherein the hemoglobinopathy is beta-thalassemia or sickle cell disease.

Figure 1


+58 Editing Efficiency by Location
Editing Percentage from Sequencing
0
10
20
30
40
50
60
60494400
60494600
60494800
60495000
60495200
60495400
Genome Coordinates (Chr 2)

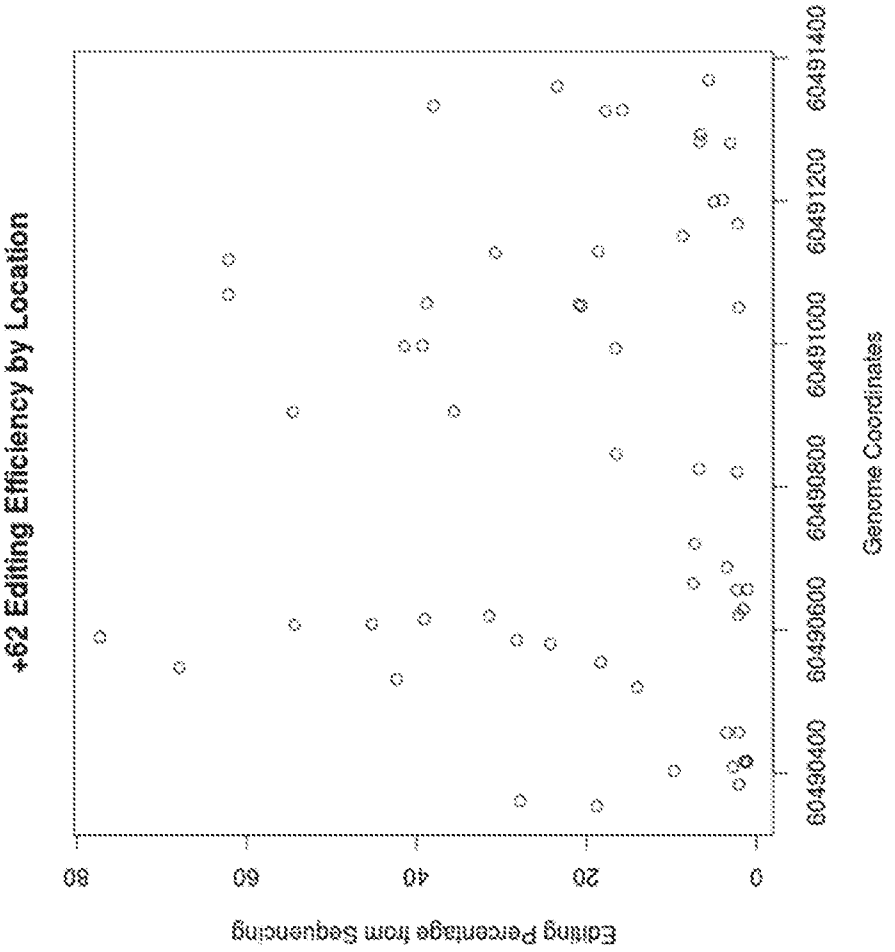

+62 Editing Efficiency by Location
Editing Percentage from Sequencing
0
20
40
60
80
Genome Coordinates
60490400
60490600
60490800
60491000
60491200
60491400

Figure 2

Figure 3

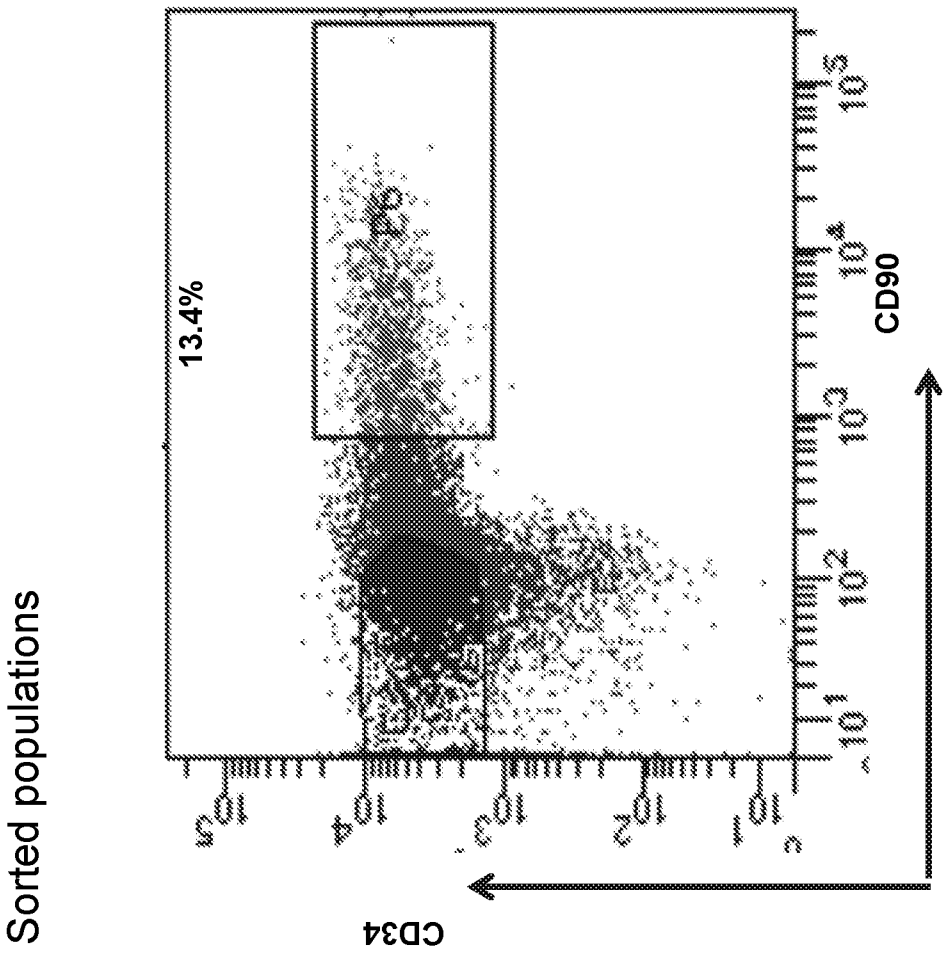


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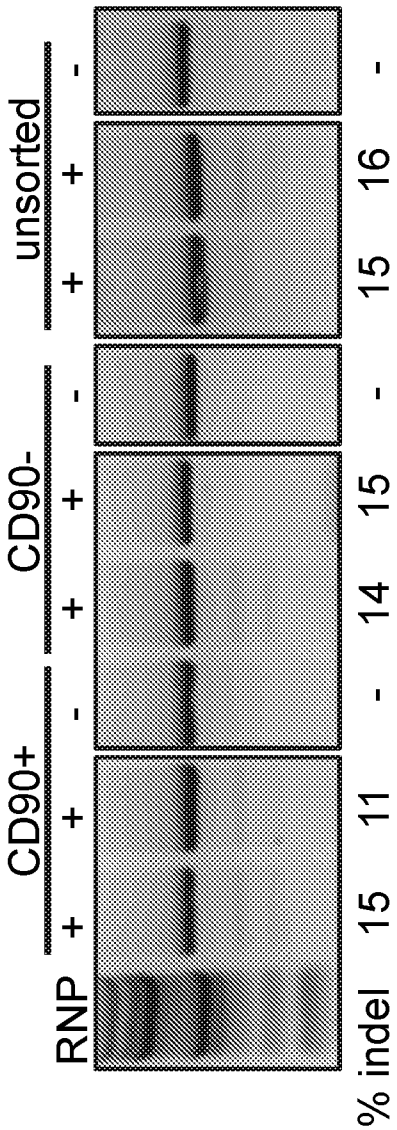


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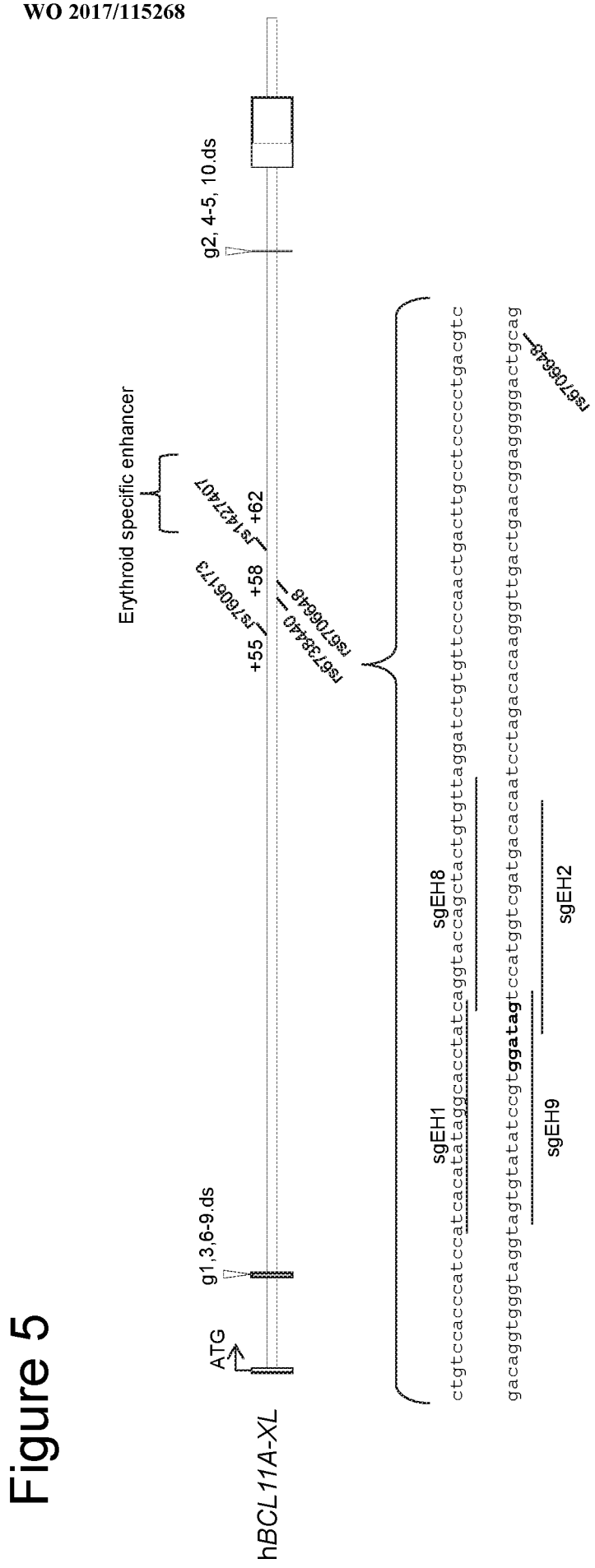

hBCL11A-XL
ATG
g1,3,6-9.ds
Erythroid specific enhancer
+55
+58
+62
g2, 4-5, 10.ds
sgEH1
sgEH8
sgEH9
sgEH2
ctgtccacccatccatcacatataggcacctatcaggtaccagctactgtgttaggatctgttcccaactgacttgcctcccccctgacgtc
gacaggtgggtaggtagtgtatatccgtggatagtccatggtcgatgacacaatcctagacacaaggggttgactgaacggaggggactgcag

Figure 6A/B

A

sgEH1	Total indel %	cacccatccatcacatataggcacct-atcaggtacc agctactgtgttaggatcctg	Average %
		cacccatccatcacatataggcacctTatcaggtacc agctactgtgttaggatcctg	17
exp1.1	67	cacccatccatcacatataggc------ ---tacc agctactgtgttaggatcctg	10
		cacccatccatcacatataggcacc--atcaggtacc agctactgtgttaggatcctg	4
		cacccatccatcacatataggcacctTatcaggtacc agctactgtgttaggatcctg	20
exp1.2	82	cacccatccatcacatataggc------ ---tacc agctactgtgttaggatcctg	14
		cacccatccatcacatat---------- aggtacc agctactgtgttaggatcctg	7
		cacccatccatcacatataggcacctTatcaggtacc agctactgtgttaggatcctg	26
exp2.1	95	cacccatccatcacatataggc------ ---tacc agctactgtgttaggatcctg	16
		cacccatccatcacatat---------- aggtacc agctactgtgttaggatcctg	7
		cacccatccatcacatataggcacctTatcaggtacc agctactgtgttaggatcctg	22
exp2.2	92	cacccatccatcacatataggc------ ---tacc agctactgtgttaggatcctg	20
		cacccatccatcacatat---------- aggtacc agctactgtgttaggatcctg	6

B

sgEH2	Total indel %	cacccatccatcacatataggcacctatc-aggtacc agctactgtgttaggatcctg	Average %
		cacccatccatcacatataggcacctAatcAaggtacc agctactgtgttaggatcctg	23
exp1.1	83	cacccatccatcacatataggc------ ---tacc agctactgtgttaggatcctg	8
		cacccatccatcacatataggcacctatc--ggtacc agctactgtgttaggatcctg	7
		cacccatccatcacatataggcacctAatcAaggtacc agctactgtgttaggatcctg	24
exp1.2	84	cacccatccatcacatataggcacc---------- agctactgtgttaggatcctg	8
		cacccatccatcacatataggcacctatc--ggtacc agctactgtgttaggatcctg	7
		cacccatccatcacatataggcacctAatcAaggtacc agctactgtgttaggatcctg	24
exp2.1	92	cacccatccatcacatataggcacctatc--ggtacc agctactgtgttaggatcctg	8
		cacccatccatcacatataggcacc---------- agctactgtgttaggatcctg	7
		cacccatccatcacatataggcacctAatcAaggtacc agctactgtgttaggatcctg	12
exp2.2	81	cacccatccatcacatataggcacc---------- agctactgtgttaggatcctg	11
		cacccatccatcacatataggcacctatc--ggtacc agctactgtgttaggatcctg	9

The same microhomology was used for both sgRNAs.

Figure 6C/D

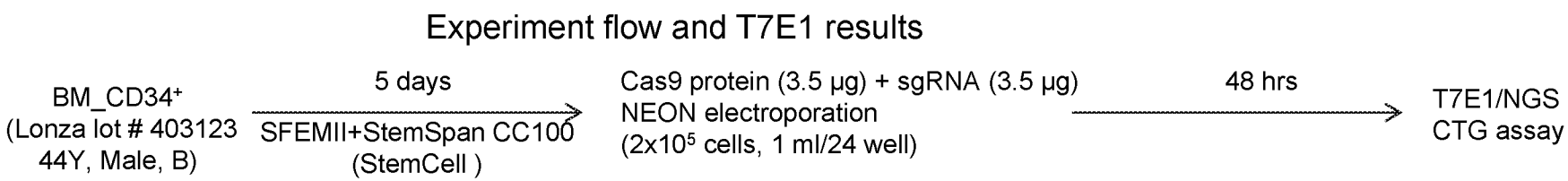
C

	Total indel %	ggcacctatcaggtaccagctactgt-gttaggatctgtgttcccaactgacttgcctccc	GATA1 deleted	Average %
		ggcacctatcaggtaccagctactgt**T**gttaggatctgtgttcccaactgacttgcctccc	No	8
sgEH8.exp1.1	30	ggcacctatcaggtaccagctact---gttaggatctgtgttcccaactgacttgcctccc	No	3
		ggcacctatcaggtaccagcta----------ctgtgttcccaactgacttgcctccc	No	2
		ggcacctatcaggtaccagctactgt**T**gttaggatctgtgttcccaactgacttgcctccc	No	9
sgEH1.exp1.2	29	ggcacctatcaggtaccagctact---gttaggatctgtgttcccaactgacttgcctccc	No	4
		ggcacctatcaggtaccagcta----------ctgtgttcccaactgacttgcctccc	No	1
		ggcacctatcaggtaccagctactgt**T**gttaggatctgtgttcccaactgacttgcctccc	No	9
sgEH1.exp2.1	32	ggcacctatcaggtaccagctact---gttaggatctgtgttcccaactgacttgcctccc	No	4
		ggcacctatcaggtaccagcta----------ctgtgttcccaactgacttgcctccc	No	1
		ggcacctatcaggtaccagctactgt**T**gttaggatctgtgttcccaactgacttgcctccc	No	9
sgEH1.exp2.2	32	ggcacctatcaggtaccagctact---gttaggatctgtgttcccaactgacttgcctccc	No	4
		ggcacctatcaggtaccagcta----------ctgtgttcccaactgacttgcctccc	No	1

D

	Total indel %	ttttcatctgtcgggctgtccacccatccatcacatataggcacctatcaggtaccagct	GATA1 deleted	Average %
		ttttcatctgtcgggctgtccacccatccatca--tataggcacctatcaggtaccagct	No	41
sgEH9.exp1.1	81	ttttcatctgtcgggctgtccacccatccat-----ataggcacctatcaggtaccagct	No	3
		ttttcatctgtcgggctgtccacccatccatca----------ggtaccagct	Yes	3
		ttttcatctgtcgggctgtccacccatccatca--tataggcacctatcaggtaccagct	No	42
sgEH9.exp1.2	80	ttttcatctgtcgggctgtccacccatccat-----ataggcacctatcaggtaccagct	No	4
		ttttcatctgtcgggctgtccacccatccatca----------ggtaccagct	Yes	2
		ttttcatctgtcgggctgtccacccatccatca--tataggcacctatcaggtaccagct	No	44
sgEH9.exp2.1	86	ttttcatctgtcgggctgtccacccatccatca----------ggtaccagct	Yes	5
		ttttcatctgtcgggctgtccacccatccat-----ataggcacctatcaggtaccagct	No	4
		ttttcatctgtcgggctgtccacccatccatca--tataggcacctatcaggtaccagct	No	47
sgEH9.exp2.2	92	ttttcatctgtcgggctgtccacccatccat-----ataggcacctatcaggtaccagct	No	4
		ttttcatctgtcgggctgtccacccatccatca----------ggtaccagct	Yes	3

Figure 7



	Total indel %	Sequences of the top 3 most frequent indels	Average %
Ref		CCTGTGGGCAGTGCCAGATGAACTTCC-CATTGGGGGACATTCTTATTTTTATCGAGCACA	
g7_1_1		CCTGTGGGCAGTGCCAGATGAACTTC--CATTGGGGGACATTCTTATTTTTATCGAGCACA	23
g7_1_2	88	CCTGTGGGCAGTGCCAGATGAACTT---CATTGGGGGACATTCTTATTTTTATCGAGCACA	14
g7_1_3		CCTGTGGGCAGTGCCAGATGAACTTCCCCATTGGGGGACATTCTTATTTTTATCGAGCACA	5
g7_2_1		CCTGTGGGCAGTGCCAGATGAACTTC--CATTGGGGGACATTCTTATTTTTATCGAGCACA	24
g7_2_2	92	CCTGTGGGCAGTGCCAGATGAACTT---CATTGGGGGACATTCTTATTTTTATCGAGCACA	14
g7_2_3		CCTGTGGGCAGTGCCAGATGAACTTCCCCATTGGGGGACATTCTTATTTTTATCGAGCACA	5
Ref		TTTTATCGAGCACAAACGGAAA**CAA**TG**CAA**TGGCAGCCTCTGCTTAGAAAAAGCTGTGGA	
g8_1_1		TTTTATCGAGCACAAACGGAAA-----**CAA**TGGCAGCCTCTGCTTAGAAAAAGCTGTGGA	39
g8_1_2	92	TTTTATCGAGCACAAACGGAAACAATG-A**A**TGGCAGCCTCTGCTTAGAAAAAGCTGTGGA	15
g8_1_3		TTTTATCGAGCACAAACGGAAA**CAA**T-**CAA**TGGCAGCCTCTGCTTAGAAAAAGCTGTGGA	3
g8_2_1		TTTTATCGAGCACAAACGGAAA-----**CAA**TGGCAGCCTCTGCTTAGAAAAAGCTGTGGA	35
g8_2_2	94	TTTTATCGAGCACAAACGGAAACAATG-A**A**TGGCAGCCTCTGCTTAGAAAAAGCTGTGGA	19
g8_2_3		TTTTATCGAGCACAAACGGAAACAAT-**CAA**TGGCAGCCTCTGCTTAGAAAAAGCTGTGGA	3
Ref		ATGAGT**GCAG**AATATGCCCC**GCAG**GTATTTGTAAGTTGAGCCTTATTTCTTCTACGAAA	
g2_1_1	85	ATGAGT--------------**GCAG**GTATTTGTAAGTTGAGCCTTATTTCTTCTAC-AAA	15
g2_1_2		ATGAGTGCAGAATAT-----**GCAG**GTATTTGTAAGTTGAGCCTTATTTCTTCTAC-AAA	12
g2_1_3		ATGAGTGCAGAATATGCCC-**GCAG**GTATTTGTAAGTTGAGCCTTATTTCTTCTACGAAA	10

Figure 8

GGGCAGTGCCAGATGAACTTCCCATTGGGGGACATTCTTATTTTTATCGAGCACAAACGGAAACAATGCAATGGCAGC

g7 g8

Reg: 5′-GTTTTAGAGCTAGAAATAGCAAGTTAAAATAAGGCTAGTCCGTTATCAACTTGAAAAAGTGGCACCGAGTCGGTGCTTTT

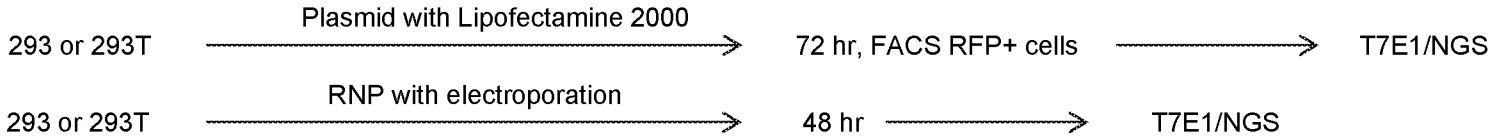
BC: 5′-GTTTAAGAGCTATGCTGGAAACAGCATAGCAAGTTTAAATAAGGCTAGTCCGTTATCAACTTGAAAAAGTGGCACCGAGTCGGTGCTTTT

Experiment flow

BM_CD34+ (Lonza lot # 402754 Donor 27328: 33 years, Female, Race: C) → 5 days, SFEMII+StemSpan CC100 (StemCell) → Cas9 protein (3.75ug) + sgRNA (3.75 ug) NEON electroporation ($2x10^5$ cells, 1 ml/24 well) → 48 hrs → T7E1/NGS CTG

	Total Indel %	Sequences of the top 3 most frequent indels	Average %
g7Ref		AGTGCCAGATGAACTTCC-CATTGGGGGACATTCTTATTTTTA	
g7BC_1_1		AGTGCCAGATGAACTTC--CATTGGGGGACATTCTTATTTTTA	19
g7BC_1_2	38	AGTGCCAGATGAACTT---CATTGGGGGACATTCTTATTTTTA	8
g7BC_1_3		AGTGCCAGATGAACTTCCCCATTGGGGGACATTCTTATTTTTA	6
g7BC_2_1		AGTGCCAGATGAACTTC--CATTGGGGGACATTCTTATTTTTA	13
g7BC_2_2	33	AGTGCCAGATGAACTT---CATTGGGGGACATTCTTATTTTTA	5
g7BC_2_3		AGTGCCAGATGAACTTCCCCATTGGGGGACATTCTTATTTTTA	4

Figure 9



cell line_number Vehicle/method	Total Indel %	CCTGTGGGCAGTGCCAGATGAACTTCC-CATTGGGGGACATTCTTATTTTTATCGAGCACA	AVG %
293_300K Plasmid/Lipo2000	71	CCTGTGGGCAGTGCCAGATGAACTTC--CATTGGGGGACATTCTTATTTTTATCGAGCACA	13%
		CCTGTGGGCAGTGCCAGATGAACTT---CATTGGGGGACATTCTTATTTTTATCGAGCACA	6%
		CCTGTGGGCAGTGCCAGATGAACTTCCCCATTGGGGGACATTCTTATTTTTATCGAGCACA	5%
293_600K Plasmid/Lipo2000	56	CCTGTGGGCAGTGCCAGATGAACTTC--CATTGGGGGACATTCTTATTTTTATCGAGCACA	14%
		CCTGTGGGCAGTGCCAGATGAACTTC---ATTGGGGGACATTCTTATTTTTATCGAGCACA	9%
		CCTGTGGGCAGTGCCAGATGAACTTCCCCATTGGGGGACATTCTTATTTTTATCGAGCACA	3%
293_1500K RNP/electroporation.1	96	CCTGTGGGCAGTGCCAGATGAACTTC--CATTGGGGGACATTCTTATTTTTATCGAGCACA	22%
		CCTGTGGGCAGTGCCAGATGAACTT---CATTGGGGGACATTCTTATTTTTATCGAGCACA	9%
		CCTGTGGGCAGTGCCAGATGAA------CATTGGGGGACATTCTTATTTTTATCGAGCACA	5%
293_1500K RNP/electroporation.1	96	CCTGTGGGCAGTGCCAGATGAACTTC--CATTGGGGGACATTCTTATTTTTATCGAGCACA	21%
		CCTGTGGGCAGTGCCAGATGAACTT---CATTGGGGGACATTCTTATTTTTATCGAGCACA	10%
		CCTGTGGGCAGTGCCAGATGAA------CATTGGGGGACATTCTTATTTTTATCGAGCACA	5%
293T_300K Plasmid/Lipo2000	73	CCTGTGGGCAGTGCCAGATGAACTTC--CATTGGGGGACATTCTTATTTTTATCGAGCACA	15%
		CCTGTGGGCAGTGCCAGATGAACTTCCCCATTGGGGGACATTCTTATTTTTATCGAGCACA	5%
		CCTGTGGGCAGTGCCAGATGAACTT---CATTGGGGGACATTCTTATTTTTATCGAGCACA	6%
293T_600K Plasmid/Lipo2000	69	CCTGTGGGCAGTGCCAGATGAACTTC--CATTGGGGGACATTCTTATTTTTATCGAGCACA	10%
		CCTGTGGGCAGTGCCAGATGAACTTCCCCATTGGGGGACATTCTTATTTTTATCGAGCACA	5%
		CCTGTGGGCAGTGCCAGATGAACTTCC---TTGGGGGACATTCTTATTTTTATCGAGCACA	3%
293T_1500K RNP/electroporation.1	72	CCTGTGGGCAGTGCCAGATGAACTTC--CATTGGGGGACATTCTTATTTTTATCGAGCACA	10%
		CCTGTGGGCAGTGCCAGATGAA------CATTGGGGGACATTCTTATTTTTATCGAGCACA	7%
		CCTGTGGGCAGTGCCAGATGAACTT---CATTGGGGGACATTCTTATTTTTATCGAGCACA	4%
293T_1500K RNP/electroporation.1	75	CCTGTGGGCAGTGCCAGATGAACTTC--CATTGGGGGACATTCTTATTTTTATCGAGCACA	11%
		CCTGTGGGCAGTGCCAGATGAA------CATTGGGGGACATTCTTATTTTTATCGAGCACA	7%
		CCTGTGGGCAGTGCCAGATGAACTT---CATTGGGGGACATTCTTATTTTTATCGAGCACA	5%

Figure 10

Sequences of the top 2 most frequent indels	Average hit% (% of overall indel)
g7Ref GGGCAGTGCCAGATGAACTTCCCATTGGGGACATTCTTATTTTTATCGAGCACAAACGGAAACAATGCAATGGTAGCCTCTGCTTAGAAAAAGC	
g7/8reg_1_1 GGGCAGTGCCAGATGAACTTCCC----------AATGGTAGCCTCTGCTTAGAAAAAGC	64
g7/8reg_1_2 GGGCAGTGCCAGATGAACTTCCCATTGGGGACATTCTTATTTTTATCGAGCACAAAC-----AATGCAATGGTAGCCTCTGCTTAGAAAAAGC	7
g7/8reg_2_1 GGGCAGTGCCAGATGAACTTCCC----------AATGGTAGCCTCTGCTTAGAAAAAGC	64
g7/8reg_2_2 GGGCAGTGCCAGATGAACTTCCCATTGGGGACATTCTTATTTTTATCGAGCACAAAC-----AATGCAATGGTAGCCTCTGCTTAGAAAAAGC	8
g7/8BC_1_1 GGGCAGTGCCAGATGAACTTCCC----------AATGGTAGCCTCTGCTTAGAAAAAGC	39
g7/8BC_1_2 GGGCAGTGCCAGATGAACTTCC----------AATGGTAGCCTCTGCTTAGAAAAAGC	4
g7/8BC_2_1 GGGCAGTGCCAGATGAACTTCCC----------AATGGTAGCCTCTGCTTAGAAAAAGC	26
g7/8BC_2_1 GGGCAGTGCCAGATGAACTTCC----------AATGGTAGCCTCTGCTTAGAAAAAGC	9

Figure 11

Targeting Domain ID	Species	Strand	Target Sequence Location	mean % indel formation in CD34+ cells (NGS)	SD
CR001131	h	-	Chr2:60495250-60495272	54%	5%
CR000310	h	-	Chr2:60495219-60495241	51%	9%
CR000312	h	-	Chr2:60495221-60495243	46%	4%
CR000311	h	-	Chr2:60495220-60495242	44%	2%
CR000309	h	+	Chr2:60495215-60495237	38%	7%
CR000313	h	-	Chr2:60495222-60495244	36%	7%
CR000308	h	-	Chr2:60495213-60495235	33%	9%
CR000260	h	-	Chr2:60494781-60494803	33%	2%
CR000315	h	-	Chr2:60495226-60495248	32%	6%
CR000314	h	-	Chr2:60495225-60495247	31%	5%
CR001124	h	-	Chr2:60495214-60495236	26%	2%
CR000245	h	+	Chr2:60494477-60494499	25%	1%
CR000246	h	+	Chr2:60494478-60494500	24%	0%
CR001126	h	-	Chr2:60495216-60495238	17%	6%
CR001127	h	-	Chr2:60495220-60495242	7%	2%

Figure 12

Targeting Domain ID	Species	Strand	Location	Mean % indel formation in CD34+ cells (NGS)	SD (%)
CR000211	h	-	Chr2:60491069-60491091	59%	5
CR000205	h	-	Chr2:60490997-60491019	54%	1
CR000206	h	-	Chr2:60490998-60491020	53%	6
CR000187	h	-	Chr2:60490590-60490612	46%	2
CR000203	h	-	Chr2:60490906-60490928	44%	0
CR000212	h	+	Chr2:60491118-60491140	40%	2
CR000191	h	-	Chr2:60490620-60490642	38%	8
CR000215	h	+	Chr2:60491151-60491173	37%	7
CR000204	h	-	Chr2:60490994-60491016	35%	2
CR000208	h	-	Chr2:60491053-60491075	32%	7
CR000183	h	-	Chr2:60490547-60490569	31%	7
CR000210	h	-	Chr2:60491057-60491079	29%	7
CR000202	h	-	Chr2:60490905-60490927	28%	6
CR000182	h	-	Chr2:60490531-60490553	28%	4
CR000174	h	-	Chr2:60490403-60490425	28%	7

Figure 13

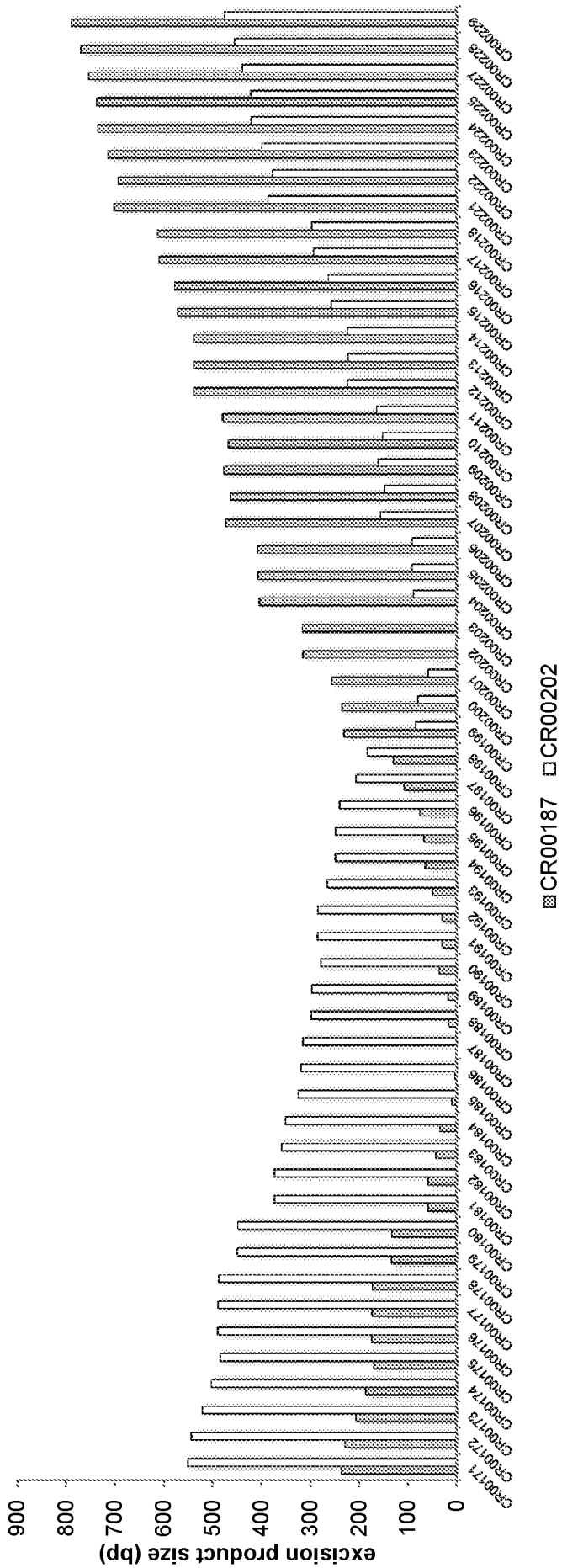

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200
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400
500
600
700
800
900
CR00187
CR00202

Figure 14

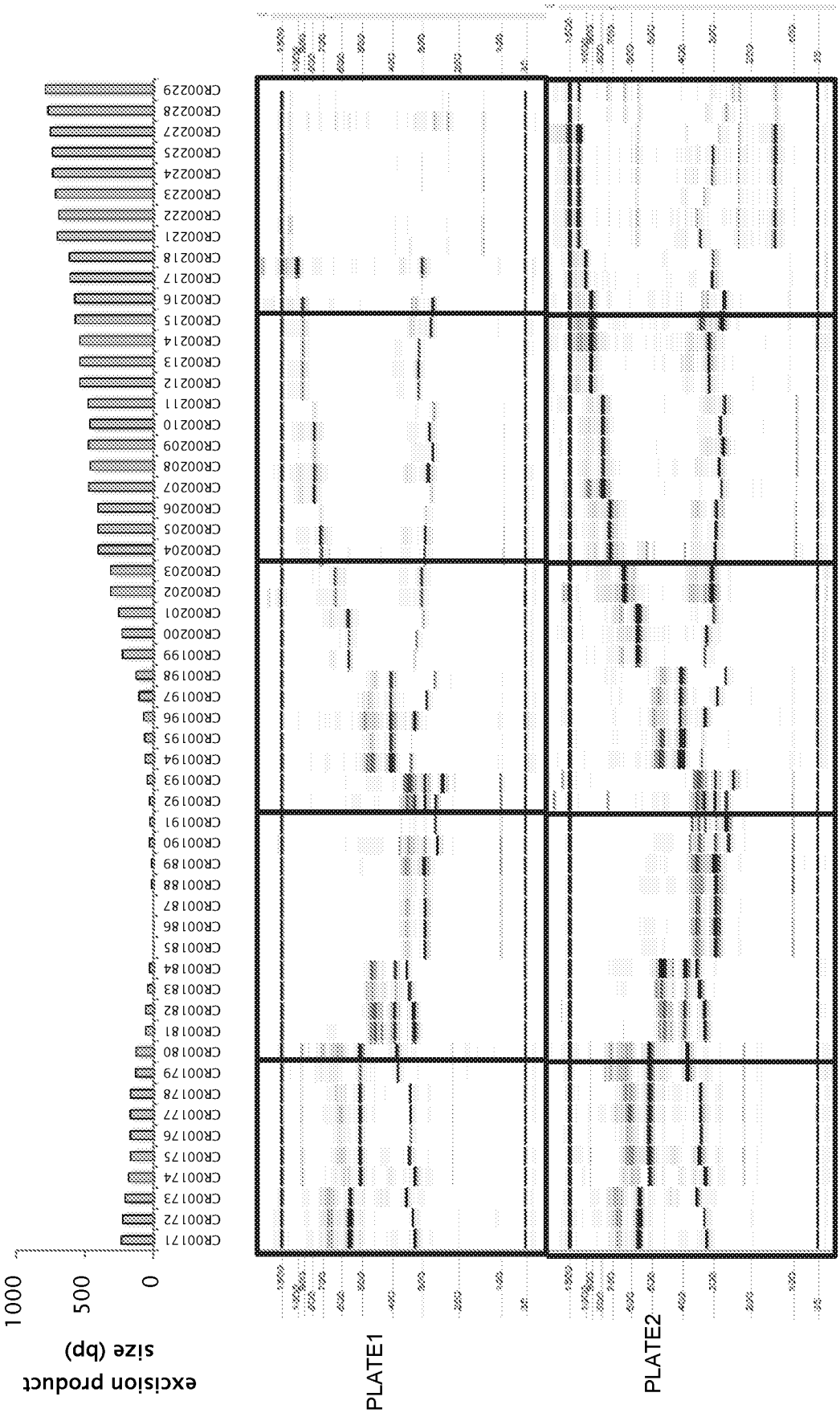


Figure 15

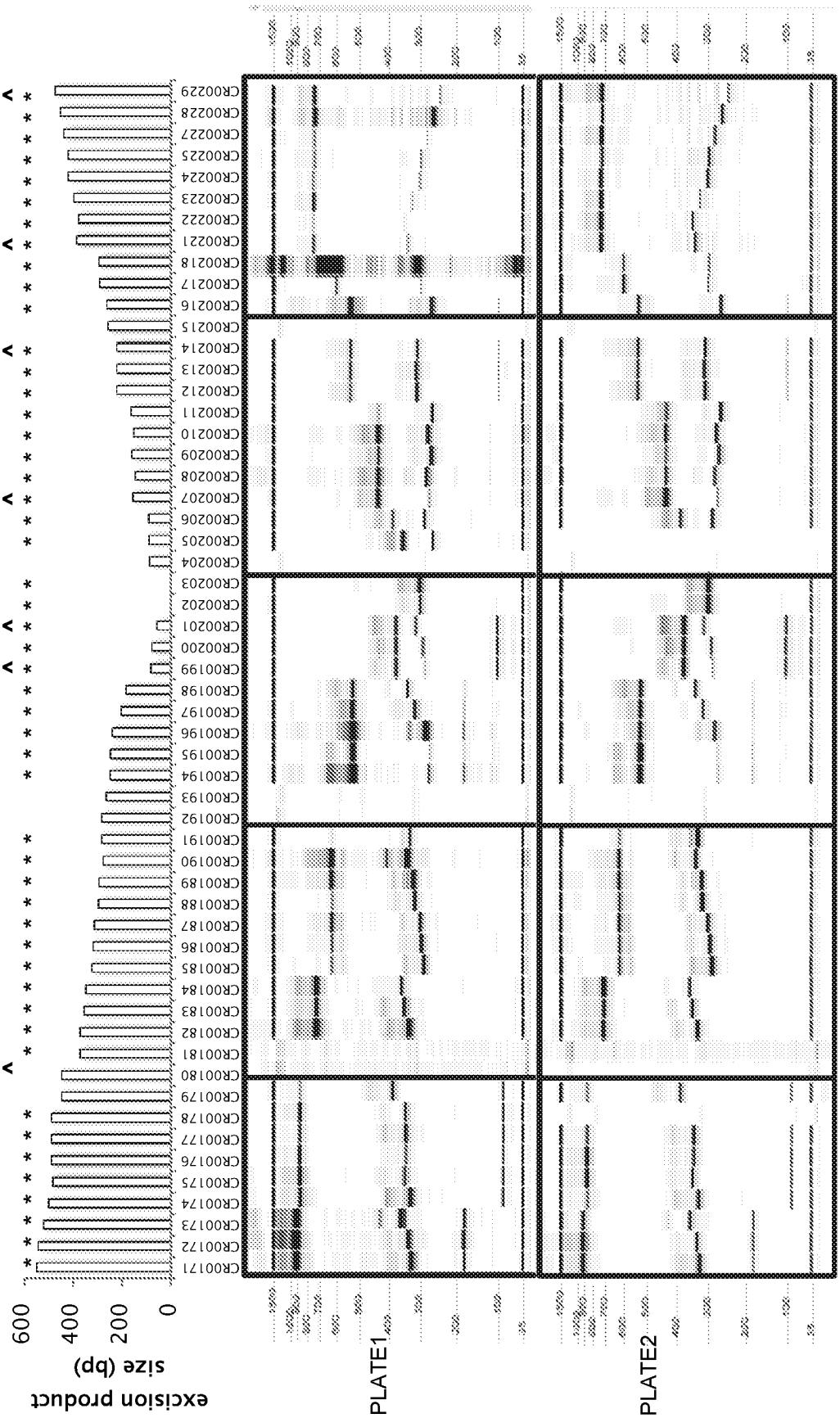


Figure 16

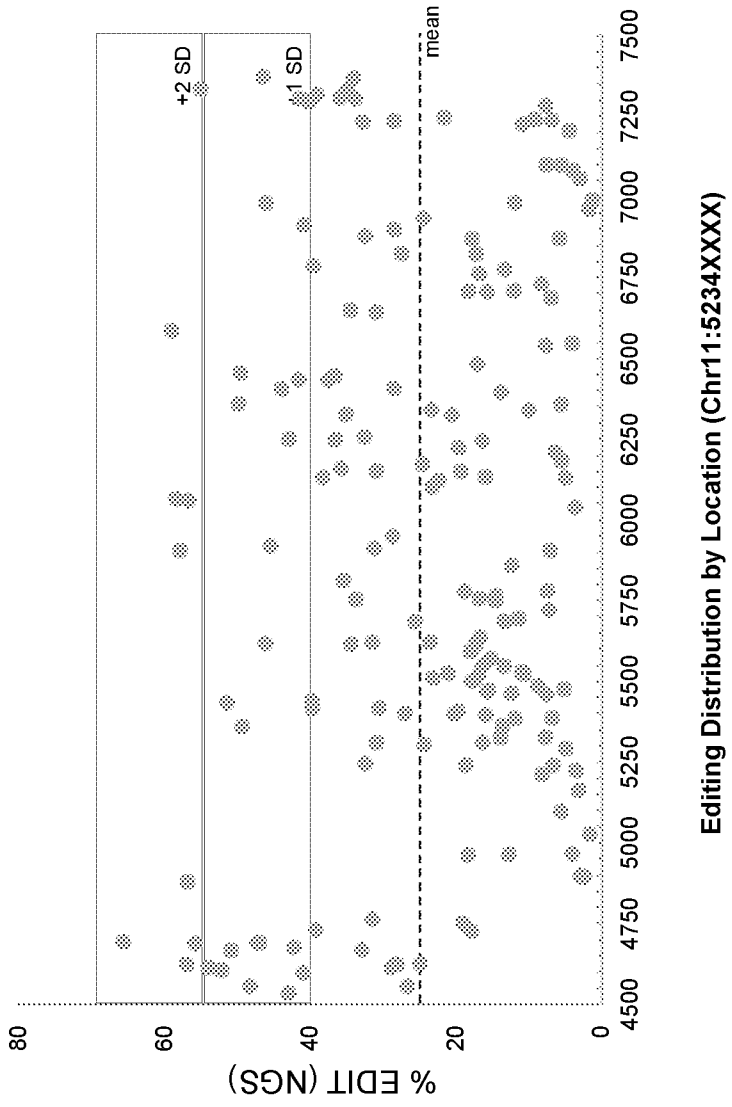

% EDIT (NGS)
80
60
40
20
0
4500
4750
5000
5250
5500
5750
6000
6250
6500
6750
7000
7250
7500
+2 SD
+1 SD
mean
Editing Distribution by Location (Chr11:5234XXXX)

Figure 17

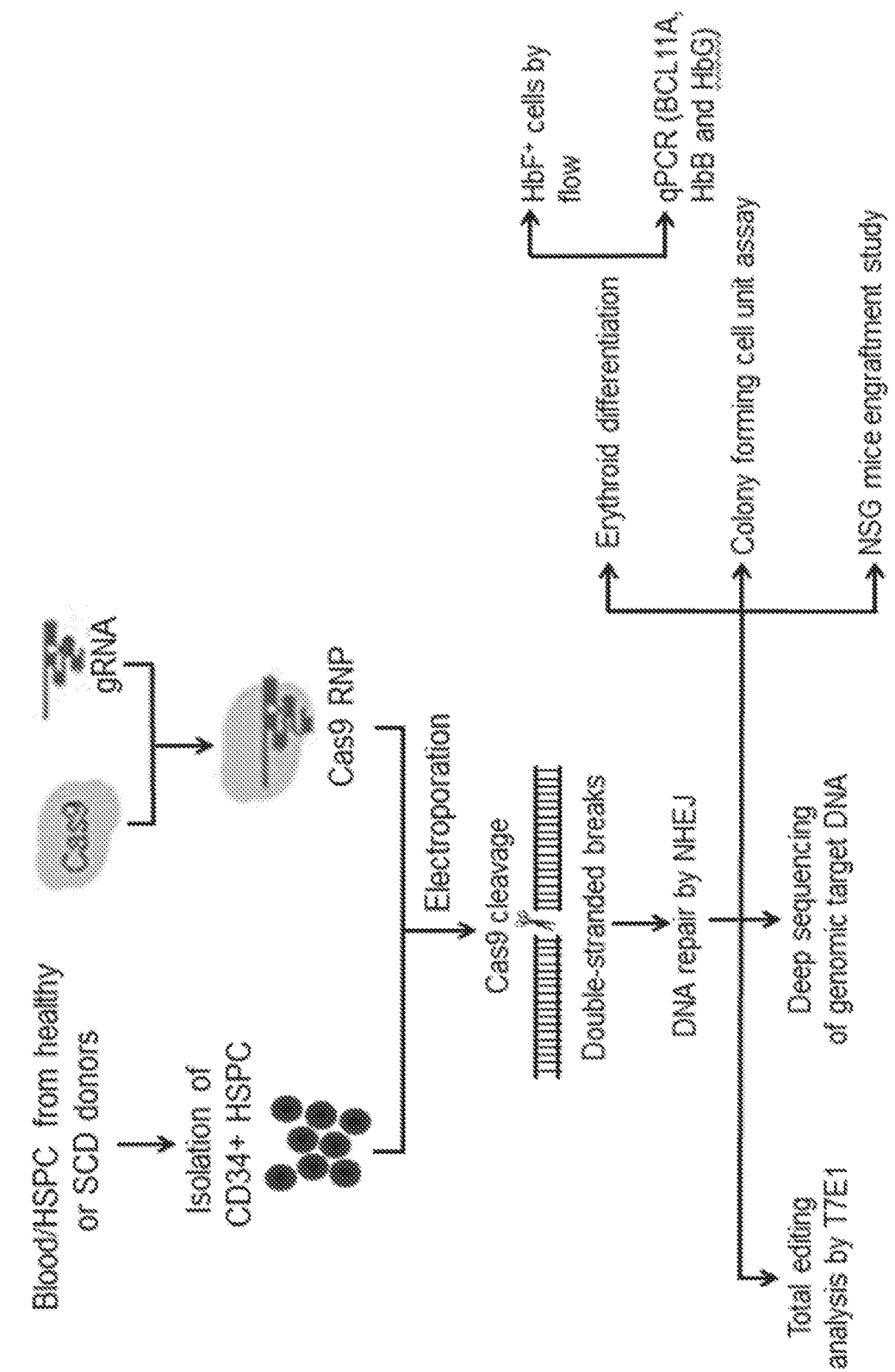

Blood/HSPC from healthy or SCD donors
Isolation of CD34+ HSPC
Cas9
gRNA
Cas9 RNP
Electroporation
Cas9 cleavage
Double-stranded breaks
DNA repair by NHEJ
Total editing analysis by T7E1
Deep sequencing of genomic target DNA
Erythroid differentiation
HbF+ cells by flow
qPCR (BCL11A, HbB and HbG)
Colony forming cell unit assay
NSG mice engraftment study

Figure 18

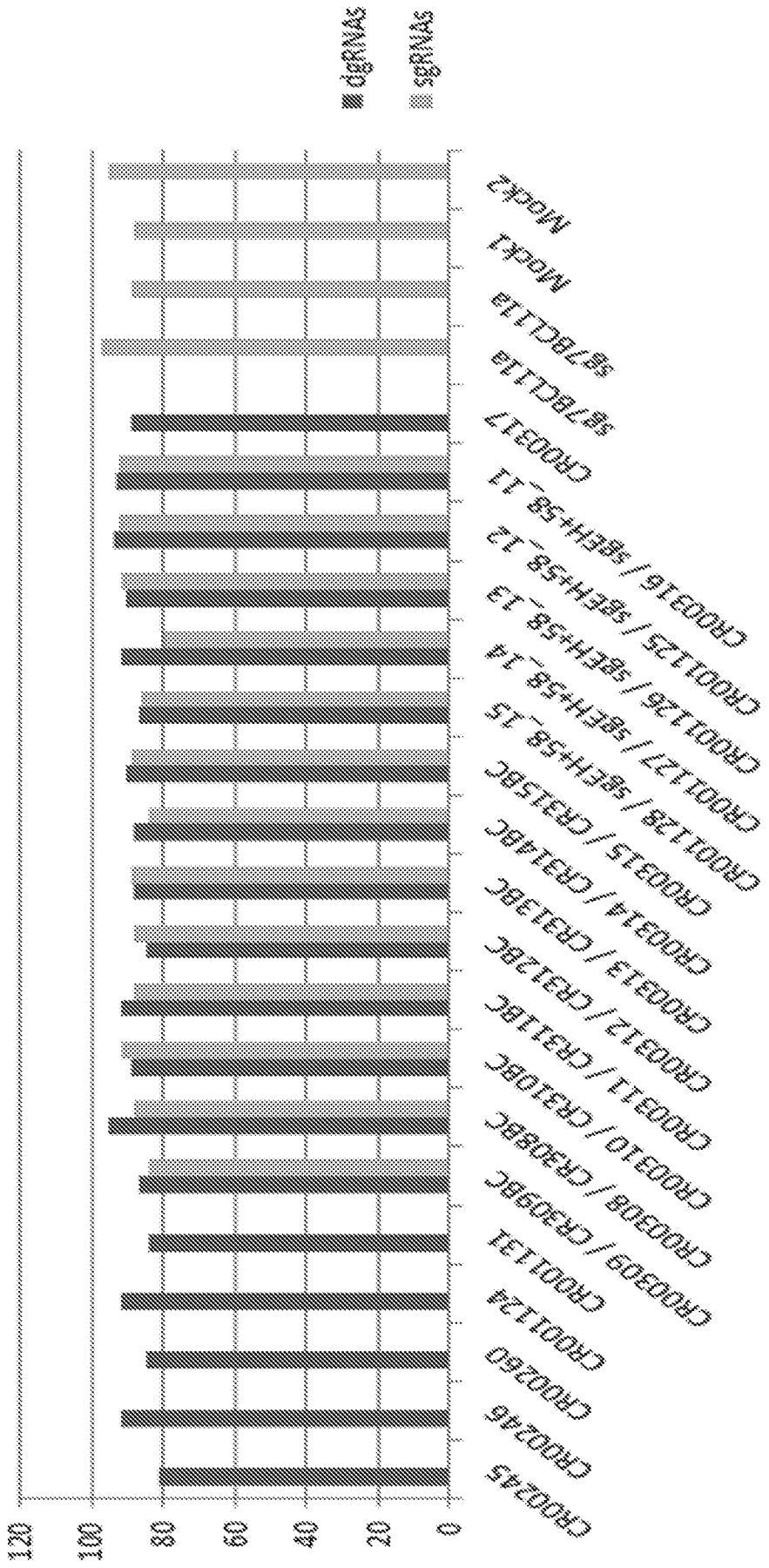

dgRNAs
sgRNAs
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100
80
60
40
20
0
CR002345
CR002346
CR002360
CR001124
CR001131
CR003309 / CR3098C
CR003308 / CR3088C
CR003310 / CR3108C
CR003311 / CR3118C
CR003312 / CR3128C
CR003313 / CR3138C
CR003314 / CR3148C
CR003315 / CR3158C
CR001128 / sgEH+58_15
CR001127 / sgEH+58_14
CR001126 / sgEH+58_13
CR001125 / sgEH+58_12
CR003116 / sgEH+58_11
CR003117
sg7BCL13
sg7BCL12
Mock1
Mock2

Figure 19

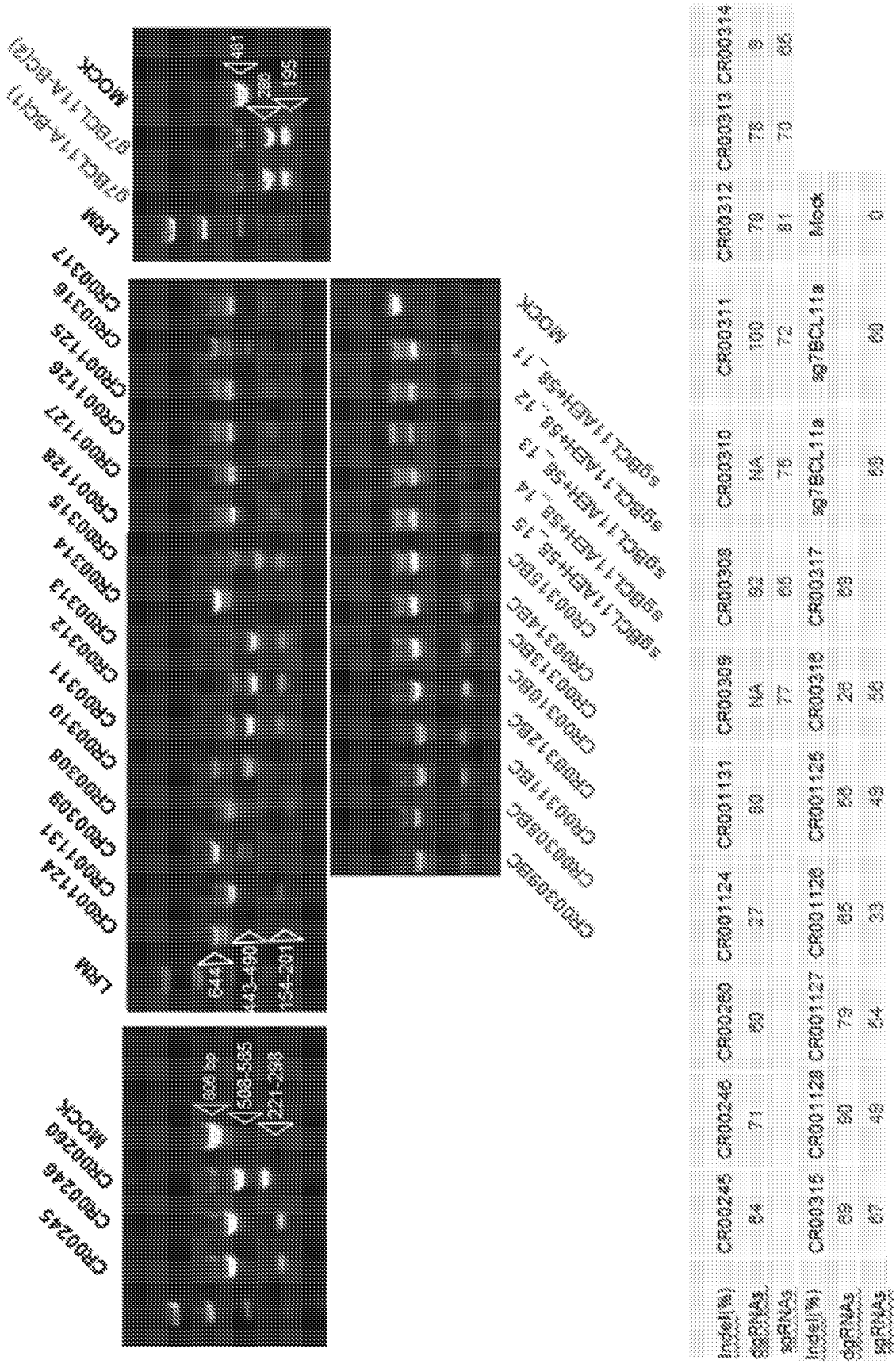
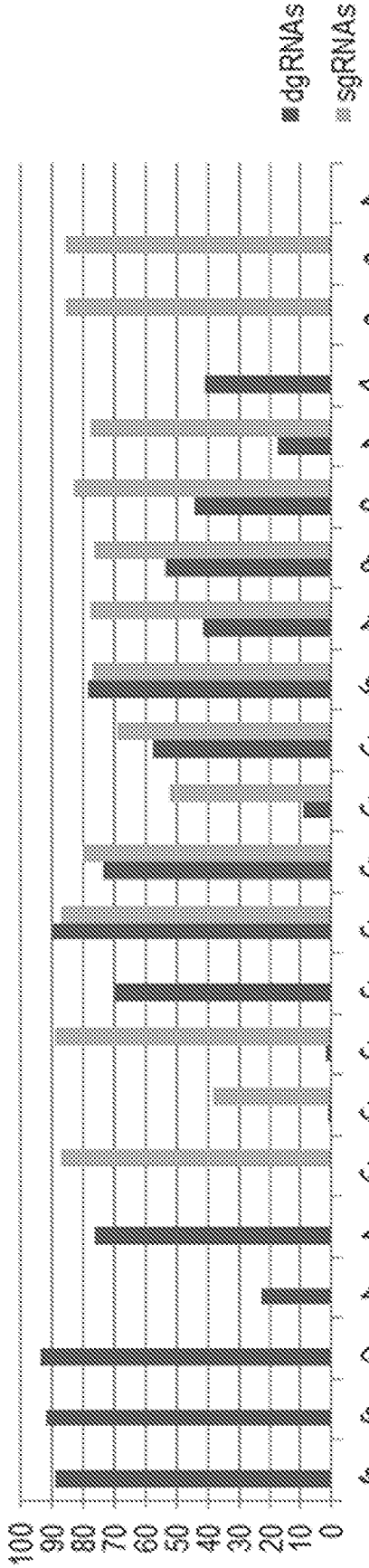

CR00245
CR00246
CR00260
MOCK
LRM
CR00124
CR00113
CR00130
CR00309
CR00308
CR00310
CR00311
CR00312
CR00313
CR00314
sgRNAs
Indel(%)
CR00316
CR00128
CR00127
CR00129
CR00125
CR00131
CR00309
CR00308
CR00317
%BCL11a
Mock
84
71
80
37
80
NA
82
NA
100
78
78
8
89
80
79
86
86
28
89
89
0
67
49
64
23
49
56
69
60

Figure 20



NGS Indel (%)	CR00245	CR00246	CR00260	CR001124	CR001131	CR00309/ CR309BC	CR00308/ CR308BC	CR00310/ CR310BC	CR00311/ CR311BC	CR00312/ CR312BC	CR00313/ CR313BC
dgRNAs	88.65	91.38	93.68	22.74	76.33	0.83	1.55	1.87	69.43	89.83	73.84
sgRNAs						86.83	38.28	89.05		86.84	80.35

NGS Indel (%)	CR00314/ CR314BC	CR00315/ CR315BC	CR001128/ sgEH+58_15sgEH+58_14sgEH+58_13sgEH+58_12sgEH+58_11	CR001127/	CR001126/	CR001123/	CR00316/	CR00317	sg7BCL11a	sg7BCL11a	Mock1
dgRNAs	9.09	57.34	78.2	41.39	53.68	44.35	17.21	40.69			
sgRNAs	51.82	69.17	77.07	77.46	76.18	82.9	77.37		85.57	85.8	

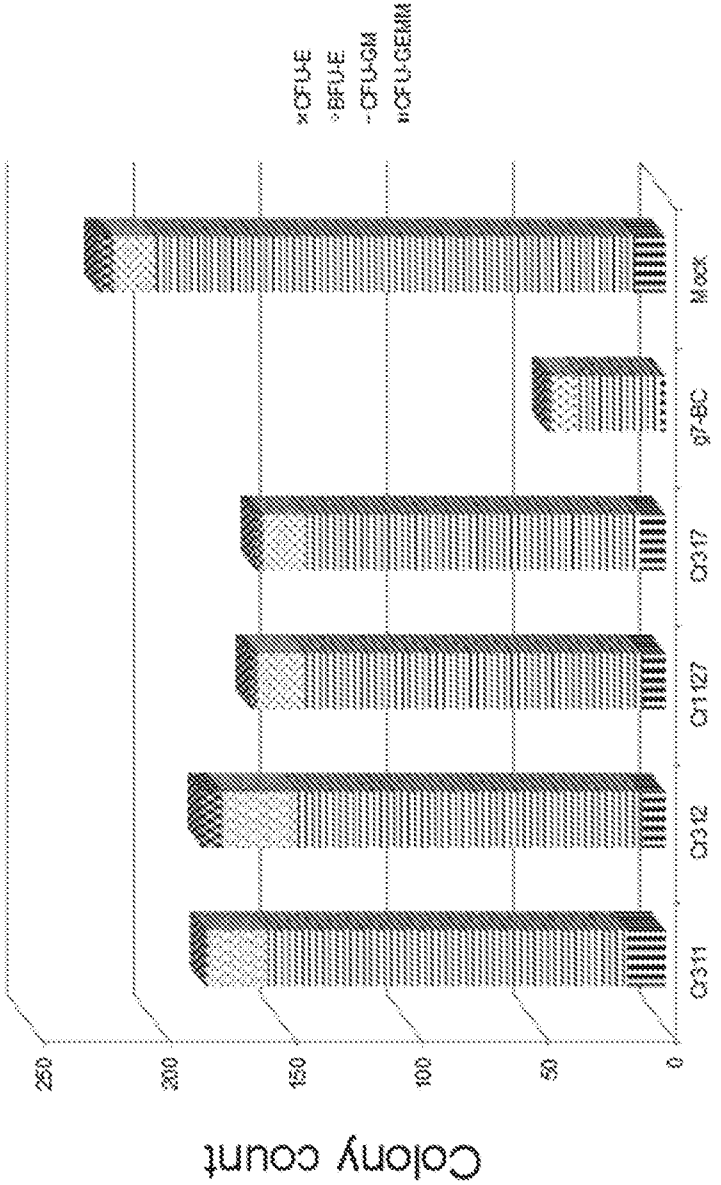

Colony count
250
200
150
100
50
0
Mock
97-8C
C317
C1127
C312
C311
CFU/GEMM
BFU-E
CFU-GM
CFU-E

Figure 21

Figure 22

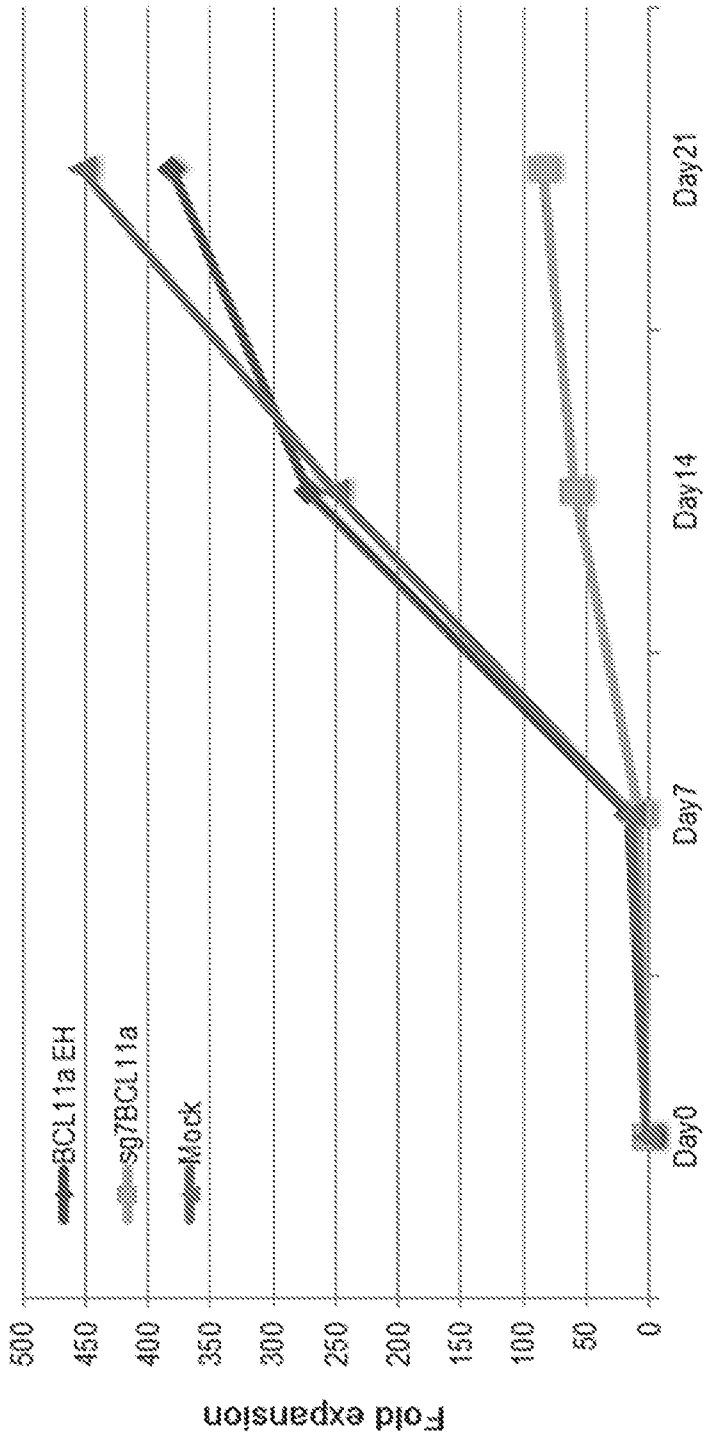

Fold expansion
500
450
400
350
300
250
200
150
100
50
0
Day0
Day7
Day14
Day21
BCL11a EH
sgBCL11a
Mock

Figure 23

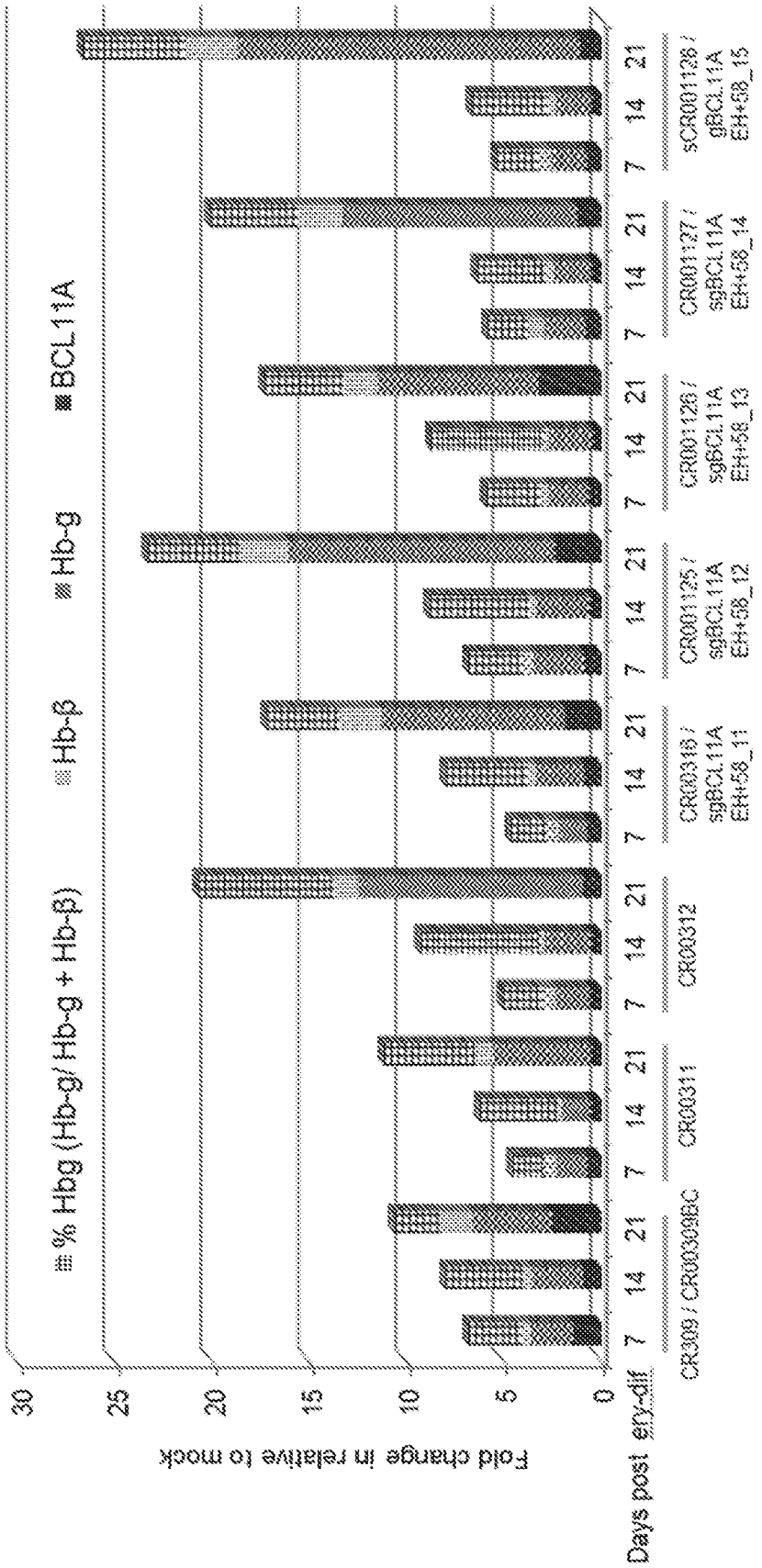

% Hbg (Hb-g/ Hb-g + Hb-β)
Hb-β
Hb-g
BCL11A
Fold change in relative to mock
0
5
10
15
20
25
30
Days post ery-diff
7 14 21 7 14 21 7 14 21 7 14 21 7 14 21 7 14 21 7 14 21
CR309 / CR00309BC
CR00311
CR00312
CR00316 / sgBCL11A EH+58_11
CR001125 / sgBCL11A EH+58_12
CR001126 / sgBCL11A EH+58_13
CR001127 / sgBCL11A EH+58_14
sCR001126 / gBCL11A EH+58_15

Figure 24A

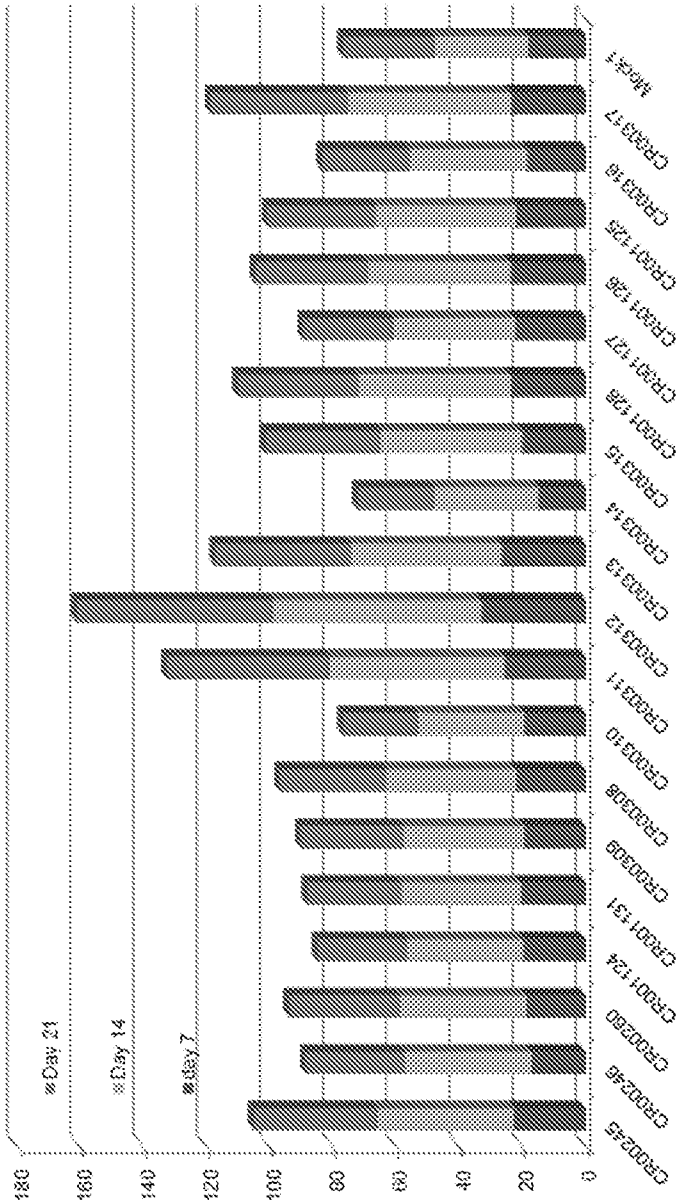

Day 21
Day 14
Day 7
180
160
140
120
100
80
60
40
20
0
Mock
CR8013.17
CR8013.16
CR8031.125
CR8031.126
CR8031.127
CR8031.128
CR8013.15
CR8013.14
CR8013.13
CR8013.12
CR8013.11
CR8013.10
CR8013.08
CR8013.09
CR8031.121
CR8031.124
CR8031.80
CR8002.46
CR8002.45

Figure 24B

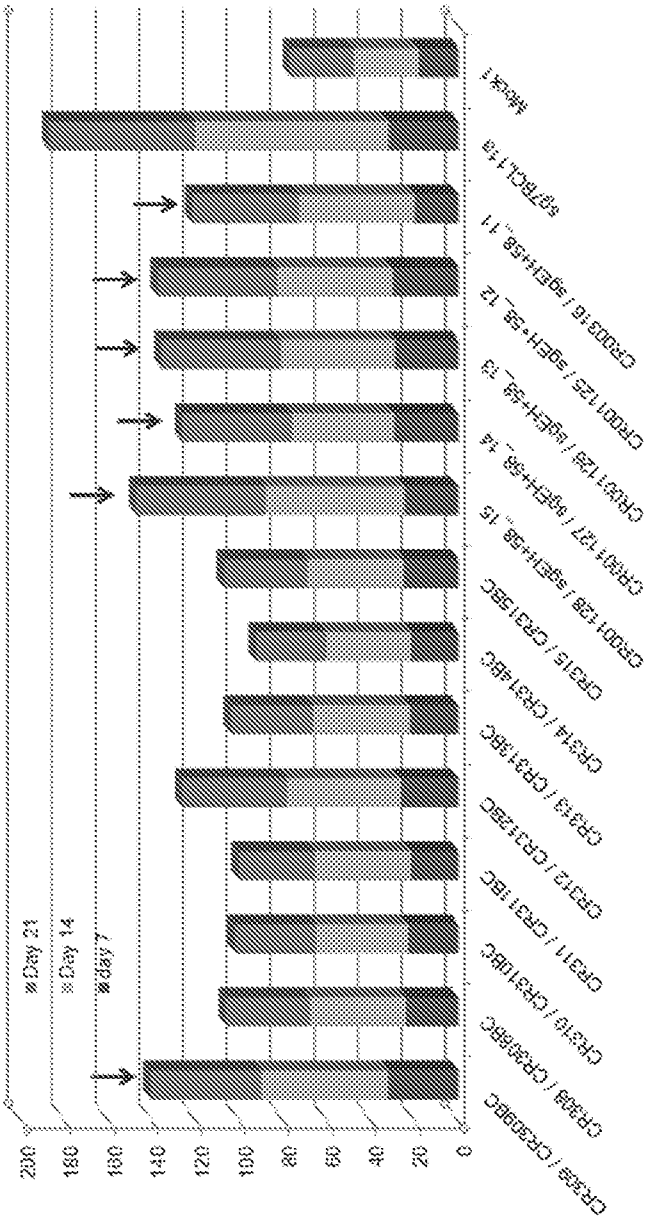

Day 21
Day 14
day 7
200
180
160
140
120
100
80
60
40
20
0
CR3039 / CR3039BC
CR3029 / CR3029BC
CR3019 / CR3019BC
CR3011 / CR3011BC
CR3012 / CR3012BC
CR3013 / CR3013BC
CR3014 / CR3014BC
CR3015 / CR3015BC
CR3001-128 / sgE1+sG8_15
CR3001-127 / sgE1+sG8_14
CR3001-126 / sgE1+sG8_13
CR3001-125 / sgE1+sG8_12
CR3003-16 / sgE1+sG8_11
sgTRCL1+sG
Mock

Figure 25

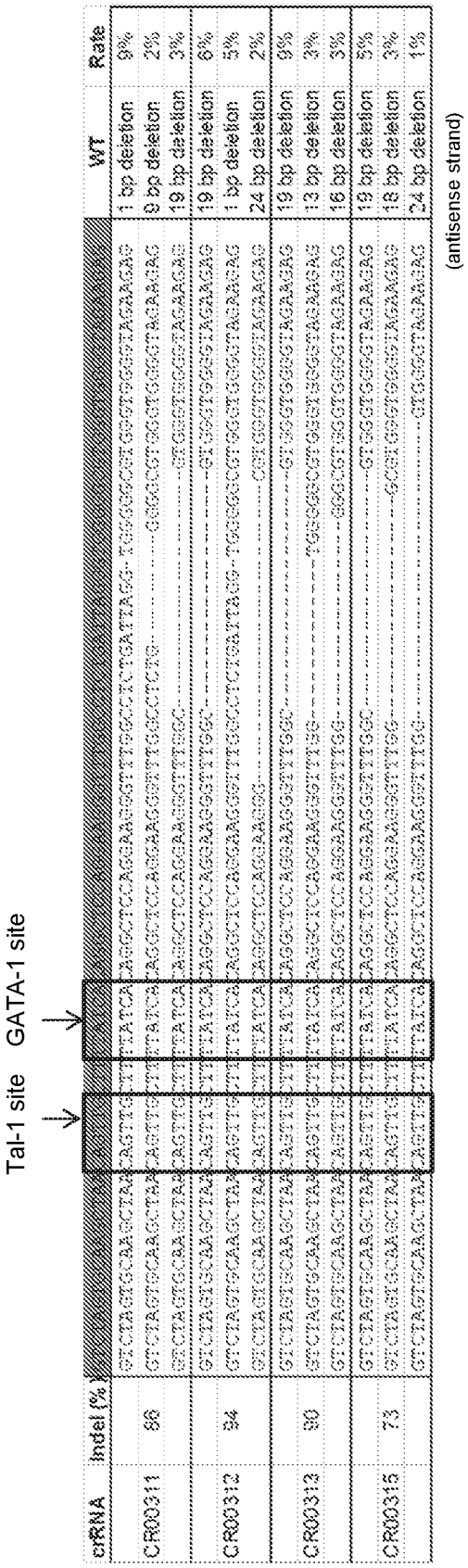

Tal-1 site
GATA-1 site
crRNA
Indel (%)
WT
Rate
CR00311
86
1 bp deletion
9%
9 bp deletion
2%
19 bp deletion
3%
CR00312
94
19 bp deletion
6%
1 bp deletion
5%
24 bp deletion
2%
CR00313
90
19 bp deletion
9%
13 bp deletion
3%
16 bp deletion
3%
CR00315
73
19 bp deletion
5%
18 bp deletion
3%
24 bp deletion
1%
(antisense strand)

Figure 26A

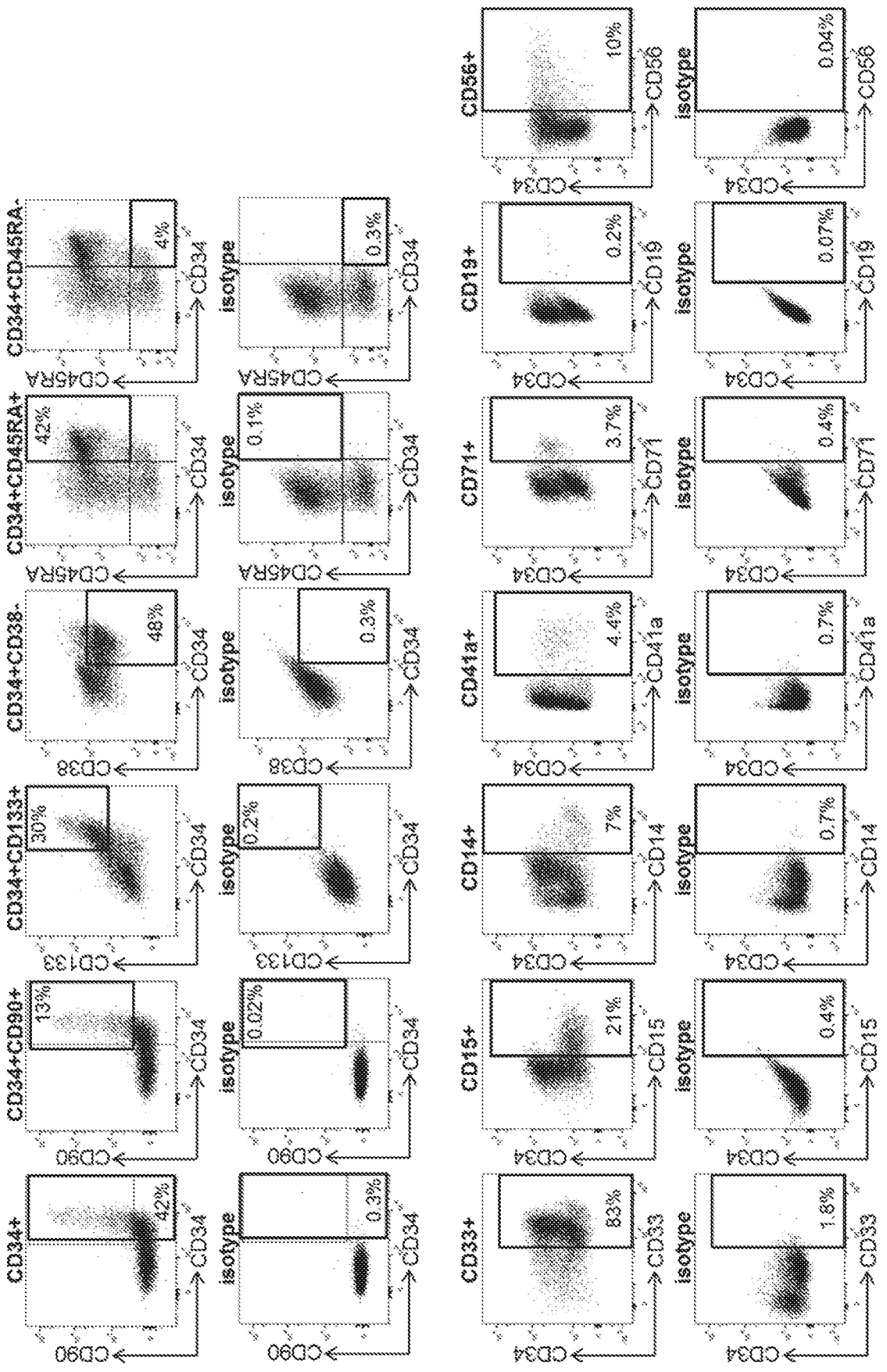

CD34+
CD90
CD34
42%
0.3%
isotype
CD34+CD90+
13%
0.02%
CD34+CD133+
30%
0.2%
CD34+CD38-
48%
0.3%
CD34+CD45RA+
42%
0.1%
CD34+CD45RA-
4%
0.3%
CD33+
83%
1.8%
CD15+
21%
0.4%
CD14+
7%
0.7%
CD41a+
4.4%
0.7%
CD71+
3.7%
0.4%
CD19+
0.2%
0.07%
CD56+
10%
0.04%
CD33
CD15
CD14
CD41a
CD71
CD19
CD56
CD34
CD38
CD133
CD45RA

Figure 26B

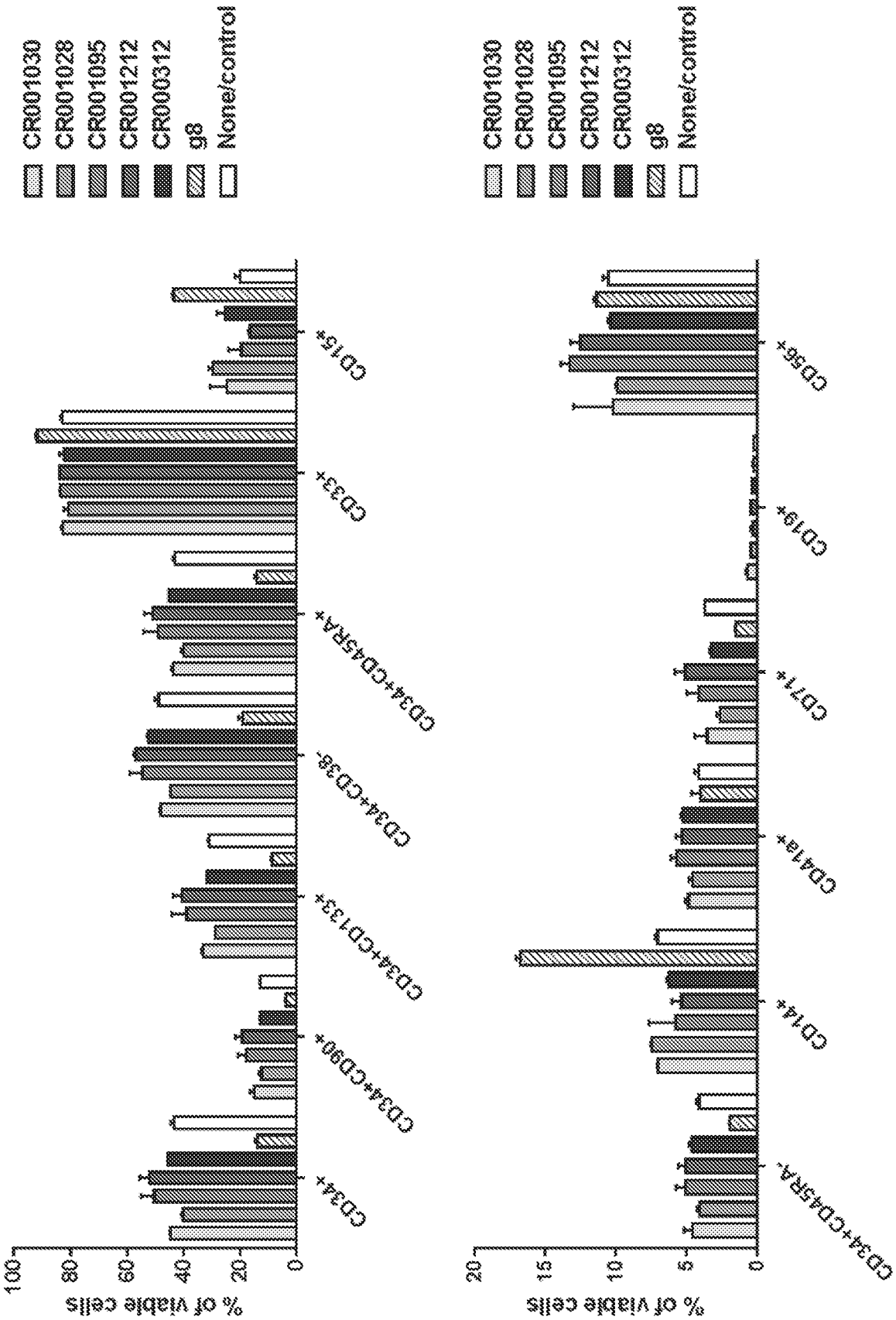

CR001030
CR001028
CR001095
CR001212
CR000312
g8
None/control
% of viable cells
100
80
60
40
20
0
CD34+
CD34+CD90+
CD34+CD133+
CD34+CD38-
CD34+CD45RA+
CD33+
CD15+
20
15
10
5
0
CD34+CD45RA-
CD14+
CD16+
CD71+
CD19+
CD56+

Figure 27

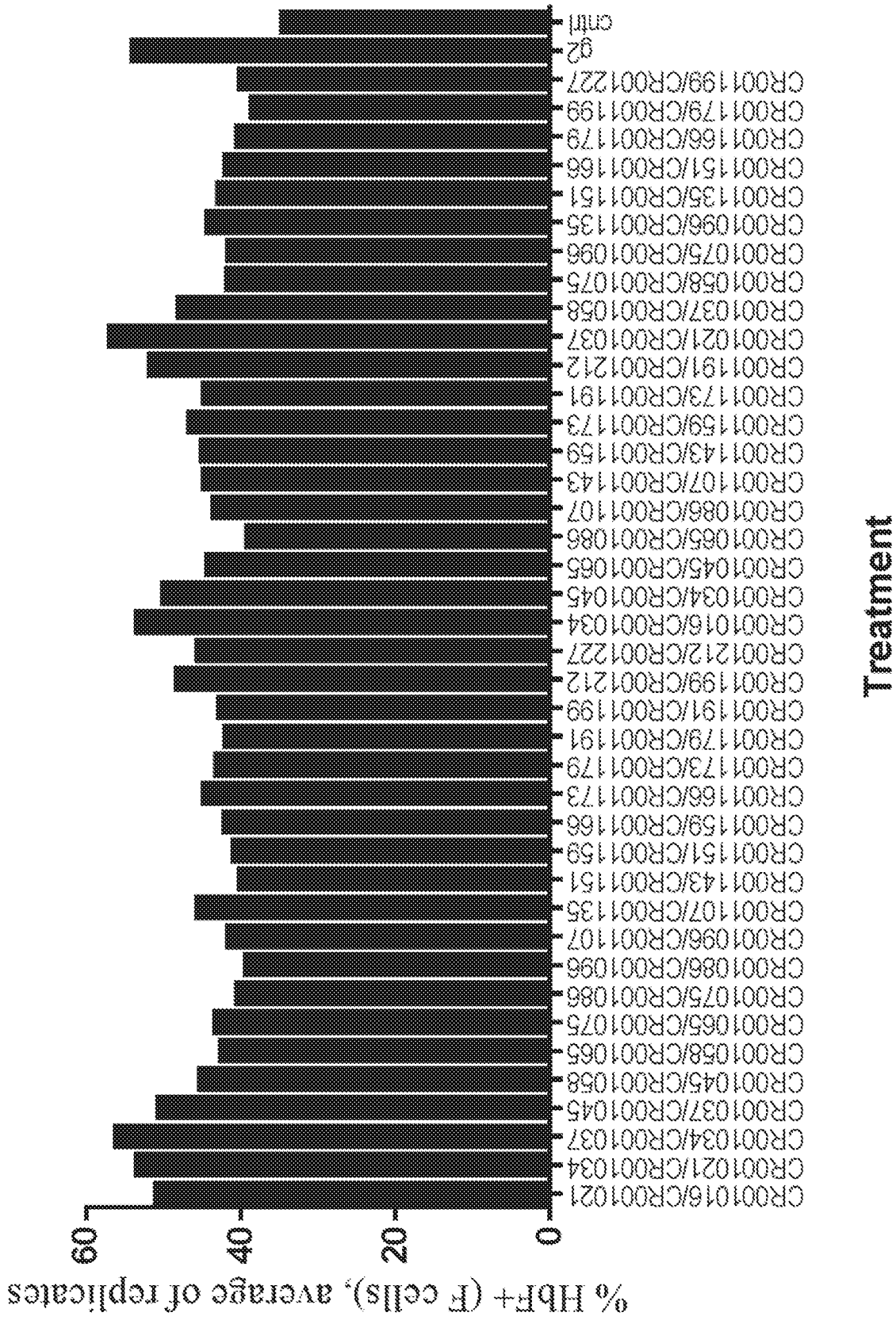

% HbF+ (F cells), average of replicates
0
20
40
60
Treatment
CR001016/CR001021
CR001021/CR001034
CR001034/CR001037
CR001037/CR001045
CR001045/CR001058
CR001058/CR001065
CR001065/CR001075
CR001075/CR001086
CR001086/CR001096
CR001096/CR001107
CR001107/CR001135
CR001143/CR001151
CR001151/CR001159
CR001159/CR001166
CR001166/CR001173
CR001173/CR001179
CR001179/CR001191
CR001191/CR001199
CR001199/CR001212
CR001212/CR001227
CR001016/CR001034
CR001034/CR001045
CR001045/CR001065
CR001065/CR001086
CR001086/CR001107
CR001107/CR001143
CR001143/CR001159
CR001159/CR001173
CR001173/CR001191
CR001191/CR001212
CR001021/CR001037
CR001037/CR001058
CR001058/CR001075
CR001075/CR001096
CR001096/CR001135
CR001135/CR001151
CR001151/CR001166
CR001166/CR001179
CR001179/CR001199
CR001199/CR001227
q2
cntl

Figure 28A

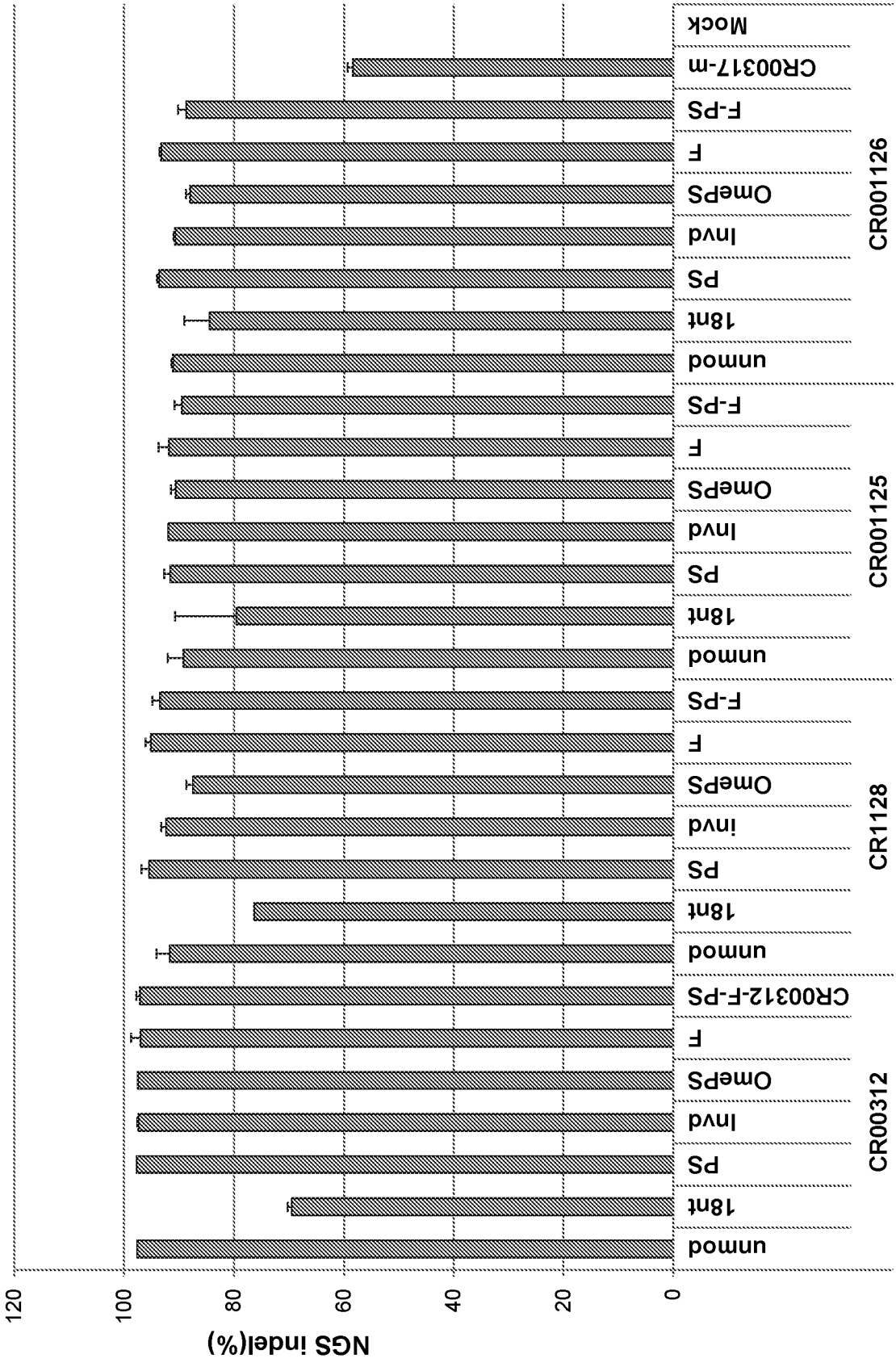

NGS indel(%)
0
20
40
60
80
100
120
unmod
18nt
PS
Invd
OmePS
F
CR00312-F-PS
unmod
18nt
PS
Invd
OmePS
F
F-PS
unmod
18nt
PS
Invd
OmePS
F
F-PS
unmod
18nt
PS
Invd
OmePS
F
F-PS
CR00317-m
Mock
CR00312
CR1128
CR001125
CR001126

Figure 28B

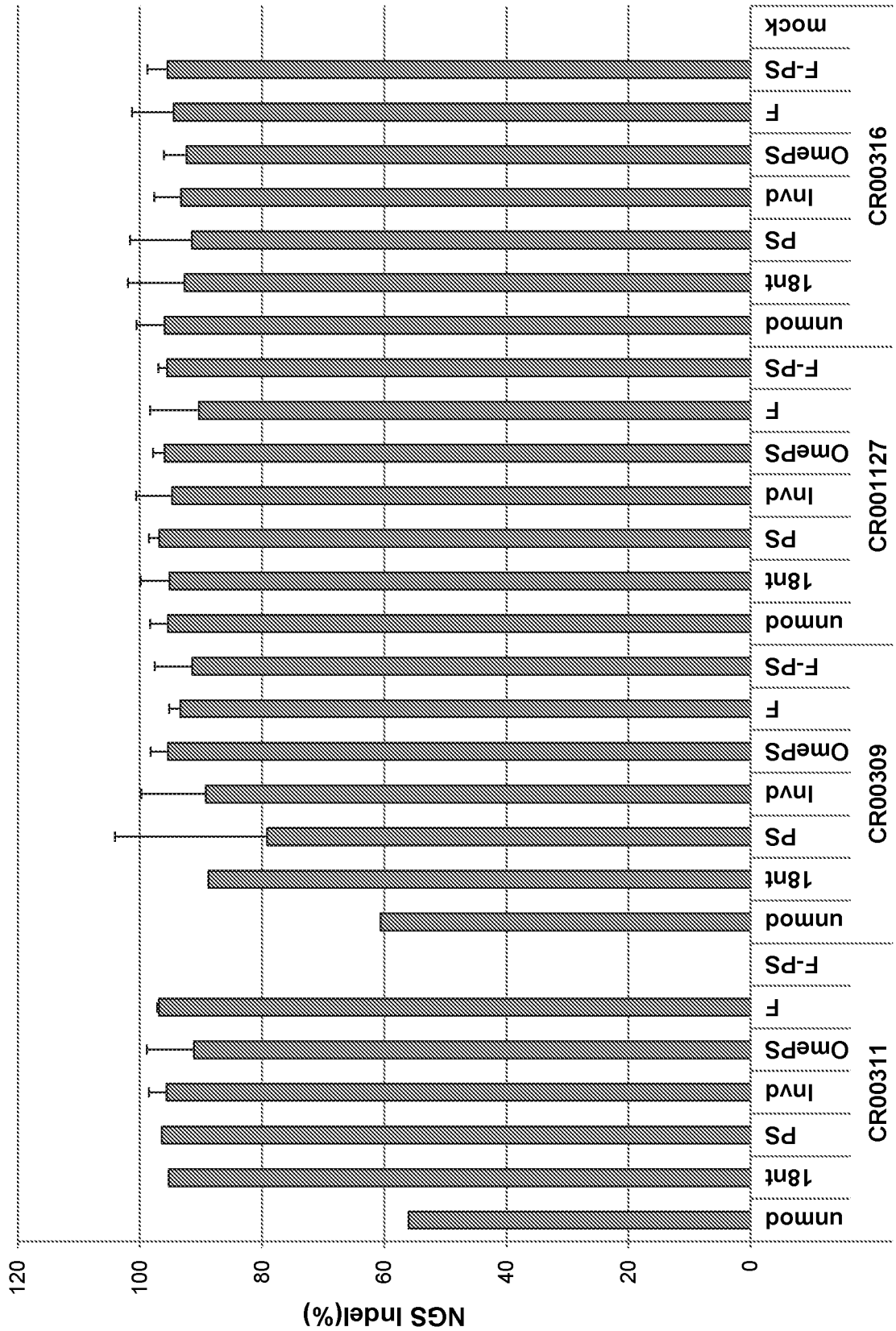

NGS Indel(%)
0
20
40
60
80
100
120
unmod
18nt
PS
Invd
OmePS
F
F-PS
mock
CR00311
CR00309
CR001127
CR00316

Figure 29


NGS-Indel(%)
0
20
40
60
80
100
120
Unmod sg312
Unmod sg1128
Unmod sg1125
Unmod sg1126
Unmod sg311
Unmod-sg309
Unmod sg1127
Unmod sg316
18 sg312
18 sg1128
18 sg1125
18 sg1126
18 sg311
18 sg309
18 sg1127
18 sg316
OMePS sg312
OMePS sg1128
OMePS sg1125
OMePS sg1126-1
OMePS sg311
OMePS sg309
MOePS sg1127
PS sg316
PS sg312
PS sg1128
PS sg1125
PS sg1126
PS sg311
PS sg309
PS sg1127
PS sg316
Cas9
Mock
WT

Figure 30A

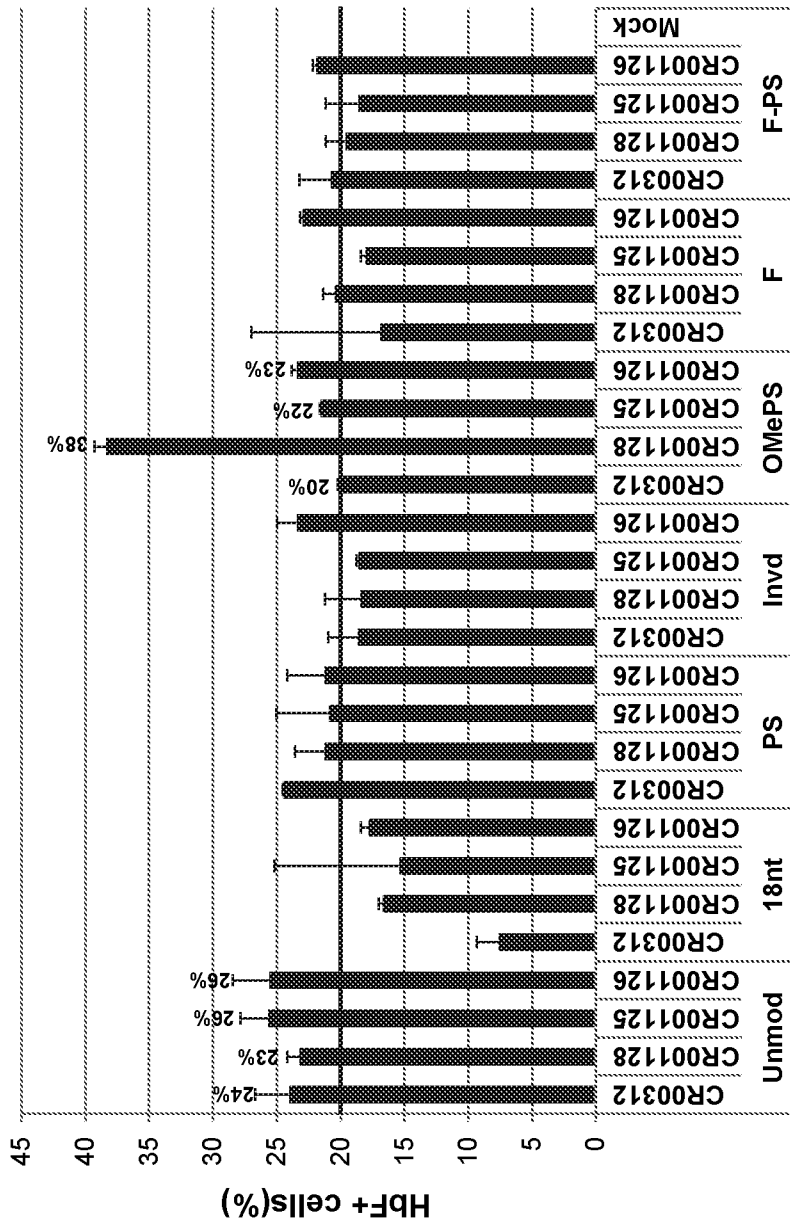

HbF+ cells(%)
45
40
35
30
25
20
15
10
5
0
24%
23%
26%
26%
38%
20%
22%
23%
Unmod
18nt
PS
Invd
OMePS
F
F-PS
Mock
CR003'12
CR001'28
CR001'25
CR001'26

Figure 30B

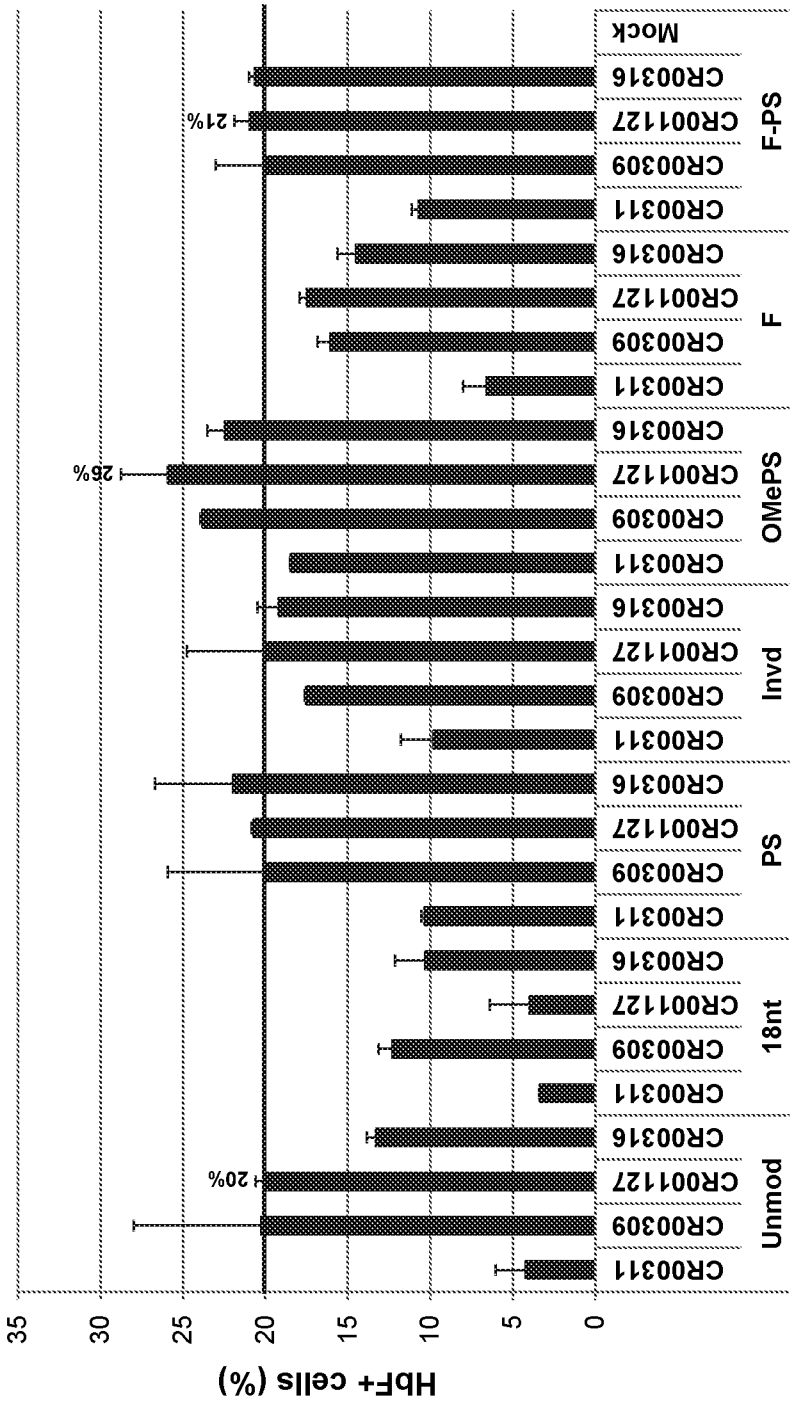

HbF+ cells (%)
0
5
10
15
20
25
30
35
20%
26%
21%
Unmod
18nt
PS
Invd
OMePS
F
F-PS
Mock
CR00311
CR00309
CR001127
CR00316

Figure 31

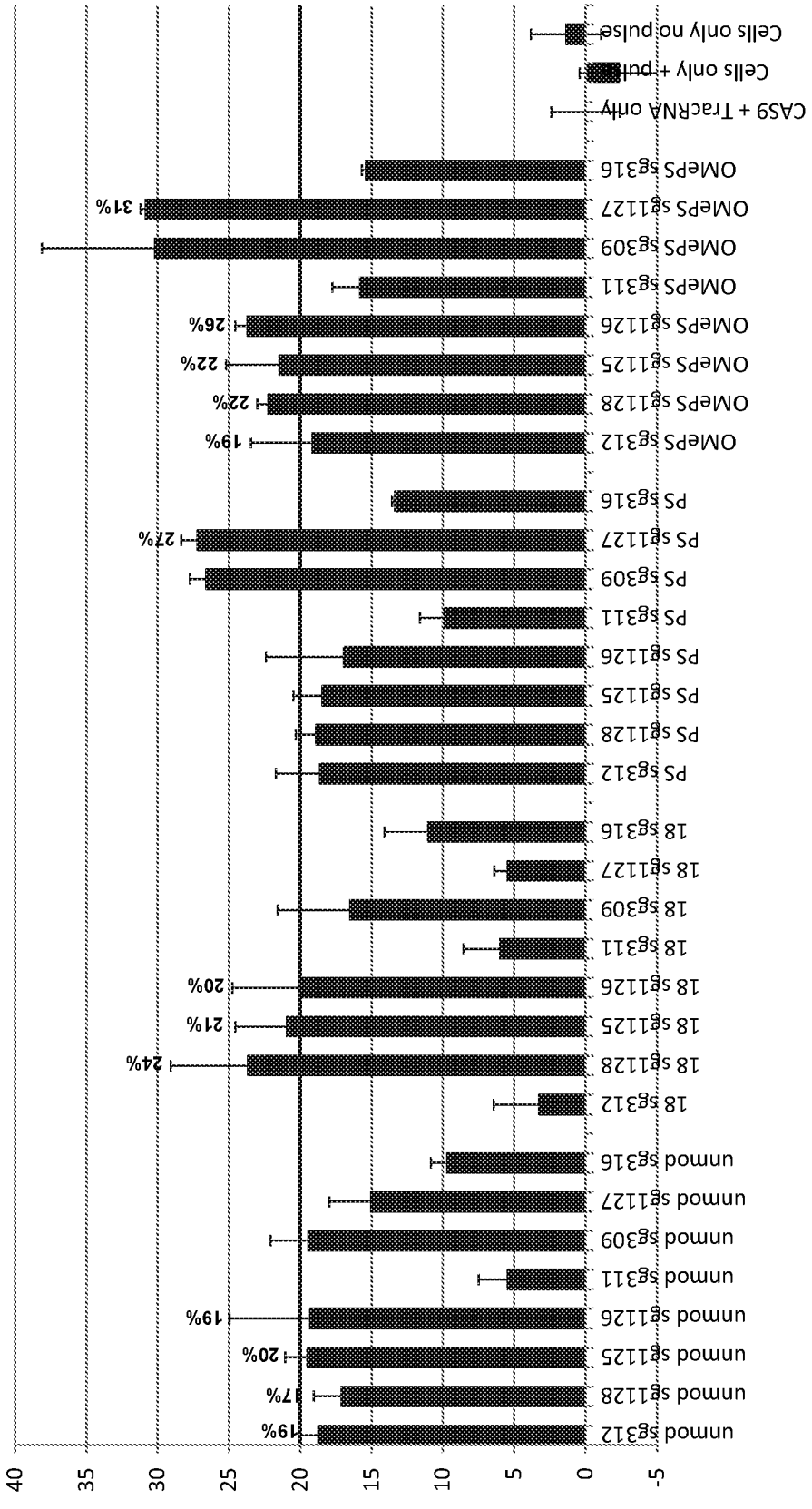

CAS9 + TracRNA only
Cells only + pulse
Cells only no pulse
unmod sg312
unmod sg1128
unmod sg1125
unmod sg1126
unmod sg311
unmod sg309
unmod sg1127
unmod sg316
18 sg312
18 sg1128
18 sg1125
18 sg1126
18 sg311
18 sg309
18 sg1127
18 sg316
PS sg312
PS sg1128
PS sg1125
PS sg1126
PS sg311
PS sg309
PS sg1127
PS sg316
OMePS sg312
OMePS sg1128
OMePS sg1125
OMePS sg1126
OMePS sg311
OMePS sg309
OMePS sg1127
OMePS sg316
19%
17%
20%
19%
24%
21%
20%
22%
22%
26%
31%
27%
19%
40
35
30
25
20
15
10
5
0
-5

Figure 32

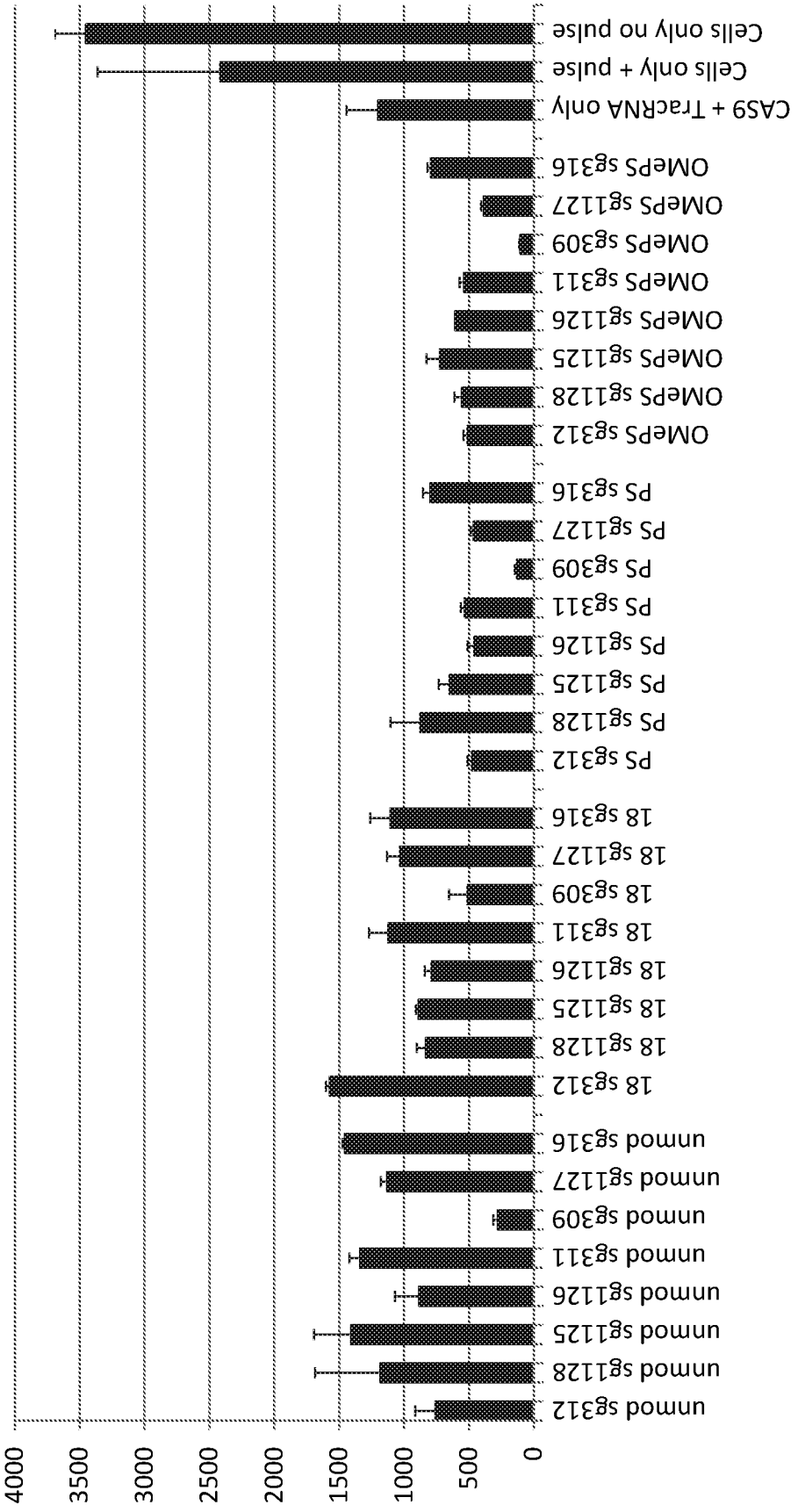

4000
3500
3000
2500
2000
1500
1000
500
0
unmod sg312
unmod sg1128
unmod sg1125
unmod sg1126
unmod sg311
unmod sg309
unmod sg1127
unmod sg316
18 sg312
18 sg1128
18 sg1125
18 sg1126
18 sg311
18 sg309
18 sg1127
18 sg316
PS sg312
PS sg1128
PS sg1125
PS sg1126
PS sg311
PS sg309
PS sg1127
PS sg316
OMePS sg312
OMePS sg1128
OMePS sg1125
OMePS sg1126
OMePS sg311
OMePS sg309
OMePS sg1127
OMePS sg316
CAS9 + TracRNA only
Cells only + pulse
Cells only no pulse

Figure 33

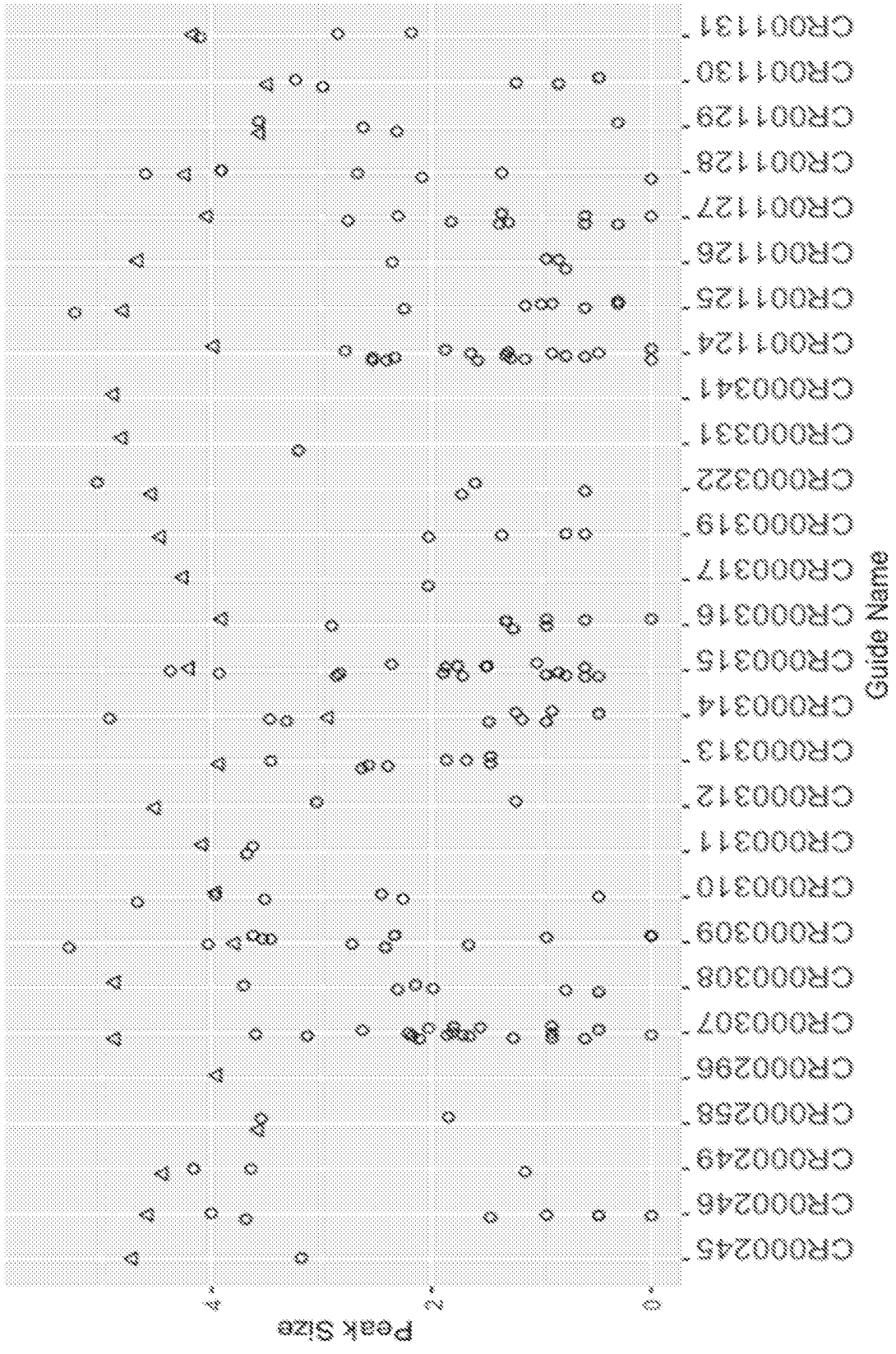

Guide Name
CR001131
CR001130
CR001129
CR001128
CR001127
CR001126
CR001125
CR001124
CR000341
CR000331
CR000322
CR000319
CR000317
CR000316
CR000315
CR000314
CR000313
CR000312
CR000311
CR000310
CR000309
CR000308
CR000307
CR000296
CR000258
CR000249
CR000246
CR000245
Peak Size

Figure 34

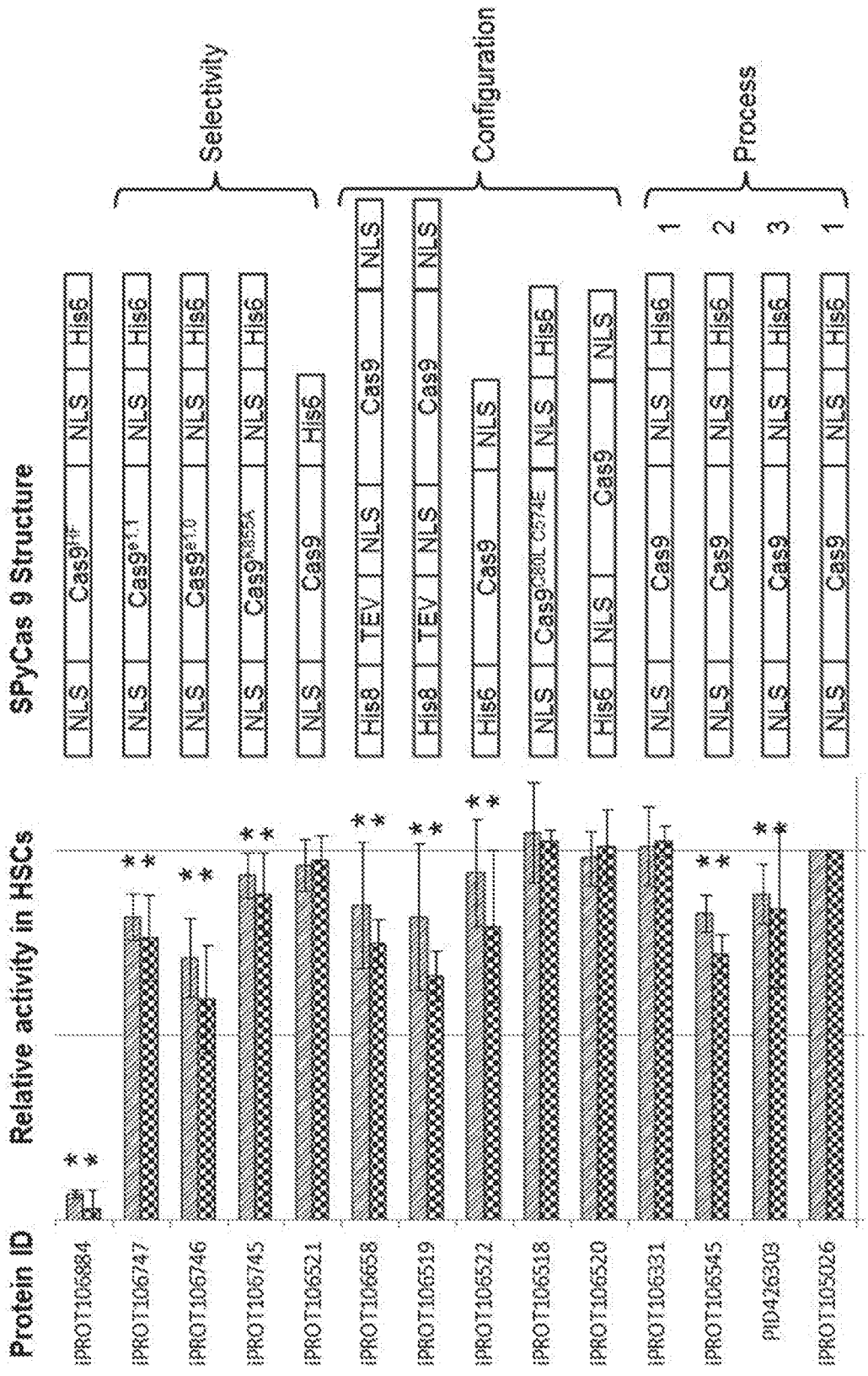

Protein ID
Relative activity in HSCs
SPyCas 9 Structure
Selectivity
Configuration
Process
iPROT106884
iPROT106747
iPROT106746
iPROT106745
iPROT106521
iPROT106658
iPROT106519
iPROT106522
iPROT106518
iPROT106520
iPROT106331
iPROT106545
PID426303
iPROT105026
NLS
Cas9
His6
TEV
0.0%
50.0%
100.0%
Relative B2M Indel% of NGS (iProt105026 = 100%)
Relative B2M KO Cells By FACS (iProt105026=100%)
* P <0,05

Figure 35

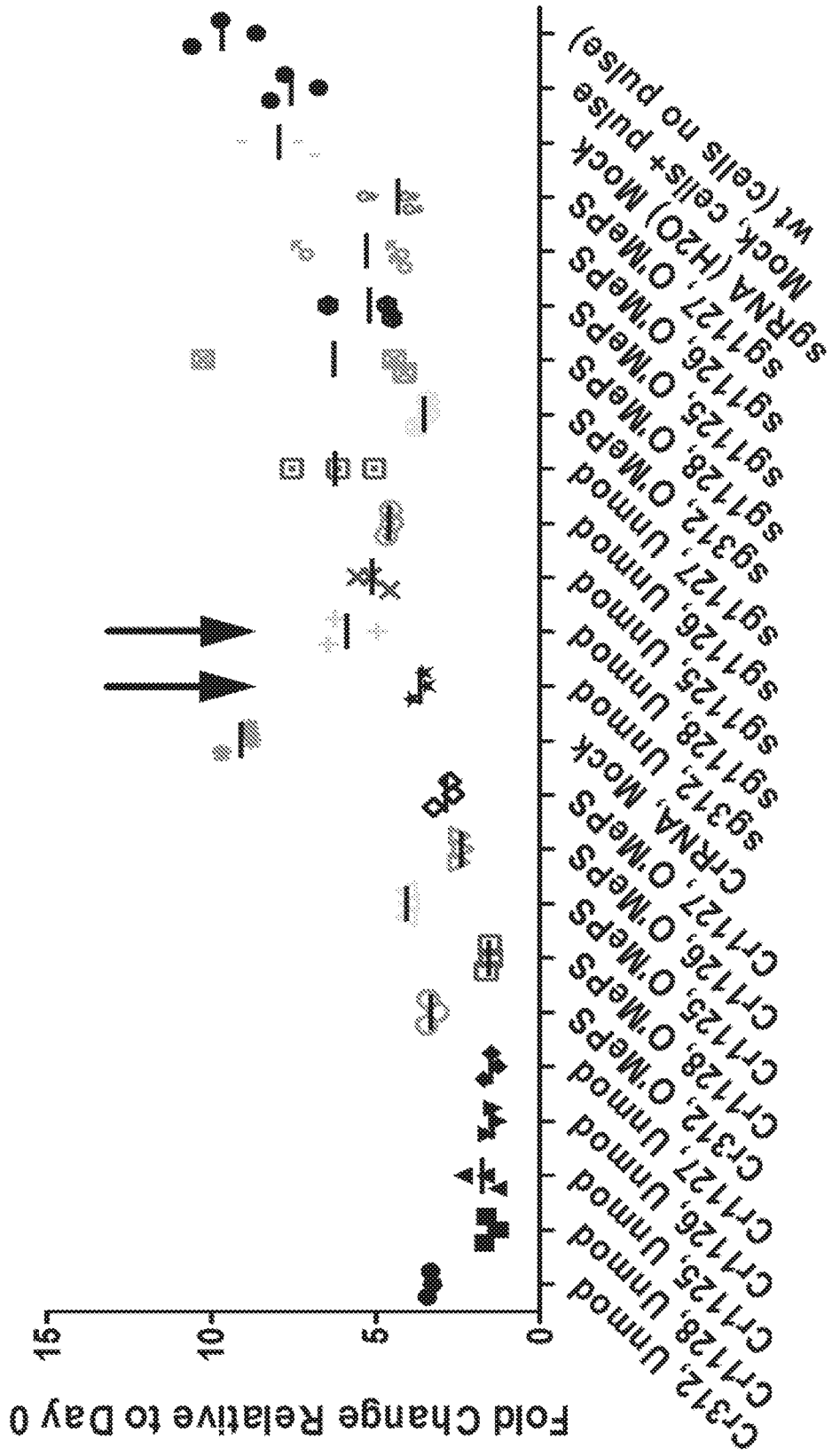

Cell Count After 7 Days of Cell Expansion
Fold Change Relative to Day 0
0
5
10
15
Cr312, Unmod
Cr128, Unmod
Cr125, Unmod
Cr126, Unmod
Cr127, Unmod
Cr312, O'Meps
Cr128, O'Meps
Cr125, O'Meps
Cr126, O'Meps
Cr127, O'Meps
sgRNA, Mock
s9312, Unmod
s9128, Unmod
s9125, Unmod
s9126, Unmod
s9127, Unmod
s9312, O'Meps
s9128, O'Meps
s9125, O'Meps
s9126, O'Meps
s9127, O'Meps
sgRNA (H2O) Mock
Mock, cells+ pulse
wt (cells no pulse)

Figure 36

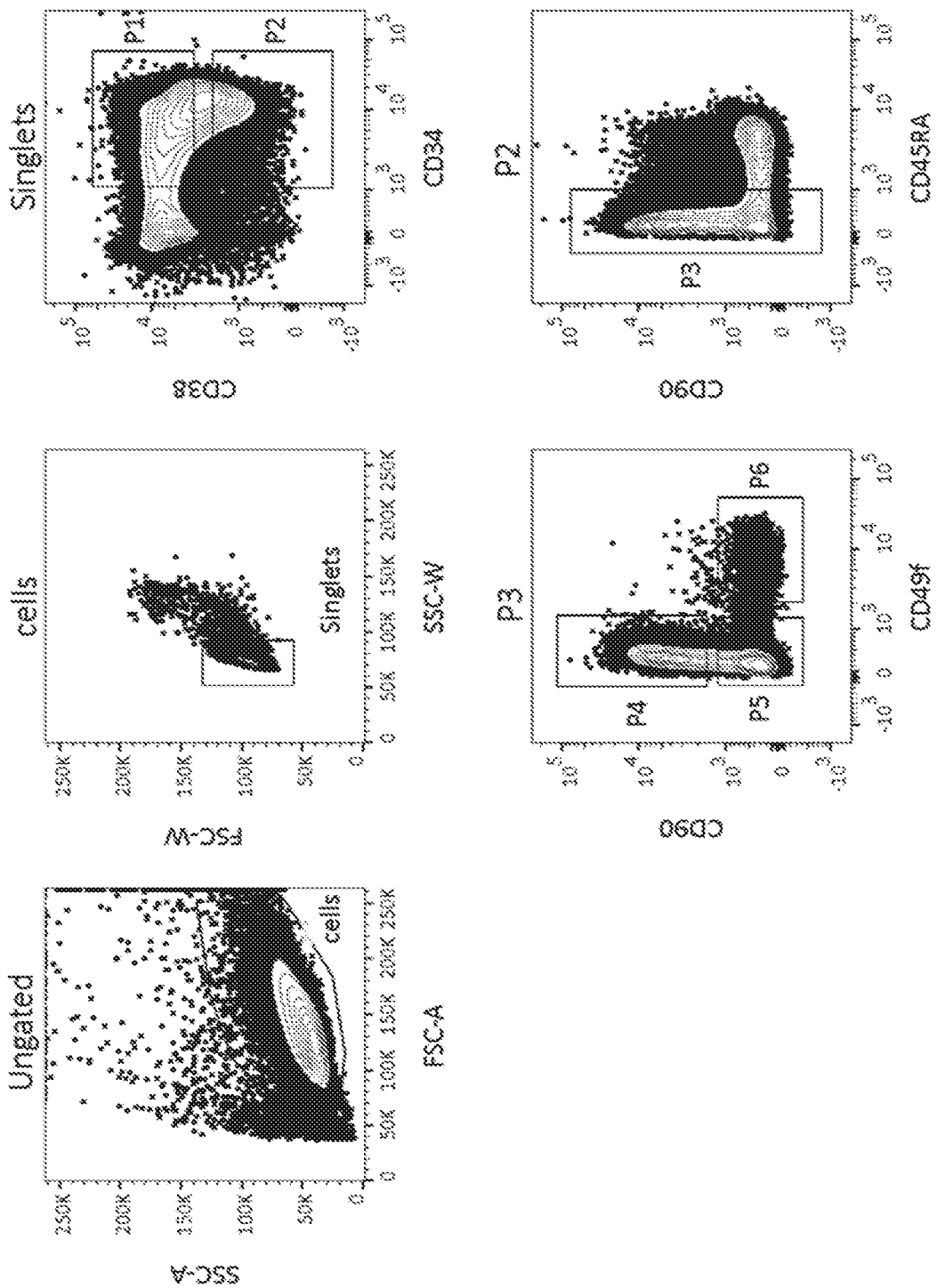

Ungated
cells
Singlets
P1
P2
P3
P4
P5
P6
SSC-A
FSC-A
FSC-W
SSC-W
CD38
CD34
CD90
CD45RA
CD49f

Figure 37

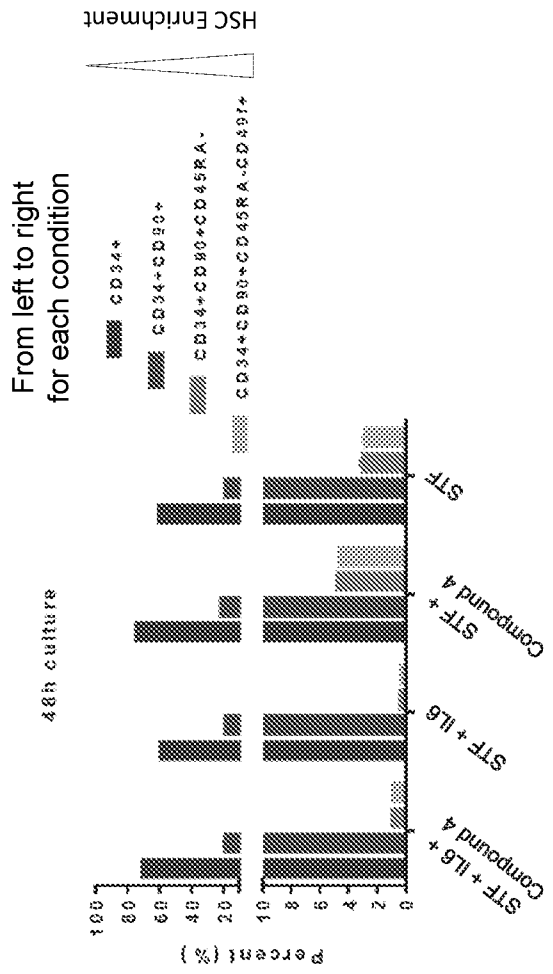

HSC Enrichment
From left to right
for each condition
CD34+
CD34+CD90+
CD34+CD90+CD45RA-
CD34+CD90+CD45RA-CD49f+
48h culture
Percent (%)
100
80
60
40
20
10
8
6
4
2
0
STF
STF + Compound 4
STF + IL6
STF + IL6 + Compound 4

Figure 38

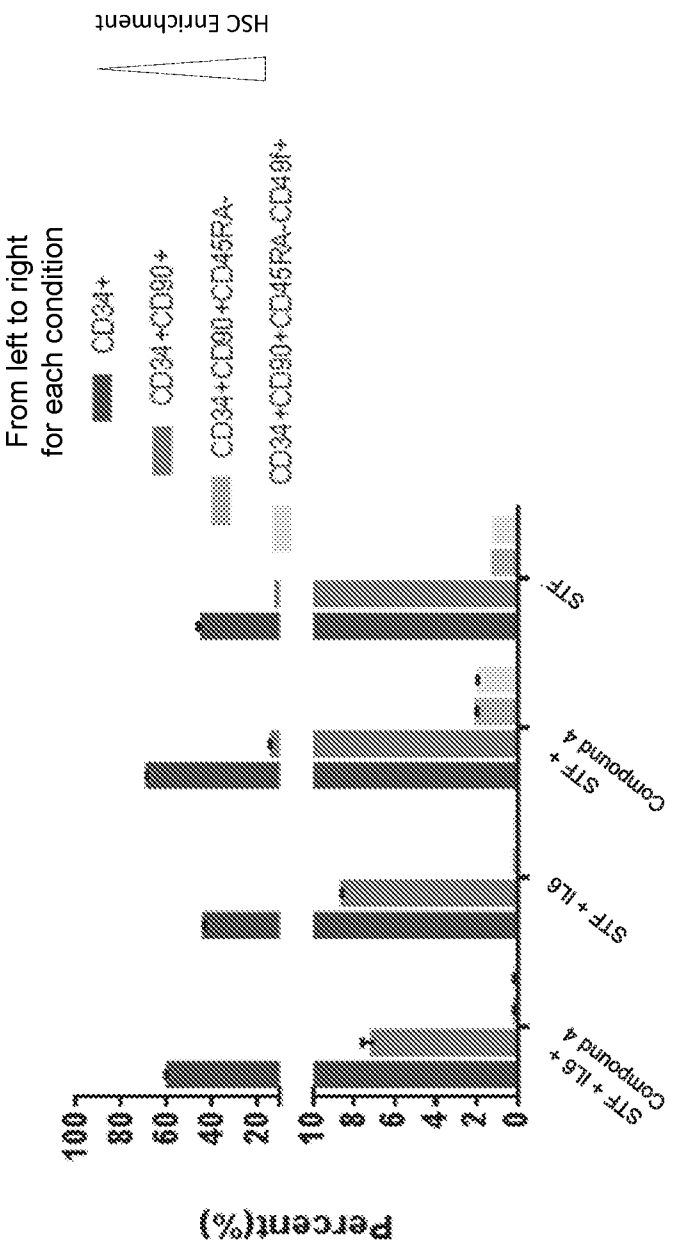

HSC Enrichment
From left to right
for each condition
CD34+
CD34+CD90+
CD34+CD90+CD45RA-
CD34+CD90+CD45RA-CD49f+
Percent(%)
100
80
60
40
20
10
8
6
4
2
0
STF
STF + Compound 4
STF + IL6
STF + IL6 + Compound 4

Figure 39A

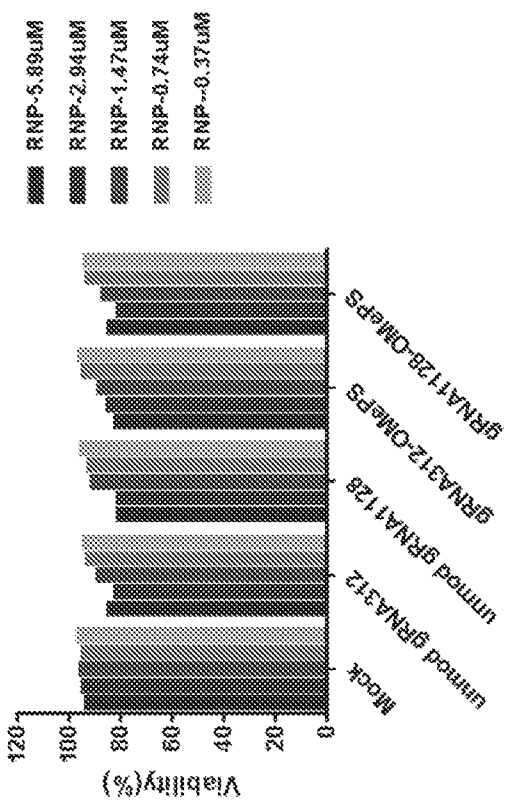


Figure 39B

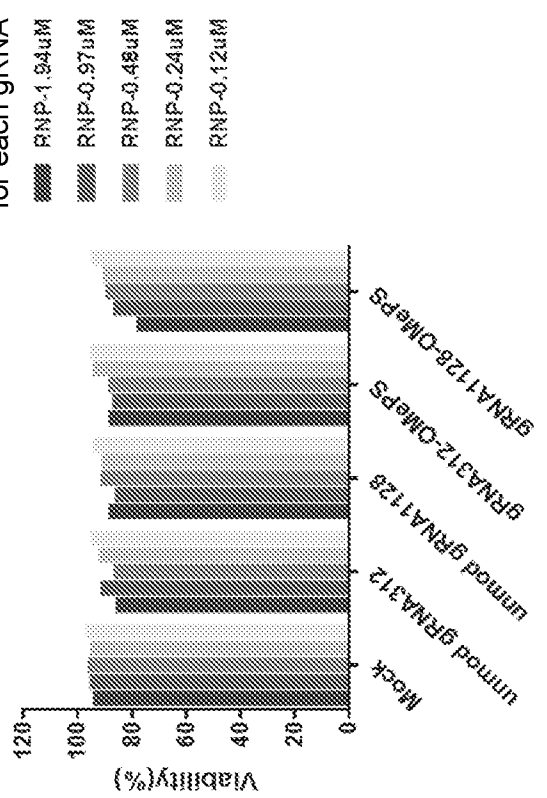


Figure 40B

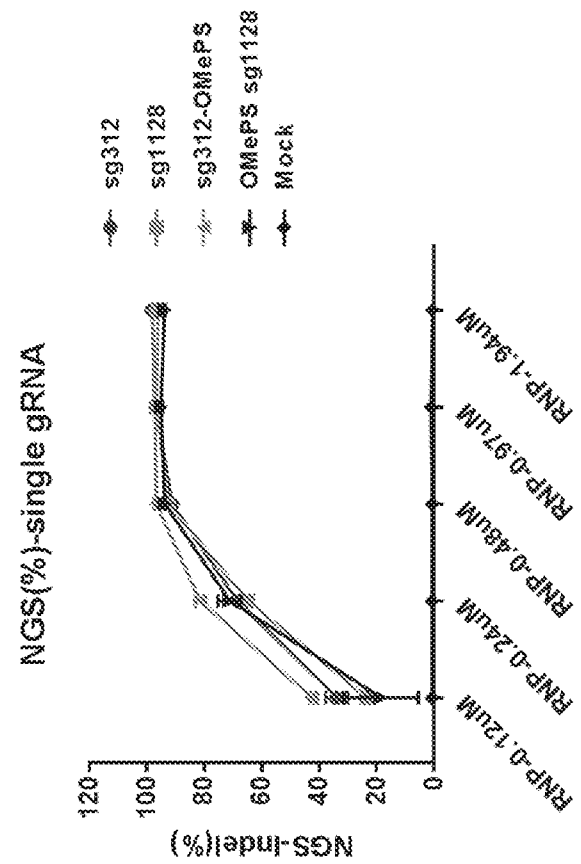


Figure 40A

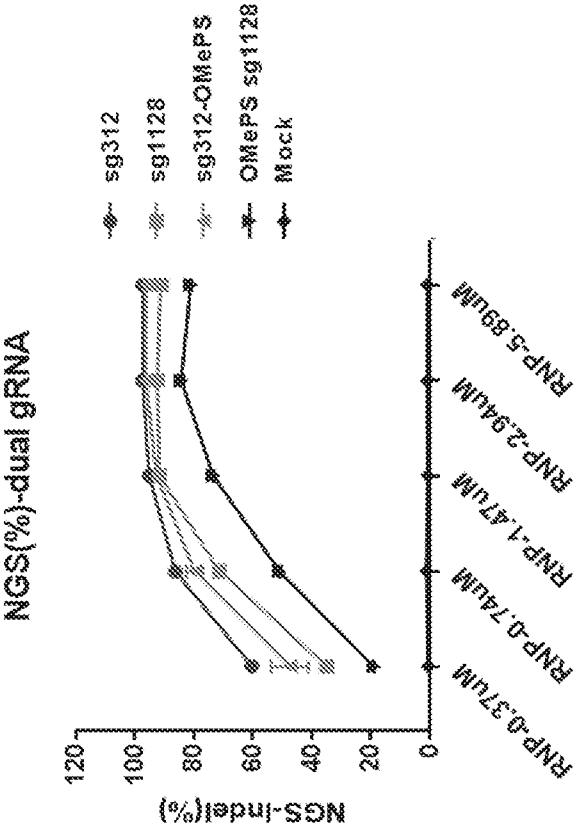


Figure 41A

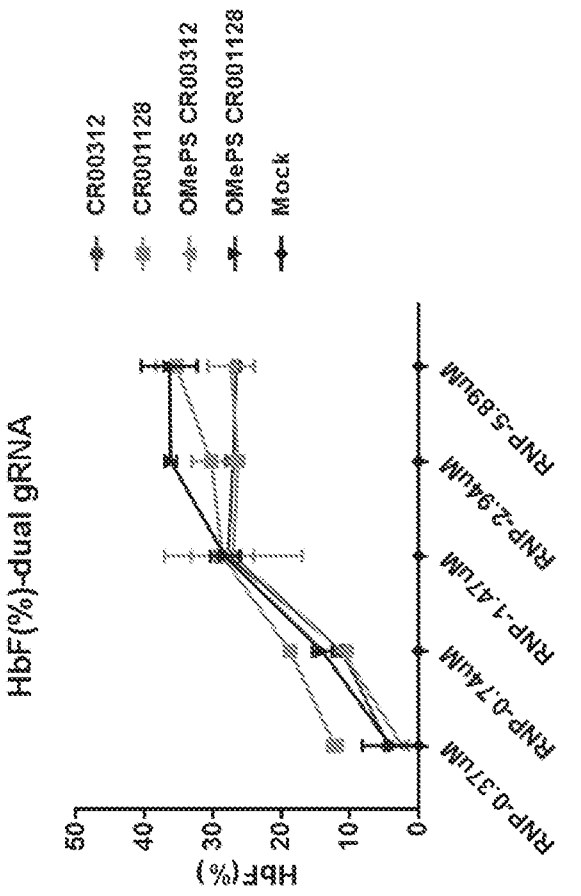


Figure 41B

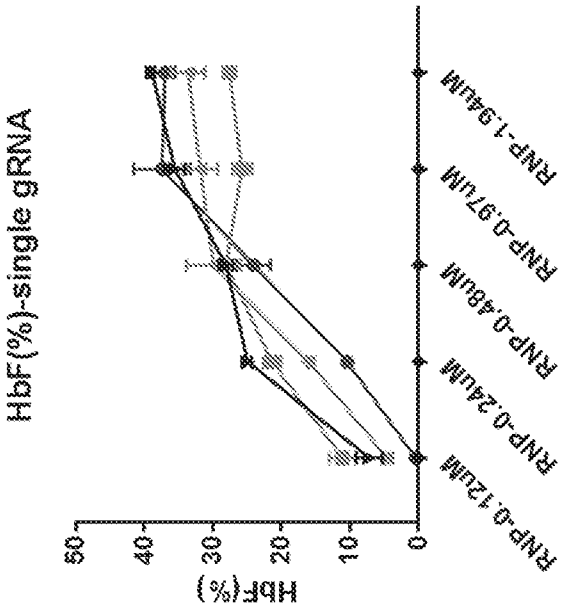


Figure 42A

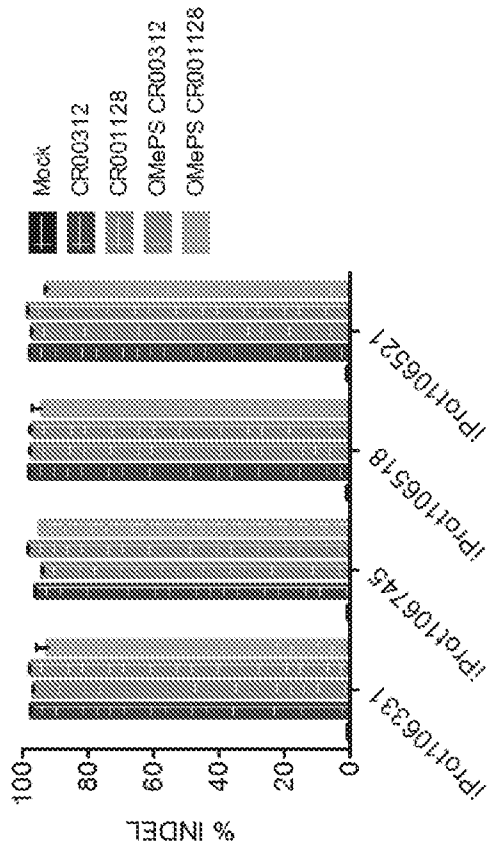


Figure 42B

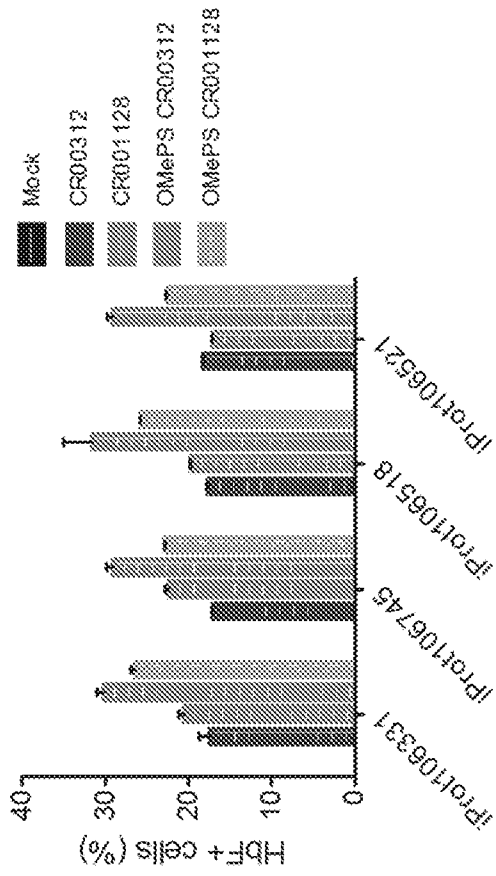


Figure 43

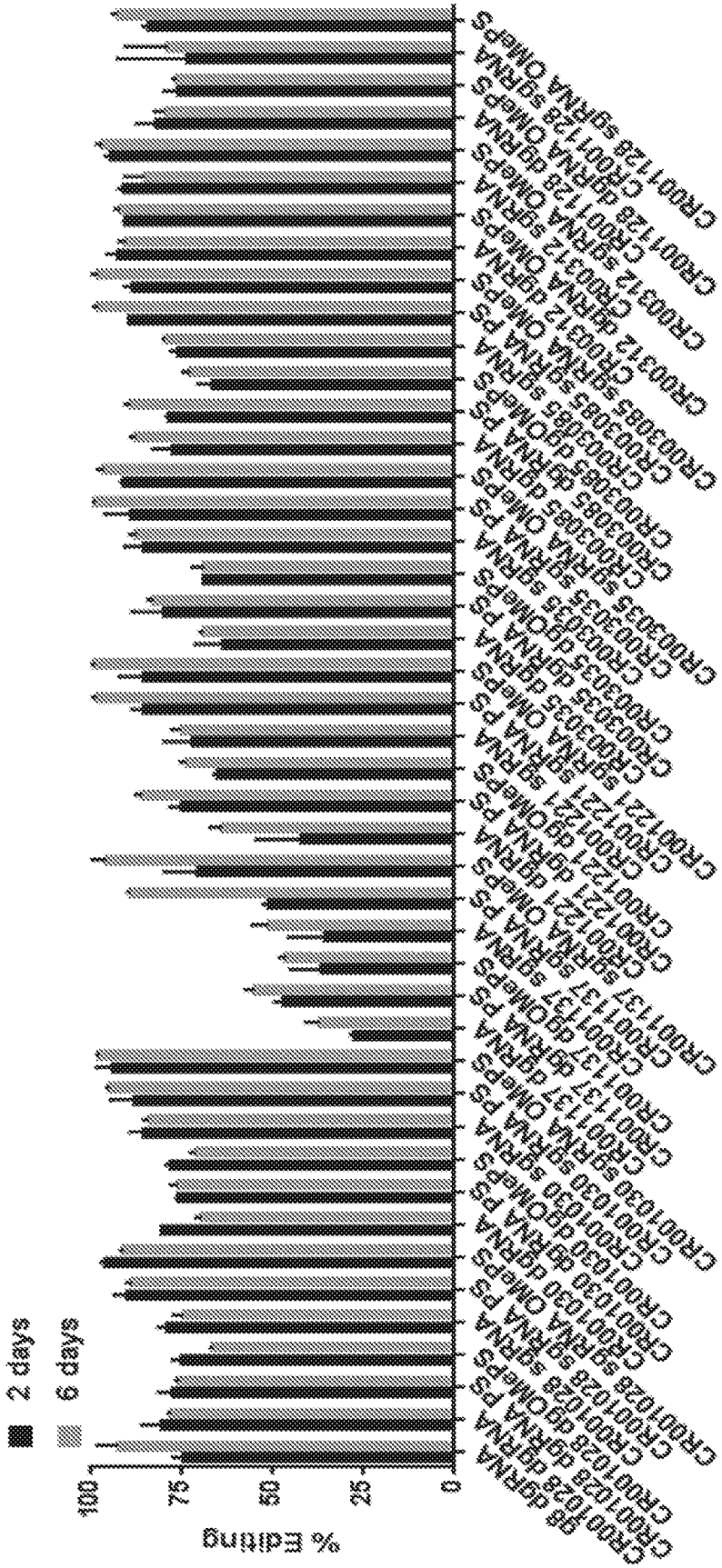

2 days
6 days
% Editing
100
75
50
25
0
CR001028 dgRNA
CR001028 dgRNA PS
CR001028 dgRNA OMeP
CR001028 dgRNA OMeP5
CR001028 sgRNA
CR001028 sgRNA PS
CR001028 sgRNA OMeP
CR001028 sgRNA OMeP5
CR001030 dgRNA
CR001030 dgRNA PS
CR001030 dgRNA OMeP
CR001030 dgRNA OMeP5
CR001030 sgRNA
CR001030 sgRNA PS
CR001030 sgRNA OMeP
CR001030 sgRNA OMeP5
CR001137 dgRNA
CR001137 dgRNA PS
CR001137 dgRNA OMeP
CR001137 dgRNA OMeP5
CR001137 sgRNA
CR001137 sgRNA PS
CR001137 sgRNA OMeP
CR001137 sgRNA OMeP5
CR001221 dgRNA
CR001221 dgRNA PS
CR001221 dgRNA OMeP
CR001221 dgRNA OMeP5
CR001221 sgRNA
CR001221 sgRNA PS
CR001221 sgRNA OMeP
CR001221 sgRNA OMeP5
CR003035 dgRNA
CR003035 dgRNA PS
CR003035 dgRNA OMeP
CR003035 dgRNA OMeP5
CR003035 sgRNA
CR003035 sgRNA PS
CR003035 sgRNA OMeP
CR003035 sgRNA OMeP5
CR003085 dgRNA
CR003085 dgRNA PS
CR003085 dgRNA OMeP
CR003085 dgRNA OMeP5
CR003085 sgRNA
CR003085 sgRNA PS
CR003085 sgRNA OMeP
CR003085 sgRNA OMeP5
CR003712 dgRNA
CR003712 dgRNA PS
CR003712 dgRNA OMeP
CR003712 dgRNA OMeP5
CR003712 sgRNA
CR003712 sgRNA PS
CR003712 sgRNA OMeP
CR003712 sgRNA OMeP5
CR001728 dgRNA
CR001728 dgRNA PS
CR001728 dgRNA OMeP
CR001728 dgRNA OMeP5
CR001728 sgRNA
CR001728 sgRNA PS
CR001728 sgRNA OMeP
CR001728 sgRNA OMeP5

Figure 44

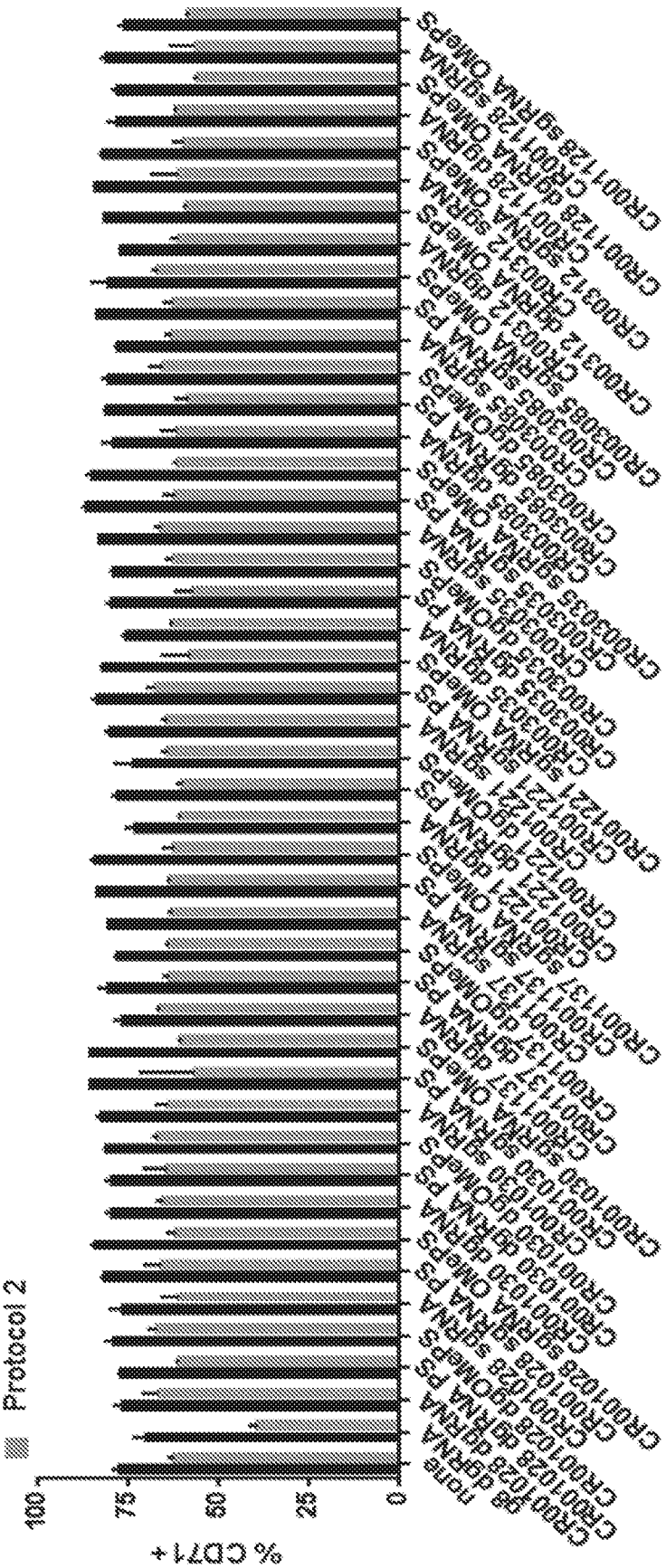

Protocol 1
Protocol 2
% CD71+
100
75
50
25
0
none
dgRNA
CR001028 dgRNA
CR001028 dgOMePS
CR001028 dgRNA PS
CR001028 sgRNA
CR001028 sgOMePS
CR001028 sgRNA PS
CR001030 dgRNA
CR001030 dgOMePS
CR001030 dgRNA PS
CR001030 sgRNA
CR001030 sgOMePS
CR001030 sgRNA PS
CR001137 dgRNA
CR001137 dgOMePS
CR001137 dgRNA PS
CR001137 sgRNA
CR001137 sgOMePS
CR001137 sgRNA PS
CR001221 dgRNA
CR001221 dgOMePS
CR001221 dgRNA PS
CR001221 sgRNA
CR001221 sgOMePS
CR001221 sgRNA PS
CR001224 dgRNA
CR001224 dgOMePS
CR001224 dgRNA PS
CR001224 sgRNA
CR001224 sgOMePS
CR001224 sgRNA PS
CR003035 dgRNA
CR003035 dgOMePS
CR003035 dgRNA PS
CR003035 sgRNA
CR003035 sgOMePS
CR003035 sgRNA PS
CR003085 dgRNA
CR003085 dgOMePS
CR003085 dgRNA PS
CR003085 sgRNA
CR003085 sgOMePS
CR003085 sgRNA PS
CR003112 dgRNA
CR003112 dgOMePS
CR003112 dgRNA PS
CR003112 sgRNA
CR003112 sgOMePS
CR003112 sgRNA PS
CR001128 dgRNA
CR001128 dgOMePS
CR001128 dgRNA PS
CR001128 sgRNA
CR001128 sgOMePS
CR001128 sgRNA PS

Figure 45

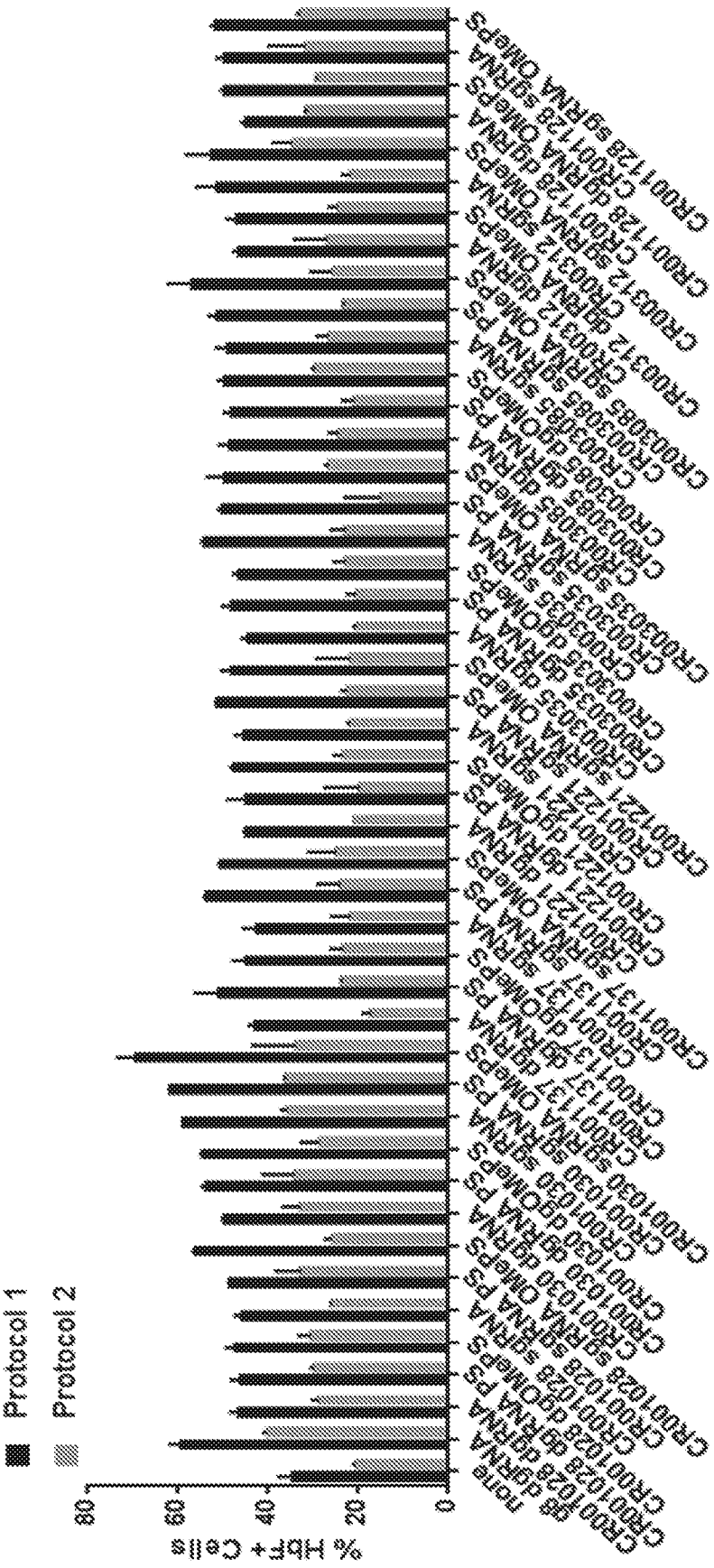

Protocol 1
Protocol 2
% HbF+ Cells
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20
40
60
80
mock
CR001028 dgRNA
CR001028 dgRNA PS
CR001028 dgOMeps
CR001028 dgOMeps PS
CR001028 sgRNA
CR001028 sgRNA PS
CR001028 sgOMeps
CR001028 sgOMeps PS
CR001030 dgRNA
CR001030 dgRNA PS
CR001030 dgOMeps
CR001030 dgOMeps PS
CR001030 sgRNA
CR001030 sgRNA PS
CR001030 sgOMeps
CR001030 sgOMeps PS
CR001137 dgRNA
CR001137 dgRNA PS
CR001137 dgOMeps
CR001137 dgOMeps PS
CR001137 sgRNA
CR001137 sgRNA PS
CR001137 sgOMeps
CR001137 sgOMeps PS
CR001221 dgRNA
CR001221 dgRNA PS
CR001221 dgOMeps
CR001221 dgOMeps PS
CR001221 sgRNA
CR001221 sgRNA PS
CR001221 sgOMeps
CR001221 sgOMeps PS
CR003035 dgRNA
CR003035 dgRNA PS
CR003035 dgOMeps
CR003035 dgOMeps PS
CR003035 sgRNA
CR003035 sgRNA PS
CR003035 sgOMeps
CR003035 sgOMeps PS
CR003085 dgRNA
CR003085 dgRNA PS
CR003085 dgOMeps
CR003085 dgOMeps PS
CR003085 sgRNA
CR003085 sgRNA PS
CR003085 sgOMeps
CR003085 sgOMeps PS
CR003112 dgRNA
CR003112 dgRNA PS
CR003112 dgOMeps
CR003112 dgOMeps PS
CR003112 sgRNA
CR003112 sgRNA PS
CR003112 sgOMeps
CR003112 sgOMeps PS
CR001128 dgRNA
CR001128 dgRNA PS
CR001128 dgOMeps
CR001128 dgOMeps PS
CR001128 sgRNA
CR001128 sgRNA PS
CR001128 sgOMeps
CR001128 sgOMeps PS

Figure 46

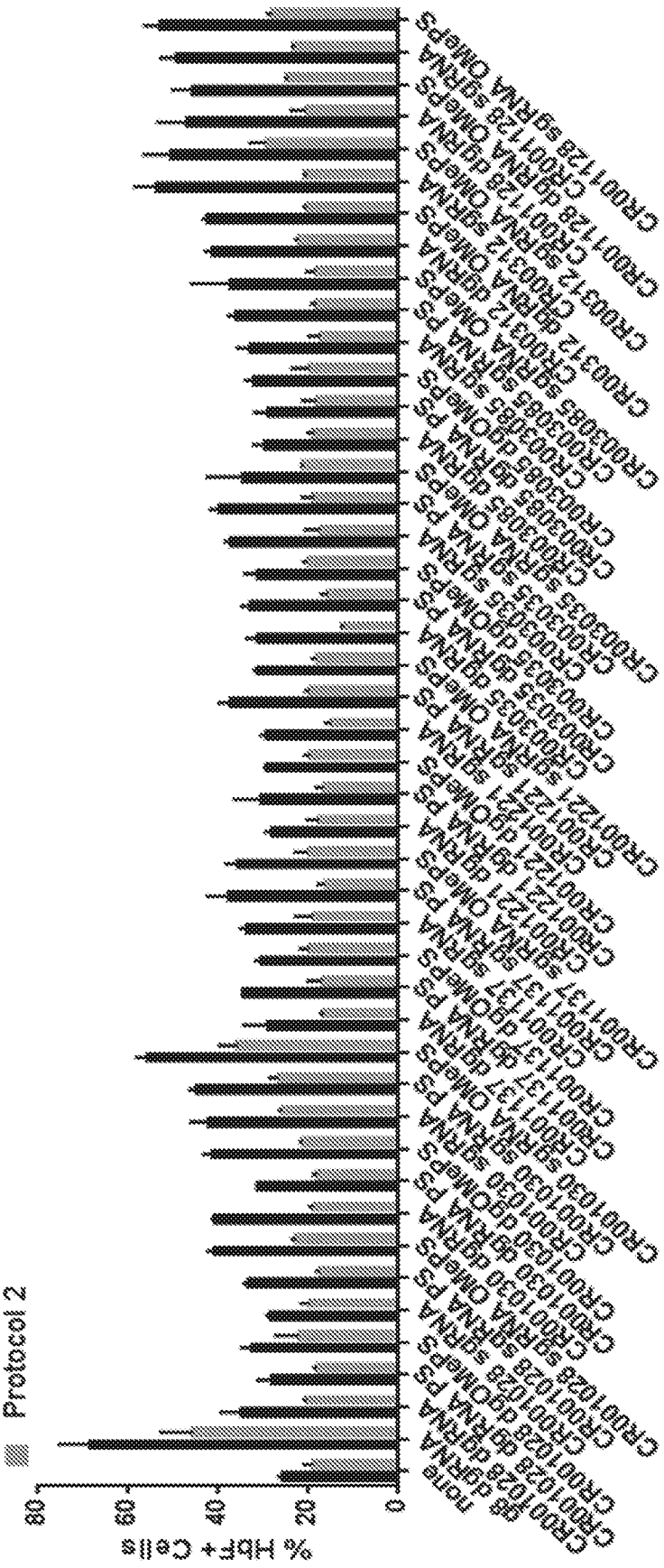

Protocol 1
Protocol 2
% HbF+ Cells
0
20
40
60
80
mock
CR001028 dgRNA
CR001028 dgRNA PS
CR001028 dgRNA OMePS
CR001028 sgRNA
CR001028 sgRNA PS
CR001028 sgRNA OMePS
CR001030 dgRNA
CR001030 dgRNA PS
CR001030 dgRNA OMePS
CR001030 sgRNA
CR001030 sgRNA PS
CR001030 sgRNA OMePS
CR001137 dgRNA
CR001137 dgRNA PS
CR001137 dgRNA OMePS
CR001137 sgRNA
CR001137 sgRNA PS
CR001137 sgRNA OMePS
CR001221 dgRNA
CR001221 dgRNA PS
CR001221 dgRNA OMePS
CR001221 sgRNA
CR001221 sgRNA PS
CR001221 sgRNA OMePS
CR003035 dgRNA
CR003035 dgRNA PS
CR003035 dgRNA OMePS
CR003035 sgRNA
CR003035 sgRNA PS
CR003035 sgRNA OMePS
CR003085 dgRNA
CR003085 dgRNA PS
CR003085 dgRNA OMePS
CR003085 sgRNA
CR003085 sgRNA PS
CR003085 sgRNA OMePS
CR003112 dgRNA
CR003112 dgRNA PS
CR003112 dgRNA OMePS
CR003112 sgRNA
CR003112 sgRNA PS
CR003112 sgRNA OMePS
CR001128 dgRNA
CR001128 dgRNA PS
CR001128 dgRNA OMePS
CR001128 sgRNA
CR001128 sgRNA PS
CR001128 sgRNA OMePS

Figure 47

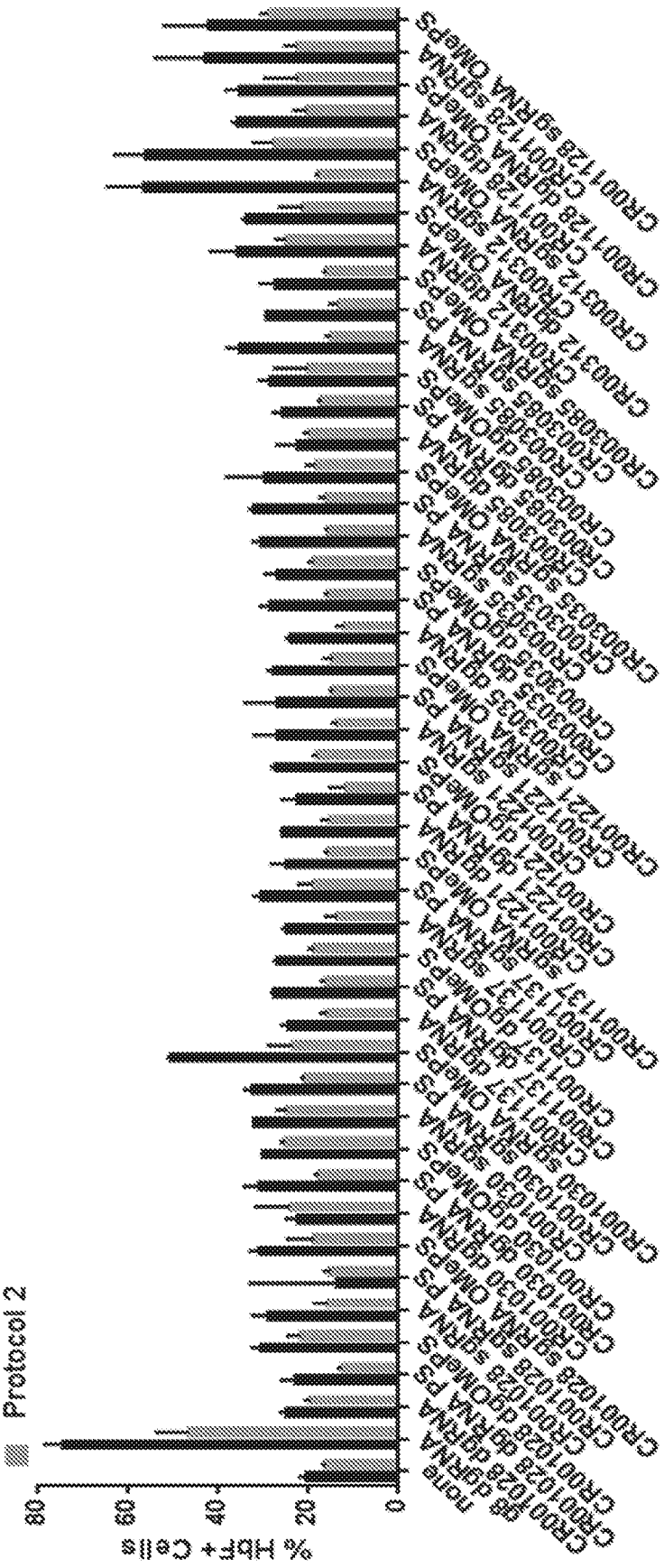

Protocol 1
Protocol 2
% HbF+ Cells
0
20
40
60
80
mock
CR001028 dgRNA
CR001028 dgRNA PS
CR001028 dgRNA OMePS
CR001028 sgRNA
CR001028 sgRNA PS
CR001028 sgRNA OMePS
CR001030 dgRNA
CR001030 dgRNA PS
CR001030 dgRNA OMePS
CR001030 sgRNA
CR001030 sgRNA PS
CR001030 sgRNA OMePS
CR001137 dgRNA
CR001137 dgRNA PS
CR001137 dgRNA OMePS
CR001137 sgRNA
CR001137 sgRNA PS
CR001137 sgRNA OMePS
CR001221 dgRNA
CR001221 dgRNA PS
CR001221 dgRNA OMePS
CR001221 sgRNA
CR001221 sgRNA PS
CR001221 sgRNA OMePS
CR003035 dgRNA
CR003035 dgRNA PS
CR003035 dgRNA OMePS
CR003035 sgRNA
CR003035 sgRNA PS
CR003035 sgRNA OMePS
CR003085 dgRNA
CR003085 dgRNA PS
CR003085 dgRNA OMePS
CR003085 sgRNA
CR003085 sgRNA PS
CR003085 sgRNA OMePS
CR003112 dgRNA
CR003112 dgRNA PS
CR003112 dgRNA OMePS
CR003112 sgRNA
CR003112 sgRNA PS
CR003112 sgRNA OMePS
CR001128 dgRNA
CR001128 dgRNA PS
CR001128 dgRNA OMePS
CR001128 sgRNA
CR001128 sgRNA PS
CR001128 sgRNA OMePS

Figure 48

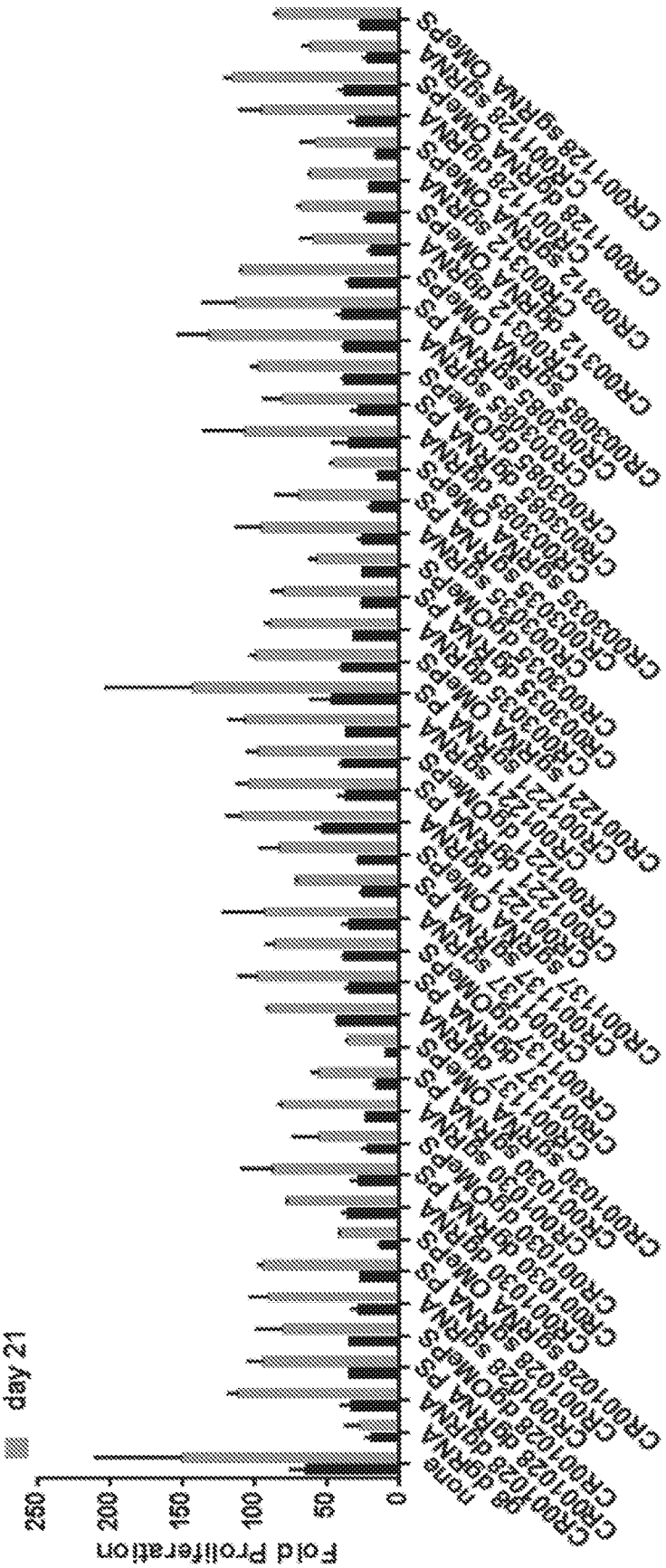
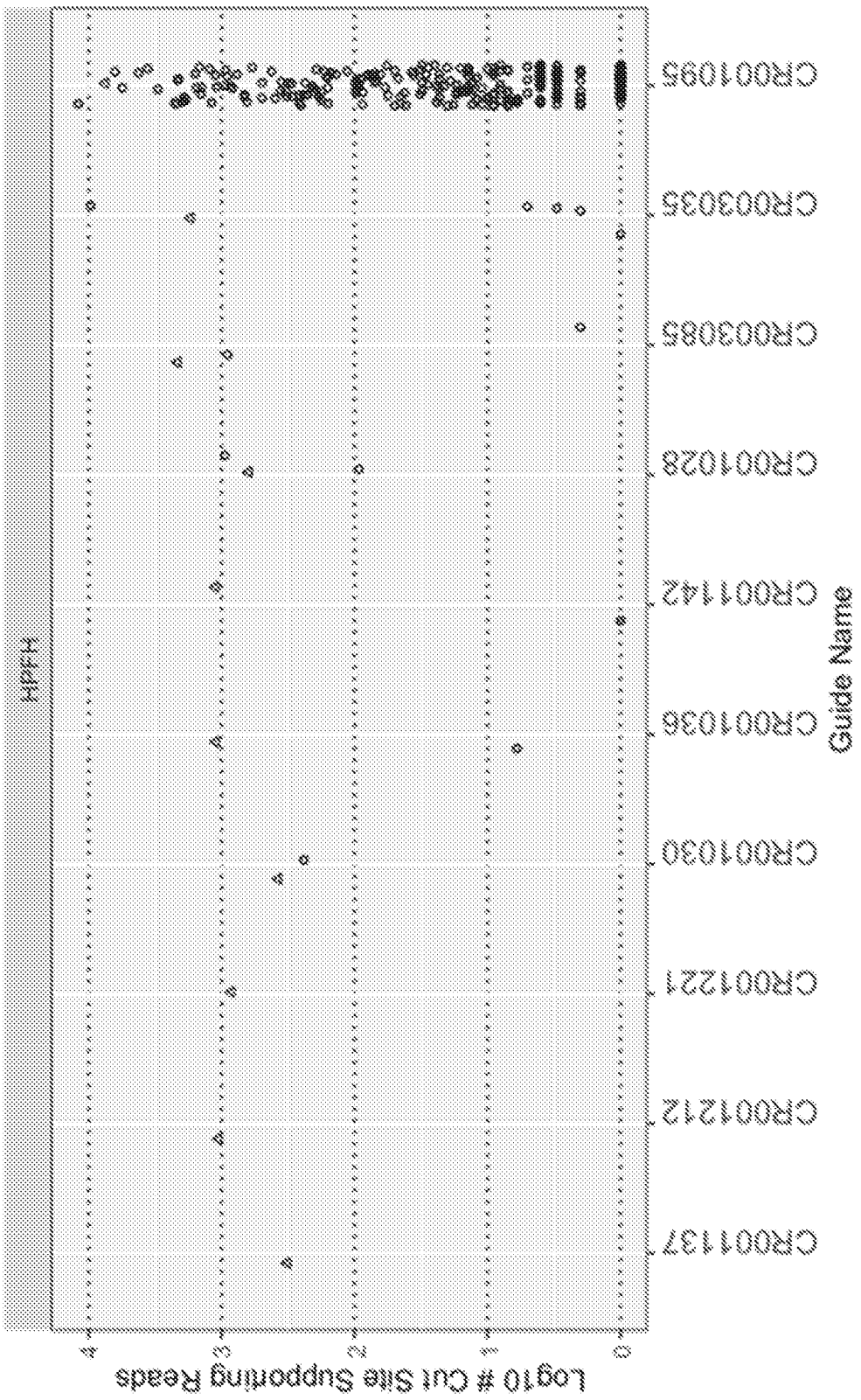

day 7
day 21
Fold Proliferation
250
200
150
100
50
0
none
CR001028 dgRNA
CR001028 dgRNA OMeps
CR001028 dgRNA PS
CR001028 dgOMeps
CR001028 sgRNA
CR001028 sgRNA OMeps
CR001028 sgRNA PS
CR001030 dgRNA
CR001030 dgRNA OMeps
CR001030 dgRNA PS
CR001030 dgOMeps
CR001030 sgRNA
CR001030 sgRNA OMeps
CR001030 sgRNA PS
CR001137 dgRNA
CR001137 dgRNA OMeps
CR001137 dgRNA PS
CR001137 dgOMeps
CR001137 sgRNA
CR001137 sgRNA OMeps
CR001137 sgRNA PS
CR001221 dgRNA
CR001221 dgRNA OMeps
CR001221 dgRNA PS
CR001221 dgOMeps
CR001221 sgRNA
CR001221 sgRNA OMeps
CR001221 sgRNA PS
CR001722 dgRNA
CR001722 dgRNA OMeps
CR001722 dgRNA PS
CR001722 dgOMeps
CR001722 sgRNA
CR001722 sgRNA OMeps
CR001722 sgRNA PS
CR003035 dgRNA
CR003035 dgRNA OMeps
CR003035 dgRNA PS
CR003035 dgOMeps
CR003035 sgRNA
CR003035 sgRNA OMeps
CR003035 sgRNA PS
CR003085 dgRNA
CR003085 dgRNA OMeps
CR003085 dgRNA PS
CR003085 dgOMeps
CR003085 sgRNA
CR003085 sgRNA OMeps
CR003085 sgRNA PS
CR003123 dgRNA
CR003123 dgRNA OMeps
CR003123 dgRNA PS
CR003123 dgOMeps
CR003123 sgRNA
CR003123 sgRNA OMeps
CR003123 sgRNA PS
CR001728 dgRNA
CR001728 dgRNA OMeps
CR001728 dgRNA PS
CR001728 dgOMeps
CR001728 sgRNA
CR001728 sgRNA OMeps
CR001728 sgRNA PS

Figure 49


HPFH
Log10 # Cut Site Supporting Reads
0
1
2
3
4
Guide Name
CR001137
CR001212
CR001221
CR001030
CR001036
CR001142
CR001028
CR003085
CR003035
CR001095

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SEQUENCE LISTING

<110> NOVARTIS AG
INTELLIA THERAPEUTICS, INC.

<120> COMPOSITIONS AND METHODS FOR THE TREATMENT OF HEMOGLOBINOPATHIES

<130> PAT057179-WO-PCT

<140> PCT/IB2016/058007
<141> 2016-12-26

<150> 62/347,484
<151> 2016-06-08

<150> 62/271,968
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<170> PatentIn version 3.5

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<400> 1
acaggccgug aaccuaagug 20

<210> 2
<211> 20
<212> RNA
<213> Artificial Sequence

<220>
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<223> /note="Description of Artificial Sequence: Synthetic oligonucleotide"

<400> 2
uagagggggg aaauuauagg 20

<210> 3
<211> 20
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<213> Artificial Sequence

<220>
<221> source

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<400> 3
cgagcgguaa auccuaaaga 20

<210> 4
<211> 20
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<400> 4
agacaaauuc aaauccugca 20

<210> 5
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<212> RNA
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic oligonucleotide"

<400> 5
gcuuuuggug gcuaccaugc 20

<210> 6
<211> 20
<212> RNA
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic oligonucleotide"

<400> 6
aauuuaugcc aucugauaag 20

<210> 7
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<220>
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<223> /note="Description of Artificial Sequence: Synthetic

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oligonucleotide"

<400> 7
uguuccuccu acccacccga 20

<210> 8
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<400> 8
auaaauguug gagcuuuagg 20

<210> 9
<211> 20
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<213> Artificial Sequence

<220>
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caaccuaauu accuguauug 20

<210> 10
<211> 20
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<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic oligonucleotide"

<400> 10
cgcugucaug agugaugccc 20

<210> 11
<211> 20
<212> RNA
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic oligonucleotide"

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<400> 11
ggcaucacuc augacagcga 20

<210> 12
<211> 20
<212> RNA
<213> Artificial Sequence

<220>
<221> source
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<400> 12
agucccauag agagggcccg 20

<210> 13
<211> 20
<212> RNA
<213> Artificial Sequence

<220>
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<400> 13
acugauucac uguuccaaug 20

<210> 14
<211> 20
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<400> 14
aggacucugu cuucgcacaa 20

<210> 15
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<400> 15
ccacgcugac gucgacuggg 20

<210> 16
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<213> Artificial Sequence

<220>
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<400> 16
guucuucaca caccccccauu 20

<210> 17
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<213> Artificial Sequence

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<400> 17
gcgcuucucc acaccgcccg 20

<210> 18
<211> 20
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<213> Artificial Sequence

<220>
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<223> /note="Description of Artificial Sequence: Synthetic oligonucleotide"

<400> 18
gucuggaguc uccgaagcua 20

<210> 19
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<220>
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<400> 19

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aaagaucccu uccuuagcuu 20

<210> 20
<211> 20
<212> RNA
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic oligonucleotide"

<400> 20
ucgccggcua cgcggccucc 20

<210> 21
<211> 20
<212> RNA
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic oligonucleotide"

<400> 21
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<210> 22
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<213> Artificial Sequence

<220>
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<400> 22
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<210> 23
<211> 20
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<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic oligonucleotide"

<400> 23
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2016381313 31 Jul 2018

<210> 24
<211> 20
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<213> Artificial Sequence

<220>
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<400> 24
caccaugccc ugcaugacgu 20

<210> 25
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<220>
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<400> 25
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<210> 26
<211> 20
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<400> 26
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<210> 27
<211> 20
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<400> 27
gcccaccaag ucgcuggugc 20

2016381313 31 Jul 2018

<210> 28
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<400> 28
cccaccaagu cgcuggugcc 20

<210> 29
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ggcgguggag agaccgucgu 20

<210> 30
<211> 20
<212> RNA
<213> Artificial Sequence

<220>
<221> source
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<400> 30
gccgcagaac ucgcaugacu 20

<210> 31
<211> 20
<212> RNA
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic oligonucleotide"

<400> 31
ccgcccccag gcgcucuaug 20

2016381313 31 Jul 2018

<210> 32
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<212> RNA
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<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic oligonucleotide"

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<210> 33
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<400> 33
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<210> 34
<211> 20
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<220>
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<223> /note="Description of Artificial Sequence: Synthetic oligonucleotide"

<400> 34
agugcagaau augccccgca 20

<210> 35
<211> 20
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<220>
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<223> /note="Description of Artificial Sequence: Synthetic oligonucleotide"

<400> 35
gcauauucug cacucauccc 20

<210> 36

2016381313 31 Jul 2018

<211> 20
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<210> 37
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<213> Artificial Sequence

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<400> 37
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<210> 38
<211> 20
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<213> Artificial Sequence

<220>
<221> source
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<210> 39
<211> 20
<212> RNA
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<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic oligonucleotide"

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<210> 40
<211> 20

2016381313 31 Jul 2018

<212> RNA
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic oligonucleotide"

<400> 40
uauccaaauu cauacaauag 20

<210> 41
<211> 20
<212> RNA
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic oligonucleotide"

<400> 41
augcccugag uaucccaaca 20

<210> 42
<211> 20
<212> RNA
<213> Artificial Sequence

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2016381313 31 Jul 2018

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2016381313 31 Jul 2018

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2016381313 31 Jul 2018

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Phe Ser Pro Glu Pro Leu Glu Ala Ile Leu Thr Asp Asp Glu Pro Asp
            20                  25                  30

His Gly Pro Leu Gly Ala Pro Glu Gly Asp His Asp Leu Leu Thr Cys
        35                  40                  45

Gly Gln Cys Gln Met Asn Phe Pro Leu Gly Asp Ile Leu Ile Phe Ile
    50                  55                  60

Glu His Lys Arg Lys Gln Cys Asn Gly Ser Leu Cys Leu Glu Lys Ala
65                  70                  75                  80

Val Asp Lys Pro Pro Ser Pro Ser Pro Ile Glu Met Lys Lys Ala Ser
                85                  90                  95

Asn Pro Val Glu Val Gly Ile Gln Val Thr Pro Glu Asp Asp Asp Cys
            100                 105                 110

Leu Ser Thr Ser Ser Arg Gly Ile Cys Pro Lys Gln Glu His Ile Ala
        115                 120                 125

Asp Lys Leu Leu His Trp Arg Gly Leu Ser Ser Pro Arg Ser Ala His
    130                 135                 140

Gly Ala Leu Ile Pro Thr Pro Gly Met Ser Ala Glu Tyr Ala Pro Gln
145                 150                 155                 160

Gly Ile Cys Lys Asp Glu Pro Ser Ser Tyr Thr Cys Thr Thr Cys Lys
                165                 170                 175

Gln Pro Phe Thr Ser Ala Trp Phe Leu Leu Gln His Ala Gln Asn Thr
            180                 185                 190

His Gly Leu Arg Ile Tyr Leu Glu Ser Glu His Gly Ser Pro Leu Thr
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Pro Arg Val Gly Ile Pro Ser Gly Leu Gly Ala Glu Cys Pro Ser Gln
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Pro Pro Leu His Gly Ile His Ile Ala Asp Asn Asn Pro Phe Asn Leu
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Leu Arg Ile Pro Gly Ser Val Ser Arg Glu Ala Ser Gly Leu Ala Glu
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Gly Arg Phe Pro Pro Thr Pro Pro Leu Phe Ser Pro Pro Pro Arg His
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His Leu Asp Pro His Arg Ile Glu Arg Leu Gly Ala Glu Glu Met Ala
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Leu Ala Thr His His Pro Ser Ala Phe Asp Arg Val Leu Arg Leu Asn
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Pro Met Ala Met Glu Pro Pro Ala Met Asp Phe Ser Arg Arg Leu Arg
305                 310                 315                 320

Glu Leu Ala Gly Asn Thr Ser Ser Pro Pro Leu Ser Pro Gly Arg Pro
                325                 330                 335

Ser Pro Met Gln Arg Leu Leu Gln Pro Phe Gln Pro Gly Ser Lys Pro
            340                 345                 350

Pro Phe Leu Ala Thr Pro Pro Leu Pro Pro Leu Gln Ser Ala Pro Pro
        355                 360                 365

Pro Ser Gln Pro Pro Val Lys Ser Lys Ser Cys Glu Phe Cys Gly Lys
    370                 375                 380

Thr Phe Lys Phe Gln Ser Asn Leu Val Val His Arg Arg Ser His Thr
385                 390                 395                 400

Gly Glu Lys Pro Tyr Lys Cys Asn Leu Cys Asp His Ala Cys Thr Gln
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Ala Ser Lys Leu Lys Arg His Met Lys Thr His Met His Lys Ser Ser
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Pro Met Thr Val Lys Ser Asp Asp Gly Leu Ser Thr Ala Ser Ser Pro
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Glu Pro Gly Thr Ser Asp Leu Val Gly Ser Ala Ser Ser Ala Leu Lys
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Ser Val Val Ala Lys Phe Lys Ser Glu Asn Asp Pro Asn Leu Ile Pro
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Glu Glu Glu Glu Glu Glu Glu Glu Leu Thr Glu Ser Glu Arg Val Asp
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Tyr Gly Phe Gly Leu Ser Leu Glu Ala Ala Arg His His Glu Asn Ser
515 520 525

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

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690 695 700

Glu Leu Asp Gly Gly Ile Ser Gly Arg Ser Gly Thr Gly Ser Gly Gly
705 710 715 720

Ser Thr Pro His Ile Ser Gly Pro Gly Pro Gly Arg Pro Ser Ser Lys
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Glu Gly Arg Arg Ser Asp Thr Cys Glu Tyr Cys Gly Lys Val Phe Lys
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Asn Cys Ser Asn Leu Thr Val His Arg Arg Ser His Thr Gly Glu Arg
755 760 765

Pro Tyr Lys Cys Glu Leu Cys Asn Tyr Ala Cys Ala Gln Ser Ser Lys
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Leu Thr Arg His Met Lys Thr His Gly Gln Val Gly Lys Asp Val Tyr
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Lys Cys Glu Ile Cys Lys Met Pro Phe Ser Val Tyr Ser Thr Leu Glu
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<210> 2017
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<400> 2017
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<210> 2018
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<223> /note="Description of Artificial Sequence: Synthetic primer"

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<210> 2019
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<400> 2024
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<210> 2033
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<400> 2037
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g 61

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<210> 2045
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<210> 2046
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<210> 2047
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<400> 2047
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<210> 2048
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<210> 2049
<211> 55
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g 61

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<210> 2053
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<210> 2055
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g 61

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<210> 2059
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<400> 2059
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<210> 2060
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<210> 2061
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<210> 2062
<211> 53
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<400> 2062
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<210> 2063
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g 61

<210> 2064
<211> 52
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<220>
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<210> 2065
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<220>
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<400> 2065

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g 61

<210> 2066
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<210> 2067
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<210> 2068
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<210> 2069
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<400> 2069
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g 61

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<400> 2070
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<210> 2071
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<400> 2071
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g 61

<210> 2072
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<400> 2072
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<210> 2073
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<223> /note="Description of Artificial Sequence: Synthetic oligonucleotide"

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<210> 2074
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<400> 2074
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g 61

<210> 2075
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<210> 2076
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<210> 2077
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<221> source
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<210> 2078
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<400> 2078
agctaacagt tgcttttatc caggaagggt ttggcctctg attagggtgg gg 52

<210> 2079
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<400> 2079
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g 61

<210> 2080
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g 61

<210> 2081
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<213> Artificial Sequence

<220>
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<210> 2082
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<400> 2082
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<210> 2083
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<220>
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<400> 2083
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t 61

<210> 2084
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<223> /note="Description of Artificial Sequence: Synthetic oligonucleotide"

<400> 2084
aacagttgct tttatcacag gcctctgatt agggtggggg cgt 43

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<212> DNA
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<220>
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<400> 2085
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<210> 2086
<211> 53
<212> DNA
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<220>
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<223> /note="Description of Artificial Sequence: Synthetic oligonucleotide"

<400> 2086
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<210> 2087
<211> 24
<212> DNA
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<220>
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<223> /note="Description of Artificial Sequence: Synthetic oligonucleotide"

<400> 2087
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<210> 2088
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<220>
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<223> /note="Description of Artificial Sequence: Synthetic oligonucleotide"

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t 61

<210> 2089

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<211> 49
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<220>
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<210> 2090
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<400> 2090
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<210> 2091
<211> 43
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<223> /note="Description of Artificial Sequence: Synthetic oligonucleotide"

<400> 2091
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<210> 2092
<211> 48
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<400> 2092
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<210> 2093
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<212> DNA
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<400> 2093
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<210> 2094
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<223> /note="Description of Artificial Sequence: Synthetic oligonucleotide"

<400> 2094
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<210> 2095
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<400> 2095
acagttgctt ttatcacagg ctccagaagg gtttggcctc tgattagggt gggggcgtg 59

<210> 2096
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<400> 2096
acagttgctt ttatcacagg gtttggcctc tgattagggt gggggcgtg 49

<210> 2097
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<213> Artificial Sequence

<220>
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g 61

<210> 2098
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<400> 2098
acagttgctt ttatcacagg cctctgatta gggtgggggc gtg 43

<210> 2099
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<400> 2099
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<210> 2100
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<400> 2100
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<210> 2101
<211> 59

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<212> DNA
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<210> 2102
<211> 49
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<220>
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<223> /note="Description of Artificial Sequence: Synthetic oligonucleotide"

<400> 2102
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<210> 2103
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<400> 2103
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g 61

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<400> 2112
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<210> 2123
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a 61

<210> 2127
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<400> 2127
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<210> 2128
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<400> 2128
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<211> 42
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<210> 2130
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c 61

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c 61

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<212> DNA
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<400> 2219
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<220>
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<210> 2229
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<400> 2231
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<220>
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<210> 2237
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<220>
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aggaagggtt tggcctctga ttagtggggg cgtgggtggg gtagaagagg actggcag 58

<210> 2243
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<220>
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<210> 2245
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<210> 2247
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<212> DNA
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<223> /note="Description of Artificial Sequence: Synthetic oligonucleotide"

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<210> 2256
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<220>
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a 61

<210> 2268
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<210> 2269
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<210> 2270
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<400> 2272
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c 61

<210> 2273
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<210> 2278
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<210> 2279
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<400> 2280
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<210> 2281
<211> 61
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<220>
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<223> /note="Description of Artificial Sequence: Synthetic oligonucleotide"

<400> 2281
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<210> 2282
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<400> 2282
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<210> 2283
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<400> 2283
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<210> 2284
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<212> DNA
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<220>
<221> source
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<400> 2284
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<210> 2285
<211> 58
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<220>
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<400> 2285
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<210> 2286
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<400> 2286
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<210> 2287
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<223> /note="Description of Artificial Sequence: Synthetic oligonucleotide"

<400> 2287
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<210> 2288
<211> 59
<212> DNA
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic oligonucleotide"

<400> 2288
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<210> 2289
<211> 58
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<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic oligonucleotide"

<400> 2289
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<210> 2290
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<400> 2290
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a 61

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<400> 2291
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<210> 2293
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<220>
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<400> 2293
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<400> 2294
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<210> 2295
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<220>
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<400> 2295
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a 61

<210> 2296
<211> 58
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<220>
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<223> /note="Description of Artificial Sequence: Synthetic oligonucleotide"

<400> 2296
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<210> 2297
<211> 57
<212> DNA
<213> Artificial Sequence

<220>
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<223> /note="Description of Artificial Sequence: Synthetic oligonucleotide"

<400> 2297
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<210> 2298
<211> 36
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<220>
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<222> (1)..(20)
<223> a, c, u, g, unknown or other

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<220>
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<210> 2300
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<220>
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<222> (1)..(20)
<223> a, c, u, g, unknown or other

<400> 2300
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<210> 2301
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<212> DNA
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<220>
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<400> 2301
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atgactaaaa tgg 73

<210> 2302
<211> 81
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<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic oligonucleotide"

<400> 2302
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gctatctaat gactaaaatg g 81

<210> 2303
<211> 77
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<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic oligonucleotide"

<400> 2303
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tctaatgact aaaatgg 77

<210> 2304
<211> 79
<212> DNA
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic oligonucleotide"

<400> 2304
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tatctaatga ctaaaatgg 79

<210> 2305
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<212> DNA

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<213> Artificial Sequence

<220>
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<223> /note="Description of Artificial Sequence: Synthetic oligonucleotide"

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gactaaaatg g 71

<210> 2306
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<212> DNA
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<400> 2306
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aaatacccat 70

<210> 2307
<211> 81
<212> DNA
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<220>
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<223> /note="Description of Artificial Sequence: Synthetic oligonucleotide"

<400> 2307
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tataacaagt gaaataccca t 81

<210> 2308
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<400> 2308
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aacaagtgaa atacccat 78

<210> 2309
<211> 78
<212> DNA
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<220>
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<223> /note="Description of Artificial Sequence: Synthetic oligonucleotide"

<400> 2309
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aacaagtgaa atacccat 78

<210> 2310
<211> 81
<212> DNA
<213> Artificial Sequence

<220>
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<223> /note="Description of Artificial Sequence: Synthetic oligonucleotide"

<400> 2310
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tataacaagt gaaataccca t 81

<210> 2311
<211> 77
<212> DNA
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<220>
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<400> 2311
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taggacatct atataaa 77

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<211> 79
<212> DNA
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<220>
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<223> /note="Description of Artificial Sequence: Synthetic oligonucleotide"

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tataggacat ctatataaa 79

<210> 2313
<211> 78
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<220>
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<400> 2313
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ataggacatc tatataaa 78

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<220>
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<400> 2314
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ataggacatc tatataaa 78

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<400> 2315
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aggacatcta tataaa 76

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<210> 2316
<211> 70
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<220>
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<223> /note="Description of Artificial Sequence: Synthetic oligonucleotide"

<400> 2316
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gtttgatata 70

<210> 2317
<211> 79
<212> DNA
<213> Artificial Sequence

<220>
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<223> /note="Description of Artificial Sequence: Synthetic oligonucleotide"

<400> 2317
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cagtacattg tttgatata 79

<210> 2318
<211> 81
<212> DNA
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<220>
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<400> 2318
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cccagtacat tgtttgatat a 81

<210> 2319
<211> 81
<212> DNA
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<220>
<221> source

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<223> /note="Description of Artificial Sequence: Synthetic oligonucleotide"

<400> 2319
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cccagtacat tgtttgatat a 81

<210> 2320
<211> 79
<212> DNA
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<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic oligonucleotide"

<400> 2320
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cagtacattg tttgatata 79

<210> 2321
<211> 69
<212> DNA
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<400> 2321
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cattgtttg 69

<210> 2322
<211> 79
<212> DNA
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<400> 2322
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aagcccagta cattgtttg 79

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<210> 2323
<211> 79
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<220>
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<400> 2323
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aagcccagta cattgtttg 79

<210> 2324
<211> 81
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<220>
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<223> /note="Description of Artificial Sequence: Synthetic oligonucleotide"

<400> 2324
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ataagcccag tacattgttt g 81

<210> 2325
<211> 81
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<400> 2325
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ataagcccag tacattgttt g 81

<210> 2326
<211> 78
<212> DNA
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<220>
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<223> /note="Description of Artificial Sequence: Synthetic oligonucleotide"

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<400> 2326
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ataactgtga atccaaga 78

<210> 2327
<211> 81
<212> DNA
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<220>
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<223> /note="Description of Artificial Sequence: Synthetic oligonucleotide"

<400> 2327
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gatataactg tgaatccaag a 81

<210> 2328
<211> 79
<212> DNA
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic oligonucleotide"

<400> 2328
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tataactgtg aatccaaga 79

<210> 2329
<211> 81
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<220>
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<223> /note="Description of Artificial Sequence: Synthetic oligonucleotide"

<400> 2329
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gatataactg tgaatccaag a 81

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<211> 82

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<212> DNA
<213> Artificial Sequence

<220>
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<223> /note="Description of Artificial Sequence: Synthetic oligonucleotide"

<400> 2330
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agatataact gtgaatccaa ga 82

<210> 2331
<211> 79
<212> DNA
<213> Artificial Sequence

<220>
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<223> /note="Description of Artificial Sequence: Synthetic oligonucleotide"

<400> 2331
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atgggttata tccttctac 79

<210> 2332
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<400> 2332
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atccttctac 70

<210> 2333
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<220>
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<223> /note="Description of Artificial Sequence: Synthetic oligonucleotide"

<400> 2333

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tgtaaggagg atgagccaca tggtatggga ctctagggtc agagaaatat gggttatatc 60

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<210> 2334
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<212> DNA
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<220>
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<400> 2334
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atatgggtta tatccttcta c 81

<210> 2335
<211> 75
<212> DNA
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<220>
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<223> /note="Description of Artificial Sequence: Synthetic oligonucleotide"

<400> 2335
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gttatatcct tctac 75

<210> 2336
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<400> 2336
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atatccttct acaaaattca c 81

<210> 2337
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<220>
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<223> /note="Description of Artificial Sequence: Synthetic oligonucleotide"

<400> 2337
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acaaaattca c 71

<210> 2338
<211> 72
<212> DNA
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic oligonucleotide"

<400> 2338
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tacaaaattc ac 72

<210> 2339
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<223> /note="Description of Artificial Sequence: Synthetic oligonucleotide"

<400> 2339
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tccttctaca aaattcac 78

<210> 2340
<211> 71
<212> DNA
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic oligonucleotide"

<400> 2340
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<210> 2341
<211> 36
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<220>
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<220>
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<223> a, c, u, g, unknown or other

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<210> 2342
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<212> RNA
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<220>
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<223> /note="Description of Artificial Sequence: Synthetic oligonucleotide"

<220>
<221> modified_base
<222> (1)..(20)
<223> a, c, u, g, unknown or other

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<220>
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<222> (1)..(20)

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<223> a, c, u, g, unknown or other

<400> 2343
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<210> 2344
<211> 36
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<220>
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<223> /note="Description of Artificial Sequence: Synthetic oligonucleotide"

<220>
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<222> (1)..(20)
<223> a, c, u, g, unknown or other

<400> 2344
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<210> 2345
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<220>
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<222> (1)..(20)
<223> a, c, u, g, unknown or other

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<400> 2346

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ctctttcagc agttgtttc 79

<210> 2347
<211> 67
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<220>
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<223> /note="Description of Artificial Sequence: Synthetic oligonucleotide"

<400> 2347
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<210> 2348
<211> 76
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<220>
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<223> /note="Description of Artificial Sequence: Synthetic oligonucleotide"

<400> 2348
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tttcagcagt tgtttc 76

<210> 2349
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<400> 2349
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tctttcagca gttgtttc 78

<210> 2350
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<220>
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ttgtttc 67

<210> 2351
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<220>
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<223> /note="Description of Artificial Sequence: Synthetic oligonucleotide"

<400> 2351
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ttgtttc 67

<210> 2352
<211> 79
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<220>
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<400> 2352
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ctctttcagc agttgtttc 79

<210> 2353
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<400> 2353
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tctttcagca gttgtttc 78

<210> 2354
<211> 76
<212> DNA
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<220>
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<223> /note="Description of Artificial Sequence: Synthetic oligonucleotide"

<400> 2354
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tttcagcagt tgtttc 76

<210> 2355
<211> 67
<212> DNA
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic oligonucleotide"

<400> 2355
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ttgtttc 67

<210> 2356
<211> 67
<212> DNA
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic oligonucleotide"

<400> 2356
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atcctcc 67

<210> 2357
<211> 79
<212> DNA
<213> Artificial Sequence

<220>

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<221> source
<223> /note="Description of Artificial Sequence: Synthetic oligonucleotide"

<400> 2357
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gtttctaaaa atatcctcc 79

<210> 2358
<211> 78
<212> DNA
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic oligonucleotide"

<400> 2358
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tttctaaaaa tatcctcc 78

<210> 2359
<211> 81
<212> DNA
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic oligonucleotide"

<400> 2359
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ttgtttctaa aaatatcctc c 81

<210> 2360
<211> 75
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<213> Artificial Sequence

<220>
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<223> /note="Description of Artificial Sequence: Synthetic oligonucleotide"

<400> 2360
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ctaaaaatat cctcc 75

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<210> 2361
<211> 67
<212> DNA
<213> Artificial Sequence

<220>
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<223> /note="Description of Artificial Sequence: Synthetic oligonucleotide"

<400> 2361
tcttgactca gaaaccctgt tctcctctac atatctcttt cagcagttgt ttctaaaaat 60

atcctcc 67

<210> 2362
<211> 79
<212> DNA
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic oligonucleotide"

<400> 2362
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gtttctaaaa atatcctcc 79

<210> 2363
<211> 78
<212> DNA
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic oligonucleotide"

<400> 2363
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tttctaaaaa tatcctcc 78

<210> 2364
<211> 81
<212> DNA
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic

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oligonucleotide"

<400> 2364
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ttgtttctaa aaatatcctc c 81

<210> 2365
<211> 79
<212> DNA
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic oligonucleotide"

<400> 2365
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gtttctaaaa atatcctcc 79

<210> 2366
<211> 79
<212> DNA
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic oligonucleotide"

<400> 2366
cctagtttca tttttgcaga agtgttttag gctaattagt ggaatgtatc ttagagttta 60

acttatttgt ttctgtcac 79

<210> 2367
<211> 78
<212> DNA
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic oligonucleotide"

<400> 2367
cctagtttca tttttgcaga agtgttttag gctaatagtg gaatgtatct tagagtttaa 60

cttatttgtt tctgtcac 78

<210> 2368

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<211> 70
<212> DNA
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic oligonucleotide"

<400> 2368
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tttctgtcac 70

<210> 2369
<211> 81
<212> DNA
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic oligonucleotide"

<400> 2369
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taacttattt gtttctgtca c 81

<210> 2370
<211> 79
<212> DNA
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic oligonucleotide"

<400> 2370
cctagtttca tttttgcaga agtgttttag gctaataagt ggaatgtatc ttagagttta 60

acttatttgt ttctgtcac 79

<210> 2371
<211> 78
<212> DNA
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic oligonucleotide"

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<400> 2371
cctagtttca tttttgcaga agtgttttag gctaatagtg gaatgtatct tagagtttaa 60

cttatttgtt tctgtcac 78

<210> 2372
<211> 79
<212> DNA
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic oligonucleotide"

<400> 2372
cctagtttca tttttgcaga agtgttttag gctaattagt ggaatgtatc ttagagttta 60

acttatttgt ttctgtcac 79

<210> 2373
<211> 70
<212> DNA
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic oligonucleotide"

<400> 2373
cctagtttca tttttgcaga agtgttttag tggaatgtat cttagagttt aacttatttg 60

tttctgtcac 70

<210> 2374
<211> 79
<212> DNA
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic oligonucleotide"

<400> 2374
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acttatttgt ttctgtcac 79

<210> 2375
<211> 68
<212> DNA

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<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic oligonucleotide"

<400> 2375
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tctgtcac 68

<210> 2376
<211> 79
<212> DNA
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic oligonucleotide"

<400> 2376
tagagatttt tgtctccaag ggaattttga gaggttgaat ggacaaatct attgctgcag 60

tttaaacttg cttgcttcc 79

<210> 2377
<211> 75
<212> DNA
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic oligonucleotide"

<400> 2377
tagagatttt tgtctccaag ggaattttga gaggttggac aaatctattg ctgcagttta 60

aacttgcttg cttcc 75

<210> 2378
<211> 71
<212> DNA
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic oligonucleotide"

<400> 2378
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tgcttgcttc c 71

<210> 2379
<211> 71
<212> DNA
<213> Artificial Sequence

<220>
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<223> /note="Description of Artificial Sequence: Synthetic oligonucleotide"

<400> 2379
tagagatttt tgtctccaag ggaattttga gaggacaaat ctattgctgc agtttaaact 60

tgcttgcttc c 71

<210> 2380
<211> 81
<212> DNA
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic oligonucleotide"

<400> 2380
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agtttaaact tgcttgcttc c 81

<210> 2381
<211> 79
<212> DNA
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic oligonucleotide"

<400> 2381
tagagatttt tgtctccaag ggaattttga gaggttgaat ggacaaatct attgctgcag 60

tttaaacttg cttgcttcc 79

<210> 2382
<211> 71
<212> DNA
<213> Artificial Sequence

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<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic oligonucleotide"

<400> 2382
tagagatttt tgtctccaag ggaattttga gaggacaaat ctattgctgc agtttaaact 60

tgcttgcttc c 71

<210> 2383
<211> 75
<212> DNA
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic oligonucleotide"

<400> 2383
tagagatttt tgtctccaag ggaattttga gaggttggac aaatctattg ctgcagttta 60

aacttgcttg cttcc 75

<210> 2384
<211> 81
<212> DNA
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<220>
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<223> /note="Description of Artificial Sequence: Synthetic oligonucleotide"

<400> 2384
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agtttaaact tgcttgcttc c 81

<210> 2385
<211> 71
<212> DNA
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<220>
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<400> 2385
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tgcttgcttc c 71

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<210> 2386
<211> 79
<212> DNA
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<220>
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<223> /note="Description of Artificial Sequence: Synthetic oligonucleotide"

<400> 2386
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aaataaataa tggagagga 79

<210> 2387
<211> 71
<212> DNA
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic oligonucleotide"

<400> 2387
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aatggagagg a 71

<210> 2388
<211> 72
<212> DNA
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic oligonucleotide"

<400> 2388
gagaaaggaa ggaaggaaga ggggaagaga gagggatgga ggagaagaag gaaaaataaa 60

taatggagag ga 72

<210> 2389
<211> 81
<212> DNA
<213> Artificial Sequence

<220>
<221> source

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<223> /note="Description of Artificial Sequence: Synthetic oligonucleotide"

<400> 2389
gagaaaggaa ggaaggaaga ggggaagaga gaggatggga agggatggag gagaagaagg 60

aaaaataaat aatggagagg a 81

<210> 2390
<211> 76
<212> DNA
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic oligonucleotide"

<400> 2390
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taaataatgg agagga 76

<210> 2391
<211> 71
<212> DNA
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic oligonucleotide"

<400> 2391
gagaaaggaa ggaaggaaga ggggaagaga gaggatggag gagaagaagg aaaaataaat 60

aatggagagg a 71

<210> 2392
<211> 79
<212> DNA
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic oligonucleotide"

<400> 2392
gagaaaggaa ggaaggaaga ggggaagaga gaggatgaag ggatggagga gaagaaggaa 60

aaataaataa tggagagga 79

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<210> 2393
<211> 71
<212> DNA
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<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic oligonucleotide"

<400> 2393
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aatggagagg a 71

<210> 2394
<211> 76
<212> DNA
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic oligonucleotide"

<400> 2394
gagaaaggaa ggaaggaaga ggggaagaga gaggaaggga tggaggagaa gaaggaaaaa 60

taaataatgg agagga 76

<210> 2395
<211> 72
<212> DNA
<213> Artificial Sequence

<220>
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<223> /note="Description of Artificial Sequence: Synthetic oligonucleotide"

<400> 2395
gagaaaggaa ggaaggaaga ggggaagaga gagggatgga ggagaagaag gaaaaataaa 60

taatggagag ga 72

<210> 2396
<211> 78
<212> DNA
<213> Artificial Sequence

<220>
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<223> /note="Description of Artificial Sequence: Synthetic oligonucleotide"

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<400> 2396
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aggggaaggg aaggaaaa 78

<210> 2397
<211> 75
<212> DNA
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic oligonucleotide"

<400> 2397
gagaaagaga aagggaaggg aagagaggaa agaagaggag agaaaagaaa cgaagagagg 60

ggaagggaag gaaaa 75

<210> 2398
<211> 65
<212> DNA
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic oligonucleotide"

<400> 2398
gagaaagaga aagggaaggg aagagaggag agaaaagaaa cgaagagagg ggaagggaag 60

gaaaa 65

<210> 2399
<211> 60
<212> DNA
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic oligonucleotide"

<400> 2399
gagaaagaga aagggaaggg aagagaggaa agaaacgaag agaggggaag ggaaggaaaa 60

<210> 2400
<211> 72
<212> DNA
<213> Artificial Sequence

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<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic oligonucleotide"

<400> 2400
gagaaagaga aagggaaggg aagagaggaa agaggagaga aaagaaacga agagagggga 60

agggaaggaa aa 72

<210> 2401
<211> 75
<212> DNA
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic oligonucleotide"

<400> 2401
gagaaagaga aagggaaggg aagagaggaa agaagaggag agaaaagaaa cgaagagagg 60

ggaagggaag gaaaa 75

<210> 2402
<211> 78
<212> DNA
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic oligonucleotide"

<400> 2402
gagaaagaga aagggaaggg aagagaggaa agaagaagag gagagaaaag aaacgaagag 60

aggggaaggg aaggaaaa 78

<210> 2403
<211> 65
<212> DNA
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic oligonucleotide"

<400> 2403
gagaaagaga aagggaaggg aagagaggag agaaaagaaa cgaagagagg ggaagggaag 60

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gaaaa 65

<210> 2404
<211> 81
<212> DNA
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic oligonucleotide"

<400> 2404
gagaaagaga aagggaaggg aagagaggaa agaagaggaa gaggagagaa aagaaacgaa 60

gagaggggaa gggaaggaaa a 81

<210> 2405
<211> 60
<212> DNA
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic oligonucleotide"

<400> 2405
gagaaagaga aagggaaggg aggagagaaa agaaacgaag agaggggaag ggaaggaaaa 60

<210> 2406
<211> 73
<212> DNA
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic oligonucleotide"

<400> 2406
aaatgcttat gacagcaata atcataaaaa cctcaaacca cttaaatgct taccaacagt 60

agaattgata aat 73

<210> 2407
<211> 81
<212> DNA
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic

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oligonucleotide"

<400> 2407
aaatgcttat gacagcaata atcataaaaa cctcaaaccg gtaggccact taaatgctta 60

ccaacagtag aattgataaa t 81

<210> 2408
<211> 81
<212> DNA
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic oligonucleotide"

<400> 2408
aaatgcttat gacagcaata atcataaaaa cctcaaaccg gtaagccact taaatgctta 60

ccaacagtag aattgataaa t 81

<210> 2409
<211> 72
<212> DNA
<213> Artificial Sequence

<220>
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<223> /note="Description of Artificial Sequence: Synthetic oligonucleotide"

<400> 2409
aaatgcttat gacagcaata atcataaaaa cctcagccac ttaaatgctt accaacagta 60

gaattgataa at 72

<210> 2410
<211> 66
<212> DNA
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic oligonucleotide"

<400> 2410
aaatgcttat gacagcaata atcataaaaa ccacttaaat gcttaccaac agtagaattg 60

ataaat 66

<210> 2411

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<211> 73
<212> DNA
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic oligonucleotide"

<400> 2411
aaatgcttat gacagcaata atcataaaaa cctcaaacca cttaaatgct taccaacagt 60

agaattgata aat 73

<210> 2412
<211> 81
<212> DNA
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic oligonucleotide"

<400> 2412
aaatgcttat gacagcaata atcataaaaa cctcaaaccg gtaggccact taaatgctta 60

ccaacagtag aattgataaa t 81

<210> 2413
<211> 81
<212> DNA
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic oligonucleotide"

<400> 2413
aaatgcttat gacagcaata atcataaaaa cctcaaaccg gtaagccact taaatgctta 60

ccaacagtag aattgataaa t 81

<210> 2414
<211> 72
<212> DNA
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic oligonucleotide"

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<400> 2414
aaatgcttat gacagcaata atcataaaaa cctcaaaccg gtaaatgctt accaacagta 60

gaattgataa at 72

<210> 2415
<211> 73
<212> DNA
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic oligonucleotide"

<400> 2415
aaatgcttat gacagcaata atcataaaaa cctcaaaccg gttaaatgct taccaacagt 60

agaattgata aat 73

<210> 2416
<211> 81
<212> DNA
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic oligonucleotide"

<400> 2416
aaatgcattt tacagcattt ggttgattaa aagtaaccca gaggtgagtt caaactatat 60

gactttattt gtatatagaa a 81

<210> 2417
<211> 73
<212> DNA
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic oligonucleotide"

<400> 2417
aaatgcattt tacagcattt ggttgattaa aagaggtgag ttcaaactat atgactttat 60

ttgtatatag aaa 73

<210> 2418
<211> 79
<212> DNA

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<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic oligonucleotide"

<400> 2418
aaatgcattt tacagcattt ggttgattaa aagtaacaga ggtgagttca aactatatga 60

ctttatttgt atatagaaa 79

<210> 2419
<211> 71
<212> DNA
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic oligonucleotide"

<400> 2419
aaatgcattt tacagcattt ggttgattaa aaggtgagtt caaactatat gactttattt 60

gtatatagaa a 71

<210> 2420
<211> 60
<212> DNA
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic oligonucleotide"

<400> 2420
aaatgcattt tacagcattt ggttgagttc aaactatatg actttatttg tatatagaaa 60

<210> 2421
<211> 81
<212> DNA
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic oligonucleotide"

<400> 2421
aaatgcattt tacagcattt ggttgattaa aagtaaccca gaggtgagtt caaactatat 60

gactttattt gtatatagaa a 81

<210> 2422
<211> 73
<212> DNA
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic oligonucleotide"

<400> 2422
aaatgcattt tacagcattt ggttgattaa aagaggtgag ttcaaactat atgactttat 60

ttgtatatag aaa 73

<210> 2423
<211> 79
<212> DNA
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic oligonucleotide"

<400> 2423
aaatgcattt tacagcattt ggttgattaa aagtaacaga ggtgagttca aactatatga 60

ctttatttgt atatagaaa 79

<210> 2424
<211> 71
<212> DNA
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic oligonucleotide"

<400> 2424
aaatgcattt tacagcattt ggttgattaa aaggtgagtt caaactatat gactttattt 60

gtatatagaa a 71

<210> 2425
<211> 60
<212> DNA
<213> Artificial Sequence

<220>
<221> source

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<223> /note="Description of Artificial Sequence: Synthetic oligonucleotide"

<400> 2425
aaatgcattt tacagcattt ggttgagttc aaactatatg actttatttg tatatagaaa 60

<210> 2426
<211> 81
<212> DNA
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic oligonucleotide"

<400> 2426
cctggaagcc aacgaaagat attgaataat tcaagaaaag gtggtggcat ggtttgattt 60

gtgtctttaa aagattattc t 81

<210> 2427
<211> 76
<212> DNA
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic oligonucleotide"

<400> 2427
cctggaagcc aacgaaagat attgaataat tcaaggtggt ggcatggttt gatttgtgtc 60

tttaaaagat tattct 76

<210> 2428
<211> 79
<212> DNA
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic oligonucleotide"

<400> 2428
cctggaagcc aacgaaagat attgaataat tcaagaaggt ggtggcatgg tttgatttgt 60

gtctttaaaa gattattct 79

<210> 2429
<211> 78

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<212> DNA
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic oligonucleotide"

<400> 2429
cctggaagcc aacgaaagat attgaataat tcaagaggtg gtggcatggt ttgatttgtg 60

tctttaaaag attattct 78

<210> 2430
<211> 75
<212> DNA
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic oligonucleotide"

<400> 2430
cctggaagcc aacgaaagat attgaataat tcaggtggtg gcatggtttg atttgtgtct 60

ttaaaagatt attct 75

<210> 2431
<211> 81
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<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic oligonucleotide"

<400> 2431
cctggaagcc aacgaaagat attgaataat tcaagaaaag gtggtggcat ggtttgattt 60

gtgtctttaa aagattattc t 81

<210> 2432
<211> 76
<212> DNA
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic oligonucleotide"

<400> 2432

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cctggaagcc aacgaaagat attgaataat tcaaggtggt ggcatggttt gatttgtgtc 60

tttaaaagat tattct 76

<210> 2433
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<220>
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<223> /note="Description of Artificial Sequence: Synthetic oligonucleotide"

<400> 2433
cctggaagcc aacgaaagat attgaataat tcaagaaggt ggtggcatgg tttgatttgt 60

gtctttaaaa gattattct 79

<210> 2434
<211> 78
<212> DNA
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic oligonucleotide"

<400> 2434
cctggaagcc aacgaaagat attgaataat tcaagaggtg gtggcatggt ttgatttgtg 60

tctttaaaag attattct 78

<210> 2435
<211> 82
<212> DNA
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic oligonucleotide"

<400> 2435
cctggaagcc aacgaaagat attgaataat tcaagaacaa ggtggtggca tggtttgatt 60

tgtgtcttta aaagattatt ct 82

<210> 2436
<211> 67
<212> DNA
<213> Artificial Sequence

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<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic oligonucleotide"

<400> 2436
ccttggcctc ccaaagtgct gggtttacaa gcctgagcca ggataaggtc taaaagtgga 60

aagaata 67

<210> 2437
<211> 79
<212> DNA
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic oligonucleotide"

<400> 2437
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tctaaaagtg gaaagaata 79

<210> 2438
<211> 75
<212> DNA
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic oligonucleotide"

<400> 2438
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aaagtggaaa gaata 75

<210> 2439
<211> 79
<212> DNA
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic oligonucleotide"

<400> 2439
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tctaaaagtg gaaagaata 79

<210> 2440
<211> 74
<212> DNA
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic oligonucleotide"

<400> 2440
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aagtggaaag aata 74

<210> 2441
<211> 67
<212> DNA
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic oligonucleotide"

<400> 2441
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aagaata 67

<210> 2442
<211> 79
<212> DNA
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic oligonucleotide"

<400> 2442
ccttggcctc ccaaagtgct gggtttacaa gcctgagcca cccatccagc caggataagg 60

tctaaaagtg gaaagaata 79

<210> 2443
<211> 79
<212> DNA
<213> Artificial Sequence

<220>

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<221> source
<223> /note="Description of Artificial Sequence: Synthetic oligonucleotide"

<400> 2443
ccttggcctc ccaaagtgct gggtttacaa gcctgagcca ccgatccagc caggataagg 60

tctaaaagtg gaaagaata 79

<210> 2444
<211> 78
<212> DNA
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic oligonucleotide"

<400> 2444
ccttggcctc ccaaagtgct gggtttacaa gcctgagcca ccgtccagcc aggataaggt 60

ctaaaagtgg aaagaata 78

<210> 2445
<211> 74
<212> DNA
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic oligonucleotide"

<400> 2445
ccttggcctc ccaaagtgct gggtttacaa gcctgagcca ccagccagga taaggtctaa 60

aagtggaaag aata 74

<210> 2446
<211> 74
<212> DNA
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic oligonucleotide"

<400> 2446
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agcatctact cttg 74

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<210> 2447
<211> 81
<212> DNA
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic oligonucleotide"

<400> 2447
aagtgctggg tttacaagcc tgagccaccg catccagcca ggattaaggt ctaaaagtgg 60

aaagaatagc atctactctt g 81

<210> 2448
<211> 81
<212> DNA
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic oligonucleotide"

<400> 2448
aagtgctggg tttacaagcc tgagccaccg catccagcca ggaataaggt ctaaaagtgg 60

aaagaatagc atctactctt g 81

<210> 2449
<211> 79
<212> DNA
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic oligonucleotide"

<400> 2449
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agaatagcat ctactcttg 79

<210> 2450
<211> 75
<212> DNA
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic

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oligonucleotide"

<400> 2450
aagtgctggg tttacaagcc tgagccaccg catccagcca ggatctaaaa gtggaaagaa 60

tagcatctac tcttg 75

<210> 2451
<211> 74
<212> DNA
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic oligonucleotide"

<400> 2451
aagtgctggg tttacaagcc tgagccaccg catccagcca ggtctaaaag tggaaagaat 60

agcatctact cttg 74

<210> 2452
<211> 81
<212> DNA
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic oligonucleotide"

<400> 2452
aagtgctggg tttacaagcc tgagccaccg catccagcca ggattaaggt ctaaaagtgg 60

aaagaatagc atctactctt g 81

<210> 2453
<211> 81
<212> DNA
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic oligonucleotide"

<400> 2453
aagtgctggg tttacaagcc tgagccaccg catccagcca ggaataaggt ctaaaagtgg 60

aaagaatagc atctactctt g 81

<210> 2454

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<211> 79
<212> DNA
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic oligonucleotide"

<400> 2454
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agaatagcat ctactcttg 79

<210> 2455
<211> 75
<212> DNA
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic oligonucleotide"

<400> 2455
aagtgctggg tttacaagcc tgagccaccg catccagcca ggatctaaaa gtggaaagaa 60

tagcatctac tcttg 75

<210> 2456
<211> 76
<212> DNA
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic oligonucleotide"

<400> 2456
tagcatctac tcttgttcag gaaacaatga ggacctgggc agtaagagtg gtgattaata 60

gatagggaca aattga 76

<210> 2457
<211> 79
<212> DNA
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic oligonucleotide"

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<400> 2457
tagcatctac tcttgttcag gaaacaatga ggacctactg ggcagtaaga gtggtgatta 60

atagataggg acaaattga 79

<210> 2458
<211> 75
<212> DNA
<213> Artificial Sequence

<220>
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<223> /note="Description of Artificial Sequence: Synthetic oligonucleotide"

<400> 2458
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atagggacaa attga 75

<210> 2459
<211> 69
<212> DNA
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic oligonucleotide"

<400> 2459
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acaaattga 69

<210> 2460
<211> 68
<212> DNA
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic oligonucleotide"

<400> 2460
tagcatctac tcttgttcag gaaacaatgg gcagtaagag tggtgattaa tagataggga 60

caaattga 68

<210> 2461
<211> 76
<212> DNA

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<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic oligonucleotide"

<400> 2461
tagcatctac tcttgttcag gaaacaatga ggacctgggc agtaagagtg gtgattaata 60

gatagggaca aattga 76

<210> 2462
<211> 79
<212> DNA
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic oligonucleotide"

<400> 2462
tagcatctac tcttgttcag gaaacaatga ggacctactg ggcagtaaga gtggtgatta 60

atagataggg acaaattga 79

<210> 2463
<211> 75
<212> DNA
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic oligonucleotide"

<400> 2463
tagcatctac tcttgttcag gaaacaatga ggactgggca gtaagagtgg tgattaatag 60

atagggacaa attga 75

<210> 2464
<211> 70
<212> DNA
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic oligonucleotide"

<400> 2464
tagcatctac tcttgttcag gaaacaatga ggacagtaag agtggtgatt aatagatagg 60

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gacaaattga 70

<210> 2465
<211> 69
<212> DNA
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic oligonucleotide"

<400> 2465
tagcatctac tcttgttcag gaaacaatga ggcagtaaga gtggtgatta atagataggg 60

acaaattga 69

<210> 2466
<211> 36
<212> RNA
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic oligonucleotide"

<220>
<221> modified_base
<222> (1)..(20)
<223> a, c, u, g, unknown or other

<400> 2466
nnnnnnnnnn nnnnnnnnnn guuuuagagc uaugcu 36

<210> 2467
<211> 36
<212> RNA
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic oligonucleotide"

<220>
<221> modified_base
<222> (1)..(20)
<223> a, c, u, g, unknown or other

<400> 2467

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nnnnnnnnnn nnnnnnnnnn guuuuagagc uaugcu 36

<210> 2468
<211> 36
<212> RNA
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic oligonucleotide"

<220>
<221> modified_base
<222> (1)..(20)
<223> a, c, u, g, unknown or other

<400> 2468
nnnnnnnnnn nnnnnnnnnn guuuuagagc uaugcu 36

<210> 2469
<211> 36
<212> RNA
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic oligonucleotide"

<220>
<221> modified_base
<222> (1)..(20)
<223> a, c, u, g, unknown or other

<400> 2469
nnnnnnnnnn nnnnnnnnnn guuuuagagc uaugcu 36

<210> 2470
<211> 36
<212> RNA
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic oligonucleotide"

<400> 2470
cacaaacgga aacaaugcaa guuuuagagc uaugcu 36

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<210> 2471
<211> 100
<212> RNA
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic polynucleotide"

<220>
<221> modified_base
<222> (1)..(20)
<223> a, c, u, g, unknown or other

<400> 2471
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cguuaucaac uugaaaaagu ggcaccgagu cggugcuuuu 100

<210> 2472
<211> 100
<212> RNA
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic polynucleotide"

<220>
<221> modified_base
<222> (1)..(20)
<223> a, c, u, g, unknown or other

<400> 2472
nnnnnnnnnn nnnnnnnnnn guuuuagagc uagaaauagc aaguuaaaau aaggcuaguc 60

cguuaucaac uugaaaaagu ggcaccgagu cggugcuuuu 100

<210> 2473
<211> 100
<212> RNA
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic polynucleotide"

<220>
<221> modified_base

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<222> (1)..(20)
<223> a, c, u, g, unknown or other

<400> 2473
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cguuaucaac uugaaaaagu ggcaccgagu cggugcuuuu 100

<210> 2474
<211> 42
<212> RNA
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic oligonucleotide"

<220>
<221> modified_base
<222> (1)..(20)
<223> a, c, u, g, unknown or other

<400> 2474
nnnnnnnnnn nnnnnnnnnn guuuuagagc uaugcuguuu ug 42

<210> 2475
<211> 42
<212> RNA
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic oligonucleotide"

<220>
<221> modified_base
<222> (1)..(20)
<223> a, c, u, g, unknown or other

<400> 2475
nnnnnnnnnn nnnnnnnnnn guuuuagagc uaugcuguuu ug 42

<210> 2476
<211> 42
<212> RNA
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic

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oligonucleotide"

<220>
<221> modified_base
<222> (1)..(20)
<223> a, c, u, g, unknown or other

<400> 2476
nnnnnnnnnn nnnnnnnnnn guuuuagagc uaugcuguuu ug 42

<210> 2477
<211> 75
<212> DNA
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic oligonucleotide"

<400> 2477
acattcttat ttttatcgag cacaaacgga aacaatggca gcctctgctt agaaaaagct 60

gtggataagc cacct 75

<210> 2478
<211> 79
<212> DNA
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic oligonucleotide"

<400> 2478
acattcttat ttttatcgag cacaaacgga aacaatgaat ggcagcctct gcttagaaaa 60

agctgtggat aagccacct 79

<210> 2479
<211> 78
<212> DNA
<213> Artificial Sequence

<220>
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<223> /note="Description of Artificial Sequence: Synthetic oligonucleotide"

<400> 2479
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gctgtggata agccacct 78

<210> 2480
<211> 74
<212> DNA
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic oligonucleotide"

<400> 2480
acattcttat ttttatcgag cacaaacgga aacaatgcag cctctgctta gaaaaagctg 60

tggataagcc acct 74

<210> 2481
<211> 79
<212> DNA
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic oligonucleotide"

<400> 2481
acattcttat ttttatcgag cacaaacgga aacaatcaat ggcagcctct gcttagaaaa 60

agctgtggat aagccacct 79

<210> 2482
<211> 81
<212> DNA
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic oligonucleotide"

<400> 2482
acattcttat ttttatcgag cacaaacgga aacaaatgca atggcagcct ctgcttagaa 60

aaagctgtgg ataagccacc t 81

<210> 2483
<211> 67
<212> DNA
<213> Artificial Sequence

<220>

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<221> source
<223> /note="Description of Artificial Sequence: Synthetic oligonucleotide"

<400> 2483
ttctgtcatg tgtgtcttga ctcagaaacc ctgttctccc caccgcatct ctttcagcag 60

ttgtttc 67

<210> 2484
<211> 80
<212> DNA
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic oligonucleotide"

<400> 2484
ttctgtcatg tgtgtcttga ctcagaaacc ctgttctcct ctgcatatct ccccaccgca 60

tctctttcag cagttgtttc 80

<210> 2485
<211> 79
<212> DNA
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic oligonucleotide"

<400> 2485
ttctgtcatg tgtgtcttga ctcagaaacc ctgttctcct ctaatatctc cccaccgcat 60

ctctttcagc agttgtttc 79

<210> 2486
<211> 67
<212> DNA
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic oligonucleotide"

<400> 2486
ttctgtcatg tgtgtcttga ctcagaaacc ctgttctcct caccgcatct ctttcagcag 60

ttgtttc 67

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<210> 2487
<211> 76
<212> DNA
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic oligonucleotide"

<400> 2487
ttctgtcatg tgtgtcttga ctcagaaacc ctgttctcct ctatctcccc accgcatctc 60

tttcagcagt tgtttc 76

<210> 2488
<211> 78
<212> DNA
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic oligonucleotide"

<400> 2488
ttctgtcatg tgtgtcttga ctcagaaacc ctgttctcct ctatatctcc ccaccgcatc 60

tctttcagca gttgtttc 78

<210> 2489
<211> 67
<212> DNA
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic oligonucleotide"

<400> 2489
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ttgtttc 67

<210> 2490
<211> 80
<212> DNA
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic

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oligonucleotide"

<400> 2490
ttctgtcatg tgtgtcttga ctcagaaacc ctgttctcct ctgcatatct ccccaccgca 60

tctctttcag cagttgtttc 80

<210> 2491
<211> 67
<212> DNA
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic oligonucleotide"

<400> 2491
ttctgtcatg tgtgtcttga ctcagaaacc ctgttctcct caccgcatct ctttcagcag 60

ttgtttc 67

<210> 2492
<211> 79
<212> DNA
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic oligonucleotide"

<400> 2492
ttctgtcatg tgtgtcttga ctcagaaacc ctgttctcct ctaatatctc cccaccgcat 60

ctctttcagc agttgtttc 79

<210> 2493
<211> 76
<212> DNA
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic oligonucleotide"

<400> 2493
ttctgtcatg tgtgtcttga ctcagaaacc ctgttctcct ctatctcccc accgcatctc 60

tttcagcagt tgtttc 76

<210> 2494

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<211> 78
<212> DNA
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic oligonucleotide"

<400> 2494
ttctgtcatg tgtgtcttga ctcagaaacc ctgttctcct ctatatctcc ccaccgcatc 60

tctttcagca gttgtttc 78

<210> 2495
<211> 67
<212> DNA
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic oligonucleotide"

<400> 2495
ttctgtcatg tgtgtcttga ctcagaaacc ctgttctccc caccgcatct ctttcagcag 60

ttgtttc 67

<210> 2496
<211> 80
<212> DNA
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic oligonucleotide"

<400> 2496
ttctgtcatg tgtgtcttga ctcagaaacc ctgttctcct ctgcatatct ccccaccgca 60

tctctttcag cagttgtttc 80

<210> 2497
<211> 76
<212> DNA
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic oligonucleotide"

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<400> 2497
ttctgtcatg tgtgtcttga ctcagaaacc ctgttctcct ctatctcccc accgcatctc 60

tttcagcagt tgtttc 76

<210> 2498
<211> 67
<212> DNA
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic oligonucleotide"

<400> 2498
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ttgtttc 67

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ttgtttc 67

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<220>
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<223> /note="Description of Artificial Sequence: Synthetic oligonucleotide"

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<210> 2518
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<210> 2519
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<400> 2521
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<400> 2522
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ttgtttctaa aaatatcctc c 81

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<400> 2529

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<210> 2532
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<400> 2532
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ttgtttctaa aaatatcctc c 81

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<220>
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gtttctaaaa atatcctcc 79

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tttctaaaaa tatcctcc 78

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tgtttctaaa aatatcctcc 80

<210> 2536
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ctaaaaatat cctcc 75

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<210> 2538
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<210> 2539
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<221> source
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atcctcc 67

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ttgtttctaa aaatatcctc c 81

<210> 2546
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gtttctaaaa atatcctcc 79

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<223> /note="Description of Artificial Sequence: Synthetic

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oligonucleotide"

<400> 2547
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<220>
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<400> 2548
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gtttctaaaa atatcctcc 79

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atcctcc 67

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<210> 2551

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<400> 2552
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ctaaaaatat cctcc 75

<210> 2553
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<400> 2553
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gtttctaaaa atatcctcc 79

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tttctaaaaa tatcctcc 78

<210> 2555
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atcctcc 67

<210> 2556
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gtttctaaaa tatcctcc 79

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tttctaaaaa tatcctcc 78

<210> 2559
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ctaaaaatat cctcc 75

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<210> 2561
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<210> 2562
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atcctcc 67

<210> 2563
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<400> 2563
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gtttctaaaa atatcctcc 79

<210> 2564
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ttgtttctaa aaatatcctc c 81

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<223> /note="Description of Artificial Sequence: Synthetic oligonucleotide"

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<210> 2568
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gaattgataa at 72

<210> 2572
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<212> DNA
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<220>
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<223> /note="Description of Artificial Sequence: Synthetic oligonucleotide"

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<400> 2572
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agaattgata aat 73

<210> 2573
<211> 74
<212> DNA
<213> Artificial Sequence

<220>
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<223> /note="Description of Artificial Sequence: Synthetic oligonucleotide"

<400> 2573
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tagaattgat aaat 74

<210> 2574
<211> 79
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<220>
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<223> /note="Description of Artificial Sequence: Synthetic oligonucleotide"

<400> 2574
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aacagtagaa ttgataaat 79

<210> 2575
<211> 81
<212> DNA
<213> Artificial Sequence

<220>
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<223> /note="Description of Artificial Sequence: Synthetic oligonucleotide"

<400> 2575
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ccaacagtag aattgataaa t 81

<210> 2576
<211> 73

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<212> DNA
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<220>
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<400> 2576
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agaattgata aat 73

<210> 2577
<211> 73
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<223> /note="Description of Artificial Sequence: Synthetic oligonucleotide"

<400> 2577
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agaattgata aat 73

<210> 2578
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<220>
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<223> /note="Description of Artificial Sequence: Synthetic oligonucleotide"

<400> 2578
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gaattgataa at 72

<210> 2579
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<220>
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<223> /note="Description of Artificial Sequence: Synthetic oligonucleotide"

<400> 2579

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ccaacagtag aattgataaa t 81

<210> 2580
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<223> /note="Description of Artificial Sequence: Synthetic oligonucleotide"

<400> 2580
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<210> 2581
<211> 64
<212> DNA
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<220>
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<223> /note="Description of Artificial Sequence: Synthetic oligonucleotide"

<400> 2581
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<210> 2582
<211> 81
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<220>
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<223> /note="Description of Artificial Sequence: Synthetic oligonucleotide"

<400> 2582
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ccaacagtag aattgataaa t 81

<210> 2583
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<220>

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<221> source
<223> /note="Description of Artificial Sequence: Synthetic oligonucleotide"

<400> 2583
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agaattgata aat 73

<210> 2584
<211> 72
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<220>
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<223> /note="Description of Artificial Sequence: Synthetic oligonucleotide"

<400> 2584
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gaattgataa at 72

<210> 2585
<211> 73
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<220>
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<400> 2585
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agaattgata aat 73

<210> 2586
<211> 81
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<220>
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<223> /note="Description of Artificial Sequence: Synthetic oligonucleotide"

<400> 2586
aaatgcttat gacagcaata atcataaaaa cctcaaaccg gtaagccact taaatgctta 60

ccaacagtag aattgataaa t 81

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<210> 2587
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<220>
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<400> 2587
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agaattgata aat 73

<210> 2588
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<220>
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<223> /note="Description of Artificial Sequence: Synthetic oligonucleotide"

<400> 2588
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<210> 2589
<211> 73
<212> DNA
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<220>
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<223> /note="Description of Artificial Sequence: Synthetic oligonucleotide"

<400> 2589
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agaattgata aat 73

<210> 2590
<211> 81
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<220>
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<223> /note="Description of Artificial Sequence: Synthetic

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oligonucleotide"

<400> 2590
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ccaacagtag aattgataaa t 81

<210> 2591
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<220>
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<223> /note="Description of Artificial Sequence: Synthetic oligonucleotide"

<400> 2591
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gaattgataa at 72

<210> 2592
<211> 81
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<220>
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<223> /note="Description of Artificial Sequence: Synthetic oligonucleotide"

<400> 2592
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ccaacagtag aattgataaa t 81

<210> 2593
<211> 77
<212> DNA
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic oligonucleotide"

<400> 2593
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cagtagaatt gataaat 77

<210> 2594

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<211> 70
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<220>
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<223> /note="Description of Artificial Sequence: Synthetic oligonucleotide"

<400> 2594
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<210> 2595
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<212> DNA
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<400> 2595
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agaattgata aat 73

<210> 2596
<211> 81
<212> DNA
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<220>
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<400> 2596
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ccaacagtag aattgataaa t 81

<210> 2597
<211> 73
<212> DNA
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<220>
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<223> /note="Description of Artificial Sequence: Synthetic oligonucleotide"

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<400> 2597
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agaattgata aat 73

<210> 2598
<211> 55
<212> DNA
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<220>
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<223> /note="Description of Artificial Sequence: Synthetic oligonucleotide"

<400> 2598
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<210> 2599
<211> 79
<212> DNA
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<220>
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<223> /note="Description of Artificial Sequence: Synthetic oligonucleotide"

<400> 2599
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aacagtagaa ttgataaat 79

<210> 2600
<211> 81
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<220>
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<223> /note="Description of Artificial Sequence: Synthetic oligonucleotide"

<400> 2600
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ccaacagtag aattgataaa t 81

<210> 2601
<211> 79
<212> DNA
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<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic oligonucleotide"

<400> 2601
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aacagtagaa ttgataaat 79

<210> 2602
<211> 77
<212> DNA
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<220>
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<400> 2602
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cagtagaatt gataaat 77

<210> 2603
<211> 73
<212> DNA
<213> Artificial Sequence

<220>
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<223> /note="Description of Artificial Sequence: Synthetic oligonucleotide"

<400> 2603
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agaattgata aat 73

<210> 2604
<211> 81
<212> DNA
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<220>
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<400> 2604
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ccaacagtag aattgataaa t 81

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<210> 2605
<211> 81
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<220>
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<400> 2605
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ccaacagtag aattgataaa t 81

<210> 2606
<211> 73
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<220>
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<223> /note="Description of Artificial Sequence: Synthetic oligonucleotide"

<400> 2606
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agaattgata aat 73

<210> 2607
<211> 72
<212> DNA
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<220>
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<400> 2607
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gaattgataa at 72

<210> 2608
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<212> DNA
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<223> /note="Description of Artificial Sequence: Synthetic oligonucleotide"

<400> 2608
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agtagaattg ataaat 76

<210> 2609
<211> 81
<212> DNA
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<220>
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<400> 2609
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ccaacagtag aattgataaa t 81

<210> 2610
<211> 76
<212> DNA
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<400> 2610
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gatagggaca aattga 76

<210> 2611
<211> 79
<212> DNA
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<220>
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<400> 2611
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atagataggg acaaattga 79

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<210> 2612
<211> 75
<212> DNA
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<400> 2612
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atagggacaa attga 75

<210> 2613
<211> 70
<212> DNA
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<220>
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<223> /note="Description of Artificial Sequence: Synthetic oligonucleotide"

<400> 2613
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gacaaattga 70

<210> 2614
<211> 70
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gacaaattga 70

<210> 2615
<211> 55
<212> DNA
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<220>
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<223> /note="Description of Artificial Sequence: Synthetic oligonucleotide"

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<400> 2615
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<210> 2616
<211> 80
<212> DNA
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<220>
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<223> /note="Description of Artificial Sequence: Synthetic oligonucleotide"

<400> 2616
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aatagatagg gacaaattga 80

<210> 2617
<211> 76
<212> DNA
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<223> /note="Description of Artificial Sequence: Synthetic oligonucleotide"

<400> 2617
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gatagggaca aattga 76

<210> 2618
<211> 79
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<400> 2618
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atagataggg acaaattga 79

<210> 2619
<211> 75
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<220>
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<223> /note="Description of Artificial Sequence: Synthetic oligonucleotide"

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atagggacaa attga 75

<210> 2620
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<220>
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<223> /note="Description of Artificial Sequence: Synthetic oligonucleotide"

<400> 2620
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tagataggga caaattga 78

<210> 2621
<211> 81
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<220>
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<223> /note="Description of Artificial Sequence: Synthetic oligonucleotide"

<400> 2621
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taatagatag ggacaaattg a 81

<210> 2622
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<220>
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<223> /note="Description of Artificial Sequence: Synthetic oligonucleotide"

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gacaaattga 70

<210> 2623
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<220>
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<223> /note="Description of Artificial Sequence: Synthetic oligonucleotide"

<400> 2623
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taatagatag ggacaaattg a 81

<210> 2624
<211> 76
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<220>
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<223> /note="Description of Artificial Sequence: Synthetic oligonucleotide"

<400> 2624
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gatagggaca aattga 76

<210> 2625
<211> 79
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<220>
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<400> 2625
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atagataggg acaaattga 79

<210> 2626
<211> 75
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<220>

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<221> source
<223> /note="Description of Artificial Sequence: Synthetic oligonucleotide"

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atagggacaa attga 75

<210> 2627
<211> 69
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<223> /note="Description of Artificial Sequence: Synthetic oligonucleotide"

<400> 2627
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acaaattga 69

<210> 2628
<211> 70
<212> DNA
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<220>
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<223> /note="Description of Artificial Sequence: Synthetic oligonucleotide"

<400> 2628
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gacaaattga 70

<210> 2629
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<220>
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<223> /note="Description of Artificial Sequence: Synthetic oligonucleotide"

<400> 2629
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taatagatag ggacaaattg a 81

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<210> 2630
<211> 68
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<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic oligonucleotide"

<400> 2630
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caaattga 68

<210> 2631
<211> 76
<212> DNA
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic oligonucleotide"

<400> 2631
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gatagggaca aattga 76

<210> 2632
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<212> DNA
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<400> 2632
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atagataggg acaaattga 79

<210> 2633
<211> 75
<212> DNA
<213> Artificial Sequence

<220>
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<223> /note="Description of Artificial Sequence: Synthetic

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oligonucleotide"

<400> 2633
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atagggacaa attga 75

<210> 2634
<211> 70
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<220>
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<223> /note="Description of Artificial Sequence: Synthetic oligonucleotide"

<400> 2634
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gacaaattga 70

<210> 2635
<211> 81
<212> DNA
<213> Artificial Sequence

<220>
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<223> /note="Description of Artificial Sequence: Synthetic oligonucleotide"

<400> 2635
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taatagatag ggacaaattg a 81

<210> 2636
<211> 68
<212> DNA
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<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic oligonucleotide"

<400> 2636
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caaattga 68

<210> 2637

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<211> 69
<212> DNA
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<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic oligonucleotide"

<400> 2637
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acaaattga 69

<210> 2638
<211> 76
<212> DNA
<213> Artificial Sequence

<220>
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<223> /note="Description of Artificial Sequence: Synthetic oligonucleotide"

<400> 2638
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gatagggaca aattga 76

<210> 2639
<211> 79
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<223> /note="Description of Artificial Sequence: Synthetic oligonucleotide"

<400> 2639
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atagataggg acaaattga 79

<210> 2640
<211> 75
<212> DNA
<213> Artificial Sequence

<220>
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<223> /note="Description of Artificial Sequence: Synthetic oligonucleotide"

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<400> 2640
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atagggacaa attga 75

<210> 2641
<211> 81
<212> DNA
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<220>
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<223> /note="Description of Artificial Sequence: Synthetic oligonucleotide"

<400> 2641
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taatagatag ggacaaattg a 81

<210> 2642
<211> 78
<212> DNA
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic oligonucleotide"

<400> 2642
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tagataggga caaattga 78

<210> 2643
<211> 70
<212> DNA
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<220>
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<223> /note="Description of Artificial Sequence: Synthetic oligonucleotide"

<400> 2643
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gacaaattga 70

<210> 2644
<211> 72
<212> DNA

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<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic oligonucleotide"

<400> 2644
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gggacaaatt ga 72

<210> 2645
<211> 76
<212> DNA
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic oligonucleotide"

<400> 2645
tagcatctac tcttgttcag gaaacaatga ggacctgggc agtaagagtg gtgattaata 60

gatagggaca aattga 76

<210> 2646
<211> 79
<212> DNA
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic oligonucleotide"

<400> 2646
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atagataggg acaaattga 79

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<211> 75
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<223> /note="Description of Artificial Sequence: Synthetic oligonucleotide"

<400> 2647
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atagggacaa attga 75

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<211> 70
<212> DNA
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gacaaattga 70

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<211> 69
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<223> /note="Description of Artificial Sequence: Synthetic oligonucleotide"

<400> 2649
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<211> 71
<212> DNA
<213> Artificial Sequence

<220>
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<223> /note="Description of Artificial Sequence: Synthetic oligonucleotide"

<400> 2650
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ggacaaattg a 71

<210> 2651
<211> 68
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<220>
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<223> /note="Description of Artificial Sequence: Synthetic oligonucleotide"

<400> 2651
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caaattga 68

<210> 2652
<211> 77
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<220>
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<223> /note="Description of Artificial Sequence: Synthetic oligonucleotide"

<400> 2652
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ggacatctat ataaata 77

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<211> 80
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<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic oligonucleotide"

<400> 2653
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ataggacatc tatataaata 80

<210> 2654
<211> 77
<212> DNA
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic oligonucleotide"

<400> 2654
ctggaagaga aatagtttta gtataacaag tgaaataccc atgagtctga ggtgcctata 60

ggacatctat ataaata 77

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<210> 2655
<211> 79
<212> DNA
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic oligonucleotide"

<400> 2655
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taggacatct atataaata 79

<210> 2656
<211> 66
<212> DNA
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic oligonucleotide"

<400> 2656
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taaata 66

<210> 2657
<211> 78
<212> DNA
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<220>
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<223> /note="Description of Artificial Sequence: Synthetic oligonucleotide"

<400> 2657
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aggacatcta tataaata 78

<210> 2658
<211> 74
<212> DNA
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<220>
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<223> /note="Description of Artificial Sequence: Synthetic oligonucleotide"

<400> 2658
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<210> 2659
<211> 77
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<220>
<221> source
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<400> 2659
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ggacatctat ataaata 77

<210> 2660
<211> 78
<212> DNA
<213> Artificial Sequence

<220>
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<223> /note="Description of Artificial Sequence: Synthetic oligonucleotide"

<400> 2660
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aggacatcta tataaata 78

<210> 2661
<211> 79
<212> DNA
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic oligonucleotide"

<400> 2661
ctggaagaga aacagtttta gtataacaag tgaaataccc atctgagtct gaggtgccta 60

taggacatct atataaata 79

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<210> 2662
<211> 78
<212> DNA
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<220>
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<400> 2662
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aggacatcta tataaata 78

<210> 2663
<211> 66
<212> DNA
<213> Artificial Sequence

<220>
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<223> /note="Description of Artificial Sequence: Synthetic oligonucleotide"

<400> 2663
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taaata 66

<210> 2664
<211> 77
<212> DNA
<213> Artificial Sequence

<220>
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<223> /note="Description of Artificial Sequence: Synthetic oligonucleotide"

<400> 2664
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ggacatctat ataaata 77

<210> 2665
<211> 79
<212> DNA
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic oligonucleotide"

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<400> 2665
ctggaagaga aacagtttta gtataacaag tgaaataccc atgtgagtct gaggtgccta 60

taggacatct atataaata 79

<210> 2666
<211> 77
<212> DNA
<213> Artificial Sequence

<220>
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<223> /note="Description of Artificial Sequence: Synthetic oligonucleotide"

<400> 2666
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ggacatctat ataaata 77

<210> 2667
<211> 80
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<220>
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<223> /note="Description of Artificial Sequence: Synthetic oligonucleotide"

<400> 2667
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ataggacatc tatataaata 80

<210> 2668
<211> 77
<212> DNA
<213> Artificial Sequence

<220>
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<223> /note="Description of Artificial Sequence: Synthetic oligonucleotide"

<400> 2668
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ggacatctat ataaata 77

<210> 2669
<211> 79

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<212> DNA
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<220>
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<223> /note="Description of Artificial Sequence: Synthetic oligonucleotide"

<400> 2669
ctggaagaga aacagtttta gtataacaag tgaaataccc atctgagtct gaggtgccta 60

taggacatct atataaata 79

<210> 2670
<211> 78
<212> DNA
<213> Artificial Sequence

<220>
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<223> /note="Description of Artificial Sequence: Synthetic oligonucleotide"

<400> 2670
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aggacatcta tataaata 78

<210> 2671
<211> 66
<212> DNA
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic oligonucleotide"

<400> 2671
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taaata 66

<210> 2672
<211> 75
<212> DNA
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic oligonucleotide"

<400> 2672

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ctggaagaga aacagtttta gtataacaag tgaaatacct gagtctgagg tgcctatagg 60

acatctatat aaata 75

<210> 2673
<211> 77
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<220>
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<400> 2673
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ggacatctat ataaata 77

<210> 2674
<211> 77
<212> DNA
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<220>
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<223> /note="Description of Artificial Sequence: Synthetic oligonucleotide"

<400> 2674
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ggacatctat ataaata 77

<210> 2675
<211> 80
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<220>
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<223> /note="Description of Artificial Sequence: Synthetic oligonucleotide"

<400> 2675
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ataggacatc tatataaata 80

<210> 2676
<211> 79
<212> DNA
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<220>
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<400> 2676
ctggaagaga aacagtttta gtataacaag tgaaataccc atctgagtct gaggtgccta 60

taggacatct atataaata 79

<210> 2677
<211> 78
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<400> 2677
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aggacatcta tataaata 78

<210> 2678
<211> 78
<212> DNA
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<220>
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<400> 2678
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aggacatcta tataaata 78

<210> 2679
<211> 79
<212> DNA
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<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic oligonucleotide"

<400> 2679
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taggacatct atataaata 79

<210> 2680
<211> 79
<212> DNA
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<220>
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<400> 2680
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taggacatct atataaata 79

<210> 2681
<211> 77
<212> DNA
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<220>
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<400> 2681
ctggaagaga aacagtttta gtataacaag tgaaataccc atgagtctga ggtgcctata 60

ggacatctat ataaata 77

<210> 2682
<211> 78
<212> DNA
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<220>
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<223> /note="Description of Artificial Sequence: Synthetic oligonucleotide"

<400> 2682
ctggaagaga aacagtttta gtataacaag tgaaataccc atggagtctg aggtgcctat 60

aggacatcta tataaata 78

<210> 2683
<211> 78
<212> DNA
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<220>

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<221> source
<223> /note="Description of Artificial Sequence: Synthetic oligonucleotide"

<400> 2683
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aggacatcta tataaata 78

<210> 2684
<211> 79
<212> DNA
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<220>
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<223> /note="Description of Artificial Sequence: Synthetic oligonucleotide"

<400> 2684
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taggacatct atataaata 79

<210> 2685
<211> 76
<212> DNA
<213> Artificial Sequence

<220>
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<223> /note="Description of Artificial Sequence: Synthetic oligonucleotide"

<400> 2685
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gacatctata taaata 76

<210> 2686
<211> 75
<212> DNA
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<220>
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<223> /note="Description of Artificial Sequence: Synthetic oligonucleotide"

<400> 2686
ctggaagaga aacagtttta gtataacaag tgaaatacct gagtctgagg tgcctatagg 60

acatctatat aaata 75

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<210> 2687
<211> 77
<212> DNA
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<220>
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<223> /note="Description of Artificial Sequence: Synthetic oligonucleotide"

<400> 2687
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ggacatctat ataaata 77

<210> 2688
<211> 77
<212> DNA
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<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic oligonucleotide"

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ggacatctat ataaata 77

<210> 2689
<211> 79
<212> DNA
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<220>
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<400> 2689
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taggacatct atataaata 79

<210> 2690
<211> 80
<212> DNA
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<223> /note="Description of Artificial Sequence: Synthetic

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oligonucleotide"

<400> 2690
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ataggacatc tatataaata 80

<210> 2691
<211> 78
<212> DNA
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<220>
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oligonucleotide"

<400> 2691
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aggacatcta tataaata 78

<210> 2692
<211> 78
<212> DNA
<213> Artificial Sequence

<220>
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<400> 2692
ctggaagaga aacagtttta gtataacaag tgaaataccc atggagtctg aggtgcctat 60

aggacatcta tataaata 78

<210> 2693
<211> 76
<212> DNA
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic
oligonucleotide"

<400> 2693
ctggaagaga aacagtttta gtataacaag tgaaataccc tgagtctgag gtgcctatag 60

gacatctata taaata 76

<210> 2694

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<211> 79
<212> DNA
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<220>
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<400> 2694
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agggtggggg cgtgggtgg 79

<210> 2695
<211> 76
<212> DNA
<213> Artificial Sequence

<220>
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<223> /note="Description of Artificial Sequence: Synthetic oligonucleotide"

<400> 2695
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gtgggggcgt gggtgg 76

<210> 2696
<211> 81
<212> DNA
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic oligonucleotide"

<400> 2696
gtctagtgca agctaacagt tgcttttatc acaggctcca ggaaagggtt tggcctctga 60

ttagggtggg ggcgtgggtg g 81

<210> 2697
<211> 75
<212> DNA
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic oligonucleotide"

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<400> 2697
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tgggggcgtg ggtgg 75

<210> 2698
<211> 44
<212> DNA
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic oligonucleotide"

<400> 2698
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<210> 2699
<211> 52
<212> DNA
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic oligonucleotide"

<400> 2699
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<210> 2700
<211> 78
<212> DNA
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<220>
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<400> 2700
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gggtgggggc gtgggtgg 78

<210> 2701
<211> 57
<212> DNA
<213> Artificial Sequence

<220>
<221> source

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<223> /note="Description of Artificial Sequence: Synthetic oligonucleotide"

<400> 2701
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<210> 2702
<211> 76
<212> DNA
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic oligonucleotide"

<400> 2702
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gtgggggcgt gggtgg 76

<210> 2703
<211> 75
<212> DNA
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic oligonucleotide"

<400> 2703
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tgggggcgtg ggtgg 75

<210> 2704
<211> 79
<212> DNA
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic oligonucleotide"

<400> 2704
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agggtggggg cgtgggtgg 79

<210> 2705
<211> 81

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<212> DNA
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<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic oligonucleotide"

<400> 2705
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ttagggtggg ggcgtgggtg g 81

<210> 2706
<211> 70
<212> DNA
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<220>
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<223> /note="Description of Artificial Sequence: Synthetic oligonucleotide"

<400> 2706
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gcgtgggtgg 70

<210> 2707
<211> 79
<212> DNA
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic oligonucleotide"

<400> 2707
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agggtggggg cgtgggtgg 79

<210> 2708
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<212> DNA
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic oligonucleotide"

<400> 2708

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gtctagtgca agctaacagt tgcttttatc acaggctcca ggtttggcct ctgattaggg 60

tgggggcgtg ggtgg 75

<210> 2709
<211> 76
<212> DNA
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic oligonucleotide"

<400> 2709
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gtgggggcgt gggtgg 76

<210> 2710
<211> 81
<212> DNA
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic oligonucleotide"

<400> 2710
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ttagggtggg ggcgtgggtg g 81

<210> 2711
<211> 53
<212> DNA
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<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic oligonucleotide"

<400> 2711
gtctagtgca agctaacagt tgcttttatc acaggctcca ggggcgtggg tgg 53

<210> 2712
<211> 50
<212> DNA
<213> Artificial Sequence

<220>

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<221> source
<223> /note="Description of Artificial Sequence: Synthetic oligonucleotide"

<400> 2712
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<210> 2713
<211> 63
<212> DNA
<213> Artificial Sequence

<220>
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<223> /note="Description of Artificial Sequence: Synthetic oligonucleotide"

<400> 2713
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tgg 63

<210> 2714
<211> 75
<212> DNA
<213> Artificial Sequence

<220>
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<223> /note="Description of Artificial Sequence: Synthetic oligonucleotide"

<400> 2714
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tgggggcgtg ggtgg 75

<210> 2715
<211> 76
<212> DNA
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic oligonucleotide"

<400> 2715
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gtgggggcgt gggtgg 76

<210> 2716

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<211> 79
<212> DNA
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic oligonucleotide"

<400> 2716
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agggtggggg cgtgggtgg 79

<210> 2717
<211> 81
<212> DNA
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic oligonucleotide"

<400> 2717
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ttagggtggg ggcgtgggtg g 81

<210> 2718
<211> 82
<212> DNA
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic oligonucleotide"

<400> 2718
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attagggtgg gggcgtgggt gg 82

<210> 2719
<211> 64
<212> DNA
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic oligonucleotide"

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<400> 2719
gtctagtgca agctaacagt tgcttttatc acaggctcca ggattagggt gggggcgtgg 60

gtgg 64

<210> 2720
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<220>
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<223> /note="Description of Artificial Sequence: Synthetic oligonucleotide"

<400> 2720
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gggtgggggc gtgggtgg 78

<210> 2721
<211> 79
<212> DNA
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic oligonucleotide"

<400> 2721
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gaggactggc agacctctc 79

<210> 2722
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<212> DNA
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<220>
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<223> /note="Description of Artificial Sequence: Synthetic oligonucleotide"

<400> 2722
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<210> 2723
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<213> Artificial Sequence

<220>
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<210> 2724
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aggactggca gacctctc 78

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<210> 2726
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<400> 2726
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<210> 2727
<211> 71
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<220>
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<400> 2727
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gcagacctct c 71

<210> 2728
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<220>
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<400> 2728
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gaggactggc agacctctc 79

<210> 2729
<211> 67
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<220>
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<223> /note="Description of Artificial Sequence: Synthetic oligonucleotide"

<400> 2729
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acctctc 67

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<223> /note="Description of Artificial Sequence: Synthetic oligonucleotide"

<400> 2730
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aggactggca gacctctc 78

<210> 2731
<211> 61
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<400> 2731
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c 61

<210> 2732
<211> 64
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<400> 2732
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tctc 64

<210> 2733
<211> 81
<212> DNA
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<220>
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<223> /note="Description of Artificial Sequence: Synthetic oligonucleotide"

<400> 2733
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aagaggactg gcagacctct c 81

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<210> 2734
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<220>
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<400> 2734
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aggactggca gacctctc 78

<210> 2735
<211> 78
<212> DNA
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic oligonucleotide"

<400> 2735
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aggactggca gacctctc 78

<210> 2736
<211> 79
<212> DNA
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic oligonucleotide"

<400> 2736
tatcacaggc tccaggaagg gtttggcctc tgattaggtg ggggcgtggg tggggtagaa 60

gaggactggc agacctctc 79

<210> 2737
<211> 51
<212> DNA
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic oligonucleotide"

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<400> 2737
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<210> 2738
<211> 81
<212> DNA
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<220>
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<400> 2738
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aagaggactg gcagacctct c 81

<210> 2739
<211> 64
<212> DNA
<213> Artificial Sequence

<220>
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<223> /note="Description of Artificial Sequence: Synthetic oligonucleotide"

<400> 2739
tatcacaggc tccaggaagg gtttgggggc gtgggtgggg tagaagagga ctggcagacc 60

tctc 64

<210> 2740
<211> 71
<212> DNA
<213> Artificial Sequence

<220>
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<223> /note="Description of Artificial Sequence: Synthetic oligonucleotide"

<400> 2740
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gcagacctct c 71

<210> 2741
<211> 74
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<220>
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<223> /note="Description of Artificial Sequence: Synthetic oligonucleotide"

<400> 2741
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ctggcagacc tctc 74

<210> 2742
<211> 67
<212> DNA
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<220>
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<400> 2742
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acctctc 67

<210> 2743
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<212> DNA
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<400> 2743
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gaggactggc agacctctc 79

<210> 2744
<211> 78
<212> DNA
<213> Artificial Sequence

<220>
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<400> 2744
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aggactggca gacctctc 78

<210> 2745
<211> 71
<212> DNA
<213> Artificial Sequence

<220>
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<223> /note="Description of Artificial Sequence: Synthetic oligonucleotide"

<400> 2745
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gcagacctct c 71

<210> 2746
<211> 64
<212> DNA
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<220>
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<400> 2746
tatcacaggc tccaggaagg gtttgggggc gtgggtgggg tagaagagga ctggcagacc 60

tctc 64

<210> 2747
<211> 61
<212> DNA
<213> Artificial Sequence

<220>
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<223> /note="Description of Artificial Sequence: Synthetic oligonucleotide"

<400> 2747
tatcacaggc tccaggaagg gtttggcgtg ggtggggtag aagaggactg gcagacctct 60

c 61

<210> 2748
<211> 58
<212> DNA
<213> Artificial Sequence

<220>

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<221> source
<223> /note="Description of Artificial Sequence: Synthetic oligonucleotide"

<400> 2748
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<210> 2749
<211> 67
<212> DNA
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic oligonucleotide"

<400> 2749
tatcacaggc tccaggaagg gtttggtggg ggcgtgggtg gggtagaaga ggactggcag 60

acctctc 67

<210> 2750
<211> 78
<212> DNA
<213> Artificial Sequence

<220>
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<223> /note="Description of Artificial Sequence: Synthetic oligonucleotide"

<400> 2750
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aggactggca gacctctc 78

<210> 2751
<211> 70
<212> DNA
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic oligonucleotide"

<400> 2751
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tatccttcta 70

<210> 2752

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<211> 79
<212> DNA
<213> Artificial Sequence

<220>
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<223> /note="Description of Artificial Sequence: Synthetic oligonucleotide"

<400> 2752
atgtaaggag gatgagccac atggtatggg aggtatctaa ggactctagg gtcagagaaa 60

tatgggttat atccttcta 79

<210> 2753
<211> 81
<212> DNA
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic oligonucleotide"

<400> 2753
atgtaaggag gatgagccac atggtatggg aggtataact aaggactcta gggtcagaga 60

aatatgggtt atatccttct a 81

<210> 2754
<211> 67
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<213> Artificial Sequence

<220>
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<223> /note="Description of Artificial Sequence: Synthetic oligonucleotide"

<400> 2754
atgtaaggag gatgagccac atggtatggg actctagggt cagagaaata tgggttatat 60

ccttcta 67

<210> 2755
<211> 66
<212> DNA
<213> Artificial Sequence

<220>
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<223> /note="Description of Artificial Sequence: Synthetic oligonucleotide"

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<400> 2755
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<210> 2756
<211> 75
<212> DNA
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<220>
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<400> 2756
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<210> 2757
<211> 77
<212> DNA
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<220>
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<400> 2757
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tgggttatat ccttcta 77

<210> 2758
<211> 79
<212> DNA
<213> Artificial Sequence

<220>
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<400> 2758
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tatgggttat atccttcta 79

<210> 2759
<211> 71
<212> DNA

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<213> Artificial Sequence

<220>
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<223> /note="Description of Artificial Sequence: Synthetic oligonucleotide"

<400> 2759
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atatccttct a 71

<210> 2760
<211> 78
<212> DNA
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<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic oligonucleotide"

<400> 2760
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atgggttata tccttcta 78

<210> 2761
<211> 81
<212> DNA
<213> Artificial Sequence

<220>
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<400> 2761
atgtaaggag gatgagccac atggtatggg aggtataact aaggactcta gggtcagaga 60

aatatgggtt atatccttct a 81

<210> 2762
<211> 70
<212> DNA
<213> Artificial Sequence

<220>
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<223> /note="Description of Artificial Sequence: Synthetic oligonucleotide"

<400> 2762
atgtaaggag gatgagccac atggtatggg aggactctag ggtcagagaa atatgggtta 60

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tatccttcta 70

<210> 2763
<211> 67
<212> DNA
<213> Artificial Sequence

<220>
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<223> /note="Description of Artificial Sequence: Synthetic oligonucleotide"

<400> 2763
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ccttcta 67

<210> 2764
<211> 79
<212> DNA
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic oligonucleotide"

<400> 2764
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tatgggttat atccttcta 79

<210> 2765
<211> 66
<212> DNA
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic oligonucleotide"

<400> 2765
atgtaaggag gatgagccac atggtaagga ctctagggtc agagaaatat gggttatatc 60

cttcta 66

<210> 2766
<211> 75
<212> DNA
<213> Artificial Sequence

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<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic oligonucleotide"

<400> 2766
atgtaaggag gatgagccac atggtatggg aggtaaggac tctagggtca gagaaatatg 60

ggttatatcc ttcta 75

<210> 2767
<211> 77
<212> DNA
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<220>
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<223> /note="Description of Artificial Sequence: Synthetic oligonucleotide"

<400> 2767
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tgggttatat ccttcta 77

<210> 2768
<211> 78
<212> DNA
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<220>
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<223> /note="Description of Artificial Sequence: Synthetic oligonucleotide"

<400> 2768
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atgggttata tccttcta 78

<210> 2769
<211> 79
<212> DNA
<213> Artificial Sequence

<220>
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<223> /note="Description of Artificial Sequence: Synthetic oligonucleotide"

<400> 2769
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tatgggttat atccttcta 79

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<210> 2770
<211> 43
<212> DNA
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic oligonucleotide"

<400> 2770
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<210> 2771
<211> 81
<212> DNA
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic oligonucleotide"

<400> 2771
atgtaaggag gatgagccac atggtatggg aggtataact aaggactcta gggtcagaga 60

aatatgggtt atatccttct a 81

<210> 2772
<211> 70
<212> DNA
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic oligonucleotide"

<400> 2772
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tatccttcta 70

<210> 2773
<211> 79
<212> DNA
<213> Artificial Sequence

<220>
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<400> 2773
atgtaaggag gatgagccac atggtatggg aggtatctaa ggactctagg gtcagagaaa 60

tatgggttat atccttcta 79

<210> 2774
<211> 67
<212> DNA
<213> Artificial Sequence

<220>
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<400> 2774
atgtaaggag gatgagccac atggtatggg actctagggt cagagaaata tgggttatat 60

ccttcta 67

<210> 2775
<211> 66
<212> DNA
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<220>
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<400> 2775
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cttcta 66

<210> 2776
<211> 75
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<220>
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<400> 2776
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ggttatatcc ttcta 75

<210> 2777
<211> 78

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<212> DNA
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<220>
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<400> 2777
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atgggttata tccttcta 78

<210> 2778
<211> 77
<212> DNA
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<220>
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<400> 2778
atgtaaggag gatgagccac atggtatggg aggtataagg actctagggt cagagaaata 60

tgggttatat ccttcta 77

<210> 2779
<211> 79
<212> DNA
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<220>
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<400> 2779
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tatgggttat atccttcta 79

<210> 2780
<211> 46
<212> DNA
<213> Artificial Sequence

<220>
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<400> 2780

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atgtaaggag gatgagccac atggtatggg aggttatatc cttcta 46

<210> 2781
<211> 70
<212> DNA
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<220>
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<400> 2781
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tatccttcta 70

<210> 2782
<211> 79
<212> DNA
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<400> 2782
atgtaaggag gatgagccac atggtatggg aggtatctaa ggactctagg gtcagagaaa 60

tatgggttat atccttcta 79

<210> 2783
<211> 81
<212> DNA
<213> Artificial Sequence

<220>
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<400> 2783
atgtaaggag gatgagccac atggtatggg aggtataact aaggactcta gggtcagaga 60

aatatgggtt atatccttct a 81

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<211> 67
<212> DNA
<213> Artificial Sequence

<220>

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<221> source
<223> /note="Description of Artificial Sequence: Synthetic oligonucleotide"

<400> 2784
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ccttcta 67

<210> 2785
<211> 66
<212> DNA
<213> Artificial Sequence

<220>
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<223> /note="Description of Artificial Sequence: Synthetic oligonucleotide"

<400> 2785
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cttcta 66

<210> 2786
<211> 75
<212> DNA
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<400> 2786
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ggttatatcc ttcta 75

<210> 2787
<211> 77
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<220>
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<223> /note="Description of Artificial Sequence: Synthetic oligonucleotide"

<400> 2787
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tgggttatat ccttcta 77

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<210> 2788
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<220>
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<400> 2788
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atgggttata tccttcta 78

<210> 2789
<211> 66
<212> DNA
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<220>
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<400> 2789
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cttcta 66

<210> 2790
<211> 79
<212> DNA
<213> Artificial Sequence

<220>
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<400> 2790
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tatgggttat atccttcta 79

<210> 2791
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<220>
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oligonucleotide"

<400> 2791
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tatgggttat atccttcta 79

<210> 2792
<211> 81
<212> DNA
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<400> 2792
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aatatgggtt atatccttct a 81

<210> 2793
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<220>
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<223> /note="Description of Artificial Sequence: Synthetic oligonucleotide"

<400> 2793
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<210> 2794
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<220>
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<400> 2794
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ccttcta 67

<210> 2795

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<211> 66
<212> DNA
<213> Artificial Sequence

<220>
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<223> /note="Description of Artificial Sequence: Synthetic oligonucleotide"

<400> 2795
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<210> 2796
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<400> 2796
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tgggttatat ccttcta 77

<210> 2797
<211> 78
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<223> /note="Description of Artificial Sequence: Synthetic oligonucleotide"

<400> 2797
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tatgggttat atccttcta 79

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ggttatatcc ttcta 75

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<220>
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<400> 2800
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<211> 70
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<220>
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<223> /note="Description of Artificial Sequence: Synthetic oligonucleotide"

<400> 2801
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tatccttcta 70

<210> 2802
<211> 79
<212> DNA

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<213> Artificial Sequence

<220>
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<223> /note="Description of Artificial Sequence: Synthetic oligonucleotide"

<400> 2802
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tatgggttat atccttcta 79

<210> 2803
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<400> 2803
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<210> 2804
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<223> /note="Description of Artificial Sequence: Synthetic oligonucleotide"

<400> 2804
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ccttcta 67

<210> 2805
<211> 66
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<220>
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<400> 2805
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cttcta 66

<210> 2806
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<400> 2806
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ggttatatcc ttcta 75

<210> 2807
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<220>
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<400> 2807
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tgggttatat ccttcta 77

<210> 2808
<211> 78
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<220>
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<400> 2808
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atgggttata tccttcta 78

<210> 2809
<211> 79
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<220>
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tatgggttat atccttcta 79

<210> 2810
<211> 66
<212> DNA
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<220>
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<400> 2810
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cttcta 66

<210> 2811
<211> 20
<212> RNA
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic oligonucleotide"

<400> 2811
ggccacggag cgagacaucu 20

<210> 2812
<211> 21
<212> DNA
<213> Artificial Sequence

<220>
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<223> /note="Description of Artificial Sequence: Synthetic primer"

<400> 2812
cagacagcaa actcacccag t 21

<210> 2813
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<212> DNA
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<220>
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<223> /note="Description of Artificial Sequence: Synthetic primer"

<400> 2813
ctgacgctta tcgacgccct 20

<210> 2814
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<212> DNA
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<400> 2814
agctccaaac tctcaaacca caggg 25

<210> 2815
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<212> DNA
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<400> 2815
tacaattttg ggagtccaca cggca 25

<210> 2816
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<223> /note="Description of Artificial Sequence: Synthetic primer"

<400> 2816
agctccaaac tctcaaacca caggg 25

<210> 2817
<211> 25
<212> DNA

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<213> Artificial Sequence

<220>
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<223> /note="Description of Artificial Sequence: Synthetic primer"

<400> 2817
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<210> 2818
<211> 42
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<220>
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<223> /note="Description of Artificial Sequence: Synthetic oligonucleotide"

<220>
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<222> (1)..(20)
<223> a, c, u, g, unknown or other

<400> 2818
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<210> 2819
<211> 33
<212> DNA
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic primer"

<400> 2819
tcgtcggcag cgtcagatgt gtataagaga cag 33

<210> 2820
<211> 34
<212> DNA
<213> Artificial Sequence

<220>
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<223> /note="Description of Artificial Sequence: Synthetic primer"

<400> 2820
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<210> 2821
<211> 51
<212> DNA
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic primer"

<220>
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<222> (30)..(37)
<223> a, c, t, g, unknown or other

<400> 2821
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<210> 2822
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<212> DNA
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<220>
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<220>
<221> modified_base
<222> (25)..(32)
<223> a, c, t, g, unknown or other

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<210> 2823
<211> 21
<212> DNA
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic primer"

<400> 2823
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<210> 2824

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<211> 22
<212> DNA
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic primer"

<400> 2824
aatgatacgg cgaccaccga ga 22

<210> 2825
<211> 23
<212> DNA
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<220>
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<400> 2825
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<210> 2826
<211> 23
<212> DNA
<213> Artificial Sequence

<220>
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<400> 2826
cacgcccaca ccttaatcag ggg 23

<210> 2827
<211> 23
<212> DNA
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<220>
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<223> /note="Description of Artificial Sequence: Synthetic oligonucleotide"

<400> 2827
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<210> 2828
<211> 23

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<212> DNA
<213> Artificial Sequence

<220>
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<223> /note="Description of Artificial Sequence: Synthetic oligonucleotide"

<400> 2828
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<210> 2829
<211> 23
<212> DNA
<213> Artificial Sequence

<220>
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<223> /note="Description of Artificial Sequence: Synthetic oligonucleotide"

<400> 2829
tttataacag gctccagaaa tgg 23

<210> 2830
<211> 23
<212> DNA
<213> Artificial Sequence

<220>
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<223> /note="Description of Artificial Sequence: Synthetic oligonucleotide"

<400> 2830
catatcacag gccccaggag ggg 23

<210> 2831
<211> 23
<212> DNA
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<220>
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<223> /note="Description of Artificial Sequence: Synthetic oligonucleotide"

<400> 2831
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<210> 2832
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<213> Artificial Sequence

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<400> 2832
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<210> 2833
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<220>
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<400> 2833
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<210> 2834
<211> 23
<212> DNA
<213> Artificial Sequence

<220>
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<223> /note="Description of Artificial Sequence: Synthetic oligonucleotide"

<400> 2834
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<210> 2835
<211> 23
<212> DNA
<213> Artificial Sequence

<220>
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<223> /note="Description of Artificial Sequence: Synthetic oligonucleotide"

<400> 2835
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<210> 2836
<211> 23
<212> DNA
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<220>
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<223> /note="Description of Artificial Sequence: Synthetic oligonucleotide"

<400> 2836
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<210> 2837
<211> 42
<212> RNA
<213> Artificial Sequence

<220>
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<220>
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<222> (1)..(20)
<223> a, c, u, g, unknown or other

<400> 2837
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<210> 2838
<211> 100
<212> RNA
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic polynucleotide"

<220>
<221> modified_base
<222> (1)..(20)
<223> a, c, u, g, unknown or other

<400> 2838
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cguuaucaac uugaaaaagu ggcaccgagu cggugcuuuu 100

<210> 2839
<211> 42
<212> RNA
<213> Artificial Sequence

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<220>
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<222> (1)..(20)
<223> a, c, u, g, unknown or other

<400> 2839
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<210> 2840
<211> 100
<212> RNA
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<220>
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<220>
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<222> (1)..(20)
<223> a, c, u, g, unknown or other

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cguuaucaac uugaaaaagu ggcaccgagu cggugcuuuu 100

<210> 2841
<211> 93
<212> DNA
<213> Artificial Sequence

<220>
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<223> /note="Description of Artificial Sequence: Synthetic oligonucleotide"

<400> 2841
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gtgttcccaa ctgacttgcc tccccctgac gtc 93

<210> 2842
<211> 56
<212> DNA
<213> Artificial Sequence

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<220>
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<223> /note="Description of Artificial Sequence: Synthetic oligonucleotide"

<400> 2842
cacccatcca tcacatatag gcacctatca ggtaccagct actgtgttag gatctg 56

<210> 2843
<211> 57
<212> DNA
<213> Artificial Sequence

<220>
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<223> /note="Description of Artificial Sequence: Synthetic oligonucleotide"

<400> 2843
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<210> 2844
<211> 45
<212> DNA
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic oligonucleotide"

<400> 2844
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<210> 2845
<211> 55
<212> DNA
<213> Artificial Sequence

<220>
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<223> /note="Description of Artificial Sequence: Synthetic oligonucleotide"

<400> 2845
cacccatcca tcacatatag gcaccatcag gtaccagcta ctgtgttagg atctg 55

<210> 2846
<211> 57
<212> DNA
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<220>
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<400> 2846
cacccatcca tcacatatag gcaccttatc aggtaccagc tactgtgtta ggatctg 57

<210> 2847
<211> 45
<212> DNA
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<220>
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<400> 2847
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<210> 2848
<211> 45
<212> DNA
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<220>
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<400> 2848
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<210> 2849
<211> 57
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<220>
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<210> 2850
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<221> source
<223> /note="Description of Artificial Sequence: Synthetic oligonucleotide"

<400> 2850
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<210> 2851
<211> 45
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<220>
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<400> 2851
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<210> 2852
<211> 57
<212> DNA
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<220>
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<400> 2852
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<210> 2853
<211> 45
<212> DNA
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<220>
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<400> 2853
cacccatcca tcacatatag gcaccagcta ctgtgttagg atctg 45

<210> 2854
<211> 45
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<220>
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<223> /note="Description of Artificial Sequence: Synthetic oligonucleotide"

<400> 2854
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<210> 2855
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<400> 2855
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<210> 2856
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<400> 2856
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<210> 2857
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<400> 2857
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<210> 2858
<211> 55
<212> DNA
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<220>
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oligonucleotide"

<400> 2858
cacccatcca tcacatatag gcacctatcg gtaccagcta ctgtgttagg atctg 55

<210> 2859
<211> 57
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<400> 2859
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<210> 2860
<211> 45
<212> DNA
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<220>
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<223> /note="Description of Artificial Sequence: Synthetic oligonucleotide"

<400> 2860
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<210> 2861
<211> 55
<212> DNA
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<220>
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<400> 2861
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<210> 2862
<211> 57
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<400> 2862
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<210> 2863
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<220>
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<223> /note="Description of Artificial Sequence: Synthetic oligonucleotide"

<400> 2863
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<210> 2864
<211> 45
<212> DNA
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<223> /note="Description of Artificial Sequence: Synthetic oligonucleotide"

<400> 2864
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<210> 2865
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<400> 2865
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<210> 2866
<211> 45
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<223> /note="Description of Artificial Sequence: Synthetic oligonucleotide"

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<400> 2866
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<210> 2867
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<212> DNA
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<220>
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<400> 2867
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<210> 2868
<211> 60
<212> DNA
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<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic oligonucleotide"

<400> 2868
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<210> 2869
<211> 61
<212> DNA
<213> Artificial Sequence

<220>
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<223> /note="Description of Artificial Sequence: Synthetic oligonucleotide"

<400> 2869
ggcacctatc aggtaccagc tactgttgtt aggatctgtg ttcccaactg acttgcctcc 60

c 61

<210> 2870
<211> 58
<212> DNA
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<220>
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<223> /note="Description of Artificial Sequence: Synthetic oligonucleotide"

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<400> 2870
ggcacctatc aggtaccagc tactgttagg atctgtgttc ccaactgact tgcctccc 58

<210> 2871
<211> 48
<212> DNA
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic oligonucleotide"

<400> 2871
ggcacctatc aggtaccagc tactgtgttc ccaactgact tgcctccc 48

<210> 2872
<211> 61
<212> DNA
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic oligonucleotide"

<400> 2872
ggcacctatc aggtaccagc tactgttgtt aggatctgtg ttcccaactg acttgcctcc 60

c 61

<210> 2873
<211> 58
<212> DNA
<213> Artificial Sequence

<220>
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<223> /note="Description of Artificial Sequence: Synthetic oligonucleotide"

<400> 2873
ggcacctatc aggtaccagc tactgttagg atctgtgttc ccaactgact tgcctccc 58

<210> 2874
<211> 48
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<220>
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<223> /note="Description of Artificial Sequence: Synthetic

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oligonucleotide"

<400> 2874
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<210> 2875
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c 61

<210> 2876
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<400> 2876
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<210> 2877
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<400> 2877
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<210> 2878
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<220>
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<223> /note="Description of Artificial Sequence: Synthetic oligonucleotide"

<400> 2878
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c 61

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<400> 2879
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<210> 2880
<211> 48
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<220>
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<400> 2880
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<210> 2881
<211> 60
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<220>
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<223> /note="Description of Artificial Sequence: Synthetic oligonucleotide"

<400> 2881
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<210> 2882
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<212> DNA
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<220>

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<221> source
<223> /note="Description of Artificial Sequence: Synthetic oligonucleotide"

<400> 2882
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<400> 2883
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<210> 2884
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<220>
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<400> 2884
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<210> 2885
<211> 58
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<220>
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<400> 2885
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<210> 2886
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<223> /note="Description of Artificial Sequence: Synthetic oligonucleotide"

<400> 2886
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<210> 2887
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<400> 2887
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<210> 2889
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<220>
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<210> 2890
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<220>
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oligonucleotide"

<400> 2890
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<220>
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<400> 2891
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<400> 2892
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<210> 2893
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<220>
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<400> 2893
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<210> 2894
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<220>
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<400> 2894
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<210> 2895
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<220>
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<400> 2895
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<400> 2896
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<210> 2897
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<220>
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<400> 2897
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a 61

<210> 2898
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oligonucleotide"

<400> 2898
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<210> 2899
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a 61

<210> 2901
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<400> 2901
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<223> /note="Description of Artificial Sequence: Synthetic oligonucleotide"

<400> 2902
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<210> 2903
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<210> 2904
<211> 59
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<220>
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<210> 2905
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<400> 2905
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oligonucleotide"

<400> 2906
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<210> 2907
<211> 59
<212> DNA
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<220>
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<223> /note="Description of Artificial Sequence: Synthetic oligonucleotide"

<400> 2907
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<210> 2908
<211> 60
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<220>
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<400> 2908
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<210> 2909
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<400> 2909
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<210> 2910
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<400> 2910
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<210> 2911
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<210> 2912
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<400> 2912
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<210> 2913
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<400> 2913
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<210> 2914
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<221> source
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<400> 2914
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<210> 2915
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<400> 2915
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<210> 2916
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<400> 2916
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<210> 2917
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<212> DNA
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<400> 2917
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<220>
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<400> 2918
agtgccagat gaacttcccc attgggggac attcttattt tta 43

<210> 2919
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<400> 2919
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<210> 2920
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<400> 2923
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<210> 2924
<211> 58
<212> DNA
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<223> /note="Description of Artificial Sequence: Synthetic oligonucleotide"

<400> 2924
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<210> 2925
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<400> 2925
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a 61

<210> 2926
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<400> 2926
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<400> 2927
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<210> 2928
<211> 61
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<223> /note="Description of Artificial Sequence: Synthetic oligonucleotide"

<400> 2928
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a 61

<210> 2929
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<210> 2930
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<220>
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<223> /note="Description of Artificial Sequence: Synthetic oligonucleotide"

<400> 2930
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<210> 2931
<211> 55
<212> DNA
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<220>
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<223> /note="Description of Artificial Sequence: Synthetic oligonucleotide"

<400> 2931
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<210> 2932
<211> 59
<212> DNA
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<223> /note="Description of Artificial Sequence: Synthetic oligonucleotide"

<400> 2932
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<210> 2933
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<220>
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<223> /note="Description of Artificial Sequence: Synthetic oligonucleotide"

<400> 2933
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<210> 2934
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<220>
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<223> /note="Description of Artificial Sequence: Synthetic oligonucleotide"

<400> 2934
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<210> 2935
<211> 59
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<400> 2935
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<210> 2936
<211> 61
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<400> 2936
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a 61

<210> 2937
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<400> 2937
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<220>
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<223> /note="Description of Artificial Sequence: Synthetic oligonucleotide"

<400> 2938
cctgtgggca gtgccagatg aacttccatt gggggacatt cttattttta tcgagcaca 59

<210> 2939
<211> 61
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<223> /note="Description of Artificial Sequence: Synthetic oligonucleotide"

<400> 2939
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a 61

<210> 2940
<211> 58
<212> DNA
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<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic oligonucleotide"

<400> 2940
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<210> 2941
<211> 59
<212> DNA
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<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic oligonucleotide"

<400> 2941
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<210> 2942
<211> 55
<212> DNA

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<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic oligonucleotide"

<400> 2942
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<210> 2943
<211> 58
<212> DNA
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<400> 2943
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<210> 2944
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<400> 2944
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<210> 2945
<211> 55
<212> DNA
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<400> 2945
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<210> 2946
<211> 58
<212> DNA
<213> Artificial Sequence

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<220>
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<223> /note="Description of Artificial Sequence: Synthetic oligonucleotide"

<400> 2946
cctgtgggca gtgccagatg aacttcattg ggggacattc ttatttttat cgagcaca 58

<210> 2947
<211> 95
<212> DNA
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<220>
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<223> /note="Description of Artificial Sequence: Synthetic oligonucleotide"

<400> 2947
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aaacaatgca atggcagcct ctgcttagaa aaagc 95

<210> 2948
<211> 49
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<220>
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<400> 2948
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<210> 2949
<211> 89
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<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic oligonucleotide"

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tgcaatggca gcctctgctt agaaaaagc 89

<210> 2950

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<211> 49
<212> DNA
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<220>
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<223> /note="Description of Artificial Sequence: Synthetic oligonucleotide"

<400> 2950
gggcagtgcc agatgaactt cccaatggca gcctctgctt agaaaaagc 49

<210> 2951
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<212> DNA
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<400> 2951
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tgcaatggca gcctctgctt agaaaaagc 89

<210> 2952
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<223> /note="Description of Artificial Sequence: Synthetic oligonucleotide"

<400> 2952
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<210> 2953
<211> 48
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<220>
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<223> /note="Description of Artificial Sequence: Synthetic oligonucleotide"

<400> 2953
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<210> 2954
<211> 49
<212> DNA
<213> Artificial Sequence

<220>
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<223> /note="Description of Artificial Sequence: Synthetic oligonucleotide"

<400> 2954
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<210> 2955
<211> 48
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<220>
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<223> /note="Description of Artificial Sequence: Synthetic oligonucleotide"

<400> 2955
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<210> 2956
<211> 90
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<211> 5
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<210> 6588
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<400> 6588
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<211> 60
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<212> RNA
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<222> (1)..(5000)
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uagcaaguua aaa 13

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<400> 6598
uagcaaguuu aaa 13

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<400> 6599
uaaggcuagu ccguuaucaa cuugaaaaag uggcaccgag ucggugc 47

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<400> 6600
uaaggcuagu ccguuaucaa cuugaaaaag uggcaccgag ucggugcuuu u 51

<210> 6601
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<213> Artificial Sequence

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<223> /note="Description of Artificial Sequence: Synthetic oligonucleotide"

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ggcaccgagu cggugc 76

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ggcaccgagu cggugc 76

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uugaaaaagu ggcaccgagu cggugc 86

<210> 6604
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<223> /note="Description of Artificial Sequence: Synthetic oligonucleotide"

<400> 6604
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uugaaaaagu ggcaccgagu cggugc 86

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<210> 6605
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<400> 6606
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<220>
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<400> 6607
guuuuagagc uaugcuguuu ug 22

<210> 6608
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<213> Artificial Sequence

<220>
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<400> 6608
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<210> 6609

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<211> 65
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<223> /note="Description of Artificial Sequence: Synthetic oligonucleotide"

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ggugc 65

<210> 6610
<211> 65
<212> RNA
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ggugc 65

<210> 6611
<211> 1368
<212> PRT
<213> Streptococcus pyogenes

<400> 6611
Met Asp Lys Lys Tyr Ser Ile Gly Leu Asp Ile Gly Thr Asn Ser Val
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Gly Trp Ala Val Ile Thr Asp Glu Tyr Lys Val Pro Ser Lys Lys Phe
20 25 30

Lys Val Leu Gly Asn Thr Asp Arg His Ser Ile Lys Lys Asn Leu Ile
35 40 45

Gly Ala Leu Leu Phe Asp Ser Gly Glu Thr Ala Glu Ala Thr Arg Leu
50 55 60

Lys Arg Thr Ala Arg Arg Arg Tyr Thr Arg Arg Lys Asn Arg Ile Cys
65 70 75 80

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Tyr Leu Gln Glu Ile Phe Ser Asn Glu Met Ala Lys Val Asp Asp Ser
85 90 95

Phe Phe His Arg Leu Glu Glu Ser Phe Leu Val Glu Glu Asp Lys Lys
100 105 110

His Glu Arg His Pro Ile Phe Gly Asn Ile Val Asp Glu Val Ala Tyr
115 120 125

His Glu Lys Tyr Pro Thr Ile Tyr His Leu Arg Lys Lys Leu Val Asp
130 135 140

Ser Thr Asp Lys Ala Asp Leu Arg Leu Ile Tyr Leu Ala Leu Ala His
145 150 155 160

Met Ile Lys Phe Arg Gly His Phe Leu Ile Glu Gly Asp Leu Asn Pro
165 170 175

Asp Asn Ser Asp Val Asp Lys Leu Phe Ile Gln Leu Val Gln Thr Tyr
180 185 190

Asn Gln Leu Phe Glu Glu Asn Pro Ile Asn Ala Ser Gly Val Asp Ala
195 200 205

Lys Ala Ile Leu Ser Ala Arg Leu Ser Lys Ser Arg Arg Leu Glu Asn
210 215 220

Leu Ile Ala Gln Leu Pro Gly Glu Lys Lys Asn Gly Leu Phe Gly Asn
225 230 235 240

Leu Ile Ala Leu Ser Leu Gly Leu Thr Pro Asn Phe Lys Ser Asn Phe
245 250 255

Asp Leu Ala Glu Asp Ala Lys Leu Gln Leu Ser Lys Asp Thr Tyr Asp
260 265 270

Asp Asp Leu Asp Asn Leu Leu Ala Gln Ile Gly Asp Gln Tyr Ala Asp
275 280 285

Leu Phe Leu Ala Ala Lys Asn Leu Ser Asp Ala Ile Leu Leu Ser Asp
290 295 300

Ile Leu Arg Val Asn Thr Glu Ile Thr Lys Ala Pro Leu Ser Ala Ser

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305 310 315 320

Met Ile Lys Arg Tyr Asp Glu His His Gln Asp Leu Thr Leu Leu Lys
325 330 335

Ala Leu Val Arg Gln Gln Leu Pro Glu Lys Tyr Lys Glu Ile Phe Phe
340 345 350

Asp Gln Ser Lys Asn Gly Tyr Ala Gly Tyr Ile Asp Gly Gly Ala Ser
355 360 365

Gln Glu Glu Phe Tyr Lys Phe Ile Lys Pro Ile Leu Glu Lys Met Asp
370 375 380

Gly Thr Glu Glu Leu Leu Val Lys Leu Asn Arg Glu Asp Leu Leu Arg
385 390 395 400

Lys Gln Arg Thr Phe Asp Asn Gly Ser Ile Pro His Gln Ile His Leu
405 410 415

Gly Glu Leu His Ala Ile Leu Arg Arg Gln Glu Asp Phe Tyr Pro Phe
420 425 430

Leu Lys Asp Asn Arg Glu Lys Ile Glu Lys Ile Leu Thr Phe Arg Ile
435 440 445

Pro Tyr Tyr Val Gly Pro Leu Ala Arg Gly Asn Ser Arg Phe Ala Trp
450 455 460

Met Thr Arg Lys Ser Glu Glu Thr Ile Thr Pro Trp Asn Phe Glu Glu
465 470 475 480

Val Val Asp Lys Gly Ala Ser Ala Gln Ser Phe Ile Glu Arg Met Thr
485 490 495

Asn Phe Asp Lys Asn Leu Pro Asn Glu Lys Val Leu Pro Lys His Ser
500 505 510

Leu Leu Tyr Glu Tyr Phe Thr Val Tyr Asn Glu Leu Thr Lys Val Lys
515 520 525

Tyr Val Thr Glu Gly Met Arg Lys Pro Ala Phe Leu Ser Gly Glu Gln
530 535 540

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Lys Lys Ala Ile Val Asp Leu Leu Phe Lys Thr Asn Arg Lys Val Thr
545 550 555 560

Val Lys Gln Leu Lys Glu Asp Tyr Phe Lys Lys Ile Glu Cys Phe Asp
565 570 575

Ser Val Glu Ile Ser Gly Val Glu Asp Arg Phe Asn Ala Ser Leu Gly
580 585 590

Thr Tyr His Asp Leu Leu Lys Ile Ile Lys Asp Lys Asp Phe Leu Asp
595 600 605

Asn Glu Glu Asn Glu Asp Ile Leu Glu Asp Ile Val Leu Thr Leu Thr
610 615 620

Leu Phe Glu Asp Arg Glu Met Ile Glu Glu Arg Leu Lys Thr Tyr Ala
625 630 635 640

His Leu Phe Asp Asp Lys Val Met Lys Gln Leu Lys Arg Arg Arg Tyr
645 650 655

Thr Gly Trp Gly Arg Leu Ser Arg Lys Leu Ile Asn Gly Ile Arg Asp
660 665 670

Lys Gln Ser Gly Lys Thr Ile Leu Asp Phe Leu Lys Ser Asp Gly Phe
675 680 685

Ala Asn Arg Asn Phe Met Gln Leu Ile His Asp Asp Ser Leu Thr Phe
690 695 700

Lys Glu Asp Ile Gln Lys Ala Gln Val Ser Gly Gln Gly Asp Ser Leu
705 710 715 720

His Glu His Ile Ala Asn Leu Ala Gly Ser Pro Ala Ile Lys Lys Gly
725 730 735

Ile Leu Gln Thr Val Lys Val Val Asp Glu Leu Val Lys Val Met Gly
740 745 750

Arg His Lys Pro Glu Asn Ile Val Ile Glu Met Ala Arg Glu Asn Gln
755 760 765

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Thr Thr Gln Lys Gly Gln Lys Asn Ser Arg Glu Arg Met Lys Arg Ile
    770                 775                 780

Glu Glu Gly Ile Lys Glu Leu Gly Ser Gln Ile Leu Lys Glu His Pro
785                 790                 795                 800

Val Glu Asn Thr Gln Leu Gln Asn Glu Lys Leu Tyr Leu Tyr Tyr Leu
                805                 810                 815

Gln Asn Gly Arg Asp Met Tyr Val Asp Gln Glu Leu Asp Ile Asn Arg
            820                 825                 830

Leu Ser Asp Tyr Asp Val Asp His Ile Val Pro Gln Ser Phe Leu Lys
        835                 840                 845

Asp Asp Ser Ile Asp Asn Lys Val Leu Thr Arg Ser Asp Lys Asn Arg
    850                 855                 860

Gly Lys Ser Asp Asn Val Pro Ser Glu Glu Val Val Lys Lys Met Lys
865                 870                 875                 880

Asn Tyr Trp Arg Gln Leu Leu Asn Ala Lys Leu Ile Thr Gln Arg Lys
                885                 890                 895

Phe Asp Asn Leu Thr Lys Ala Glu Arg Gly Gly Leu Ser Glu Leu Asp
            900                 905                 910

Lys Ala Gly Phe Ile Lys Arg Gln Leu Val Glu Thr Arg Gln Ile Thr
        915                 920                 925

Lys His Val Ala Gln Ile Leu Asp Ser Arg Met Asn Thr Lys Tyr Asp
    930                 935                 940

Glu Asn Asp Lys Leu Ile Arg Glu Val Lys Val Ile Thr Leu Lys Ser
945                 950                 955                 960

Lys Leu Val Ser Asp Phe Arg Lys Asp Phe Gln Phe Tyr Lys Val Arg
                965                 970                 975

Glu Ile Asn Asn Tyr His His Ala His Asp Ala Tyr Leu Asn Ala Val
            980                 985                 990
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Val Gly Thr Ala Leu Ile Lys Lys  Tyr Pro Lys Leu Glu  Ser Glu Phe
        995                 1000                1005

Val Tyr  Gly Asp Tyr Lys Val  Tyr Asp Val Arg Lys  Met Ile Ala
    1010                1015                1020

Lys Ser  Glu Gln Glu Ile Gly  Lys Ala Thr Ala Lys  Tyr Phe Phe
    1025                1030                1035

Tyr Ser  Asn Ile Met Asn Phe  Phe Lys Thr Glu Ile  Thr Leu Ala
    1040                1045                1050

Asn Gly  Glu Ile Arg Lys Arg  Pro Leu Ile Glu Thr  Asn Gly Glu
    1055                1060                1065

Thr Gly  Glu Ile Val Trp Asp  Lys Gly Arg Asp Phe  Ala Thr Val
    1070                1075                1080

Arg Lys  Val Leu Ser Met Pro  Gln Val Asn Ile Val  Lys Lys Thr
    1085                1090                1095

Glu Val  Gln Thr Gly Gly Phe  Ser Lys Glu Ser Ile  Leu Pro Lys
    1100                1105                1110

Arg Asn  Ser Asp Lys Leu Ile  Ala Arg Lys Lys Asp  Trp Asp Pro
    1115                1120                1125

Lys Lys  Tyr Gly Gly Phe Asp  Ser Pro Thr Val Ala  Tyr Ser Val
    1130                1135                1140

Leu Val  Val Ala Lys Val Glu  Lys Gly Lys Ser Lys  Lys Leu Lys
    1145                1150                1155

Ser Val  Lys Glu Leu Leu Gly  Ile Thr Ile Met Glu  Arg Ser Ser
    1160                1165                1170

Phe Glu  Lys Asn Pro Ile Asp  Phe Leu Glu Ala Lys  Gly Tyr Lys
    1175                1180                1185

Glu Val  Lys Lys Asp Leu Ile  Ile Lys Leu Pro Lys  Tyr Ser Leu
    1190                1195                1200

Phe Glu  Leu Glu Asn Gly Arg  Lys Arg Met Leu Ala  Ser Ala Gly
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    1205                1210                1215

Glu Leu  Gln Lys Gly Asn Glu  Leu Ala Leu Pro Ser  Lys Tyr Val
    1220                1225                1230

Asn Phe  Leu Tyr Leu Ala Ser  His Tyr Glu Lys Leu  Lys Gly Ser
    1235                1240                1245

Pro Glu  Asp Asn Glu Gln Lys  Gln Leu Phe Val Glu  Gln His Lys
    1250                1255                1260

His Tyr  Leu Asp Glu Ile Ile  Glu Gln Ile Ser Glu  Phe Ser Lys
    1265                1270                1275

Arg Val  Ile Leu Ala Asp Ala  Asn Leu Asp Lys Val  Leu Ser Ala
    1280                1285                1290

Tyr Asn  Lys His Arg Asp Lys  Pro Ile Arg Glu Gln  Ala Glu Asn
    1295                1300                1305

Ile Ile  His Leu Phe Thr Leu  Thr Asn Leu Gly Ala  Pro Ala Ala
    1310                1315                1320

Phe Lys  Tyr Phe Asp Thr Thr  Ile Asp Arg Lys Arg  Tyr Thr Ser
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Thr Lys  Glu Val Leu Asp Ala  Thr Leu Ile His Gln  Ser Ile Thr
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Gly Leu  Tyr Glu Thr Arg Ile  Asp Leu Ser Gln Leu  Gly Gly Asp
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<210> 6612
<211> 7
<212> PRT
<213> Simian virus 40

<400> 6612
Pro Lys Lys Lys Arg Lys Val
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<210> 6613
<211> 16
<212> PRT
<213> Unknown
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<220>
<221> source
<223> /note="Description of Unknown:
Nucleoplasmin bipartite NLS sequence"

<400> 6613
Lys Arg Pro Ala Ala Thr Lys Lys Ala Gly Gln Ala Lys Lys Lys Lys
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<210> 6614
<211> 9
<212> PRT
<213> Unknown

<220>
<221> source
<223> /note="Description of Unknown:
C-myc NLS sequence"

<400> 6614
Pro Ala Ala Lys Arg Val Lys Leu Asp
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<210> 6615
<211> 11
<212> PRT
<213> Unknown

<220>
<221> source
<223> /note="Description of Unknown:
C-myc NLS sequence"

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<400> 7794
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<210> 7795

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<210> 7796

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<210> 7801

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<210> 7802

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<400> 7802
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<210> 7803

<400> 7803
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<210> 7804

<400> 7804
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<210> 7805

<400> 7805
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<210> 7806
<211> 16
<212> RNA
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic oligonucleotide"

<400> 7806
guuuuagagc uaugcu 16

<210> 7807
<211> 90
<212> RNA
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic oligonucleotide"

<400> 7807
guuuaagagc uaugcuggaa acagcauagc aaguuuaaau aaggcuaguc cguuaucaac 60

uugaaaaagu ggcaccgagu cggugcuuuu 90

<210> 7808
<211> 67
<212> RNA
<213> Artificial Sequence

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<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic oligonucleotide"

<400> 7808
agcauagcaa guuaaaauaa ggcuaguccg uuaucaacuu gaaaaagugg caccgagucg 60

gugcuuu 67

<210> 7809
<211> 85
<212> RNA
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic oligonucleotide"

<400> 7809
guuggaacca uucaaaacag cauagcaagu uaaaauaagg cuaguccguu aucaacuuga 60

aaaaguggca ccgagucggu gcuuu 85

<210> 7810
<211> 7
<212> PRT
<213> Tobacco etch virus

<400> 7810
Glu Asn Leu Tyr Phe Gln Gly
1 5

<210> 7811
<211> 80
<212> RNA
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic oligonucleotide"

<400> 7811
guuuuagagc uagaaauagc aaguuaaaau aaggcuaguc cguuaucaac uugaaaaagu 60

ggcaccgagu cggugcuuuu 80

<210> 7812
<211> 67
<212> RNA
<213> Artificial Sequence

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<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic oligonucleotide"

<400> 7812
aacagcauag caaguuaaaa uaaggcuagu ccguuaucaa cuugaaaaag uggcaccgag 60

ucggugc 67

<210> 7813

<400> 7813
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<210> 7814

<400> 7814
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<210> 7815

<400> 7815
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<210> 7816

<400> 7816
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<210> 7817

<400> 7817
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<210> 7818

<400> 7818
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<210> 7819

<400> 7819
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<210> 7820

<400> 7820

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<210> 7821
<211> 1393
<212> PRT
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic polypeptide"

<400> 7821

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Met Ala Pro Lys Lys Lys Arg Lys Val Asp Lys Lys Tyr Ser Ile Gly
1               5                  10                  15

Leu Asp Ile Gly Thr Asn Ser Val Gly Trp Ala Val Ile Thr Asp Glu
            20                  25                  30

Tyr Lys Val Pro Ser Lys Lys Phe Lys Val Leu Gly Asn Thr Asp Arg
        35                  40                  45

His Ser Ile Lys Lys Asn Leu Ile Gly Ala Leu Leu Phe Asp Ser Gly
    50                  55                  60

Glu Thr Ala Glu Ala Thr Arg Leu Lys Arg Thr Ala Arg Arg Arg Tyr
65                  70                  75                  80

Thr Arg Arg Lys Asn Arg Ile Cys Tyr Leu Gln Glu Ile Phe Ser Asn
                85                  90                  95

Glu Met Ala Lys Val Asp Asp Ser Phe Phe His Arg Leu Glu Glu Ser
            100                 105                 110

Phe Leu Val Glu Glu Asp Lys Lys His Glu Arg His Pro Ile Phe Gly
        115                 120                 125

Asn Ile Val Asp Glu Val Ala Tyr His Glu Lys Tyr Pro Thr Ile Tyr
    130                 135                 140

His Leu Arg Lys Lys Leu Val Asp Ser Thr Asp Lys Ala Asp Leu Arg
145                 150                 155                 160

Leu Ile Tyr Leu Ala Leu Ala His Met Ile Lys Phe Arg Gly His Phe
                165                 170                 175
```

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```
Leu Ile Glu Gly Asp Leu Asn Pro Asp Asn Ser Asp Val Asp Lys Leu
            180                 185                 190

Phe Ile Gln Leu Val Gln Thr Tyr Asn Gln Leu Phe Glu Glu Asn Pro
        195                 200                 205

Ile Asn Ala Ser Gly Val Asp Ala Lys Ala Ile Leu Ser Ala Arg Leu
    210                 215                 220

Ser Lys Ser Arg Arg Leu Glu Asn Leu Ile Ala Gln Leu Pro Gly Glu
225                 230                 235                 240

Lys Lys Asn Gly Leu Phe Gly Asn Leu Ile Ala Leu Ser Leu Gly Leu
                245                 250                 255

Thr Pro Asn Phe Lys Ser Asn Phe Asp Leu Ala Glu Asp Ala Lys Leu
            260                 265                 270

Gln Leu Ser Lys Asp Thr Tyr Asp Asp Asp Leu Asp Asn Leu Leu Ala
        275                 280                 285

Gln Ile Gly Asp Gln Tyr Ala Asp Leu Phe Leu Ala Ala Lys Asn Leu
    290                 295                 300

Ser Asp Ala Ile Leu Leu Ser Asp Ile Leu Arg Val Asn Thr Glu Ile
305                 310                 315                 320

Thr Lys Ala Pro Leu Ser Ala Ser Met Ile Lys Arg Tyr Asp Glu His
                325                 330                 335

His Gln Asp Leu Thr Leu Leu Lys Ala Leu Val Arg Gln Gln Leu Pro
            340                 345                 350

Glu Lys Tyr Lys Glu Ile Phe Phe Asp Gln Ser Lys Asn Gly Tyr Ala
        355                 360                 365

Gly Tyr Ile Asp Gly Gly Ala Ser Gln Glu Glu Phe Tyr Lys Phe Ile
    370                 375                 380

Lys Pro Ile Leu Glu Lys Met Asp Gly Thr Glu Glu Leu Leu Val Lys
385                 390                 395                 400
```

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Leu Asn Arg Glu Asp Leu Leu Arg Lys Gln Arg Thr Phe Asp Asn Gly
405 410 415

Ser Ile Pro His Gln Ile His Leu Gly Glu Leu His Ala Ile Leu Arg
420 425 430

Arg Gln Glu Asp Phe Tyr Pro Phe Leu Lys Asp Asn Arg Glu Lys Ile
435 440 445

Glu Lys Ile Leu Thr Phe Arg Ile Pro Tyr Tyr Val Gly Pro Leu Ala
450 455 460

Arg Gly Asn Ser Arg Phe Ala Trp Met Thr Arg Lys Ser Glu Glu Thr
465 470 475 480

Ile Thr Pro Trp Asn Phe Glu Glu Val Val Asp Lys Gly Ala Ser Ala
485 490 495

Gln Ser Phe Ile Glu Arg Met Thr Asn Phe Asp Lys Asn Leu Pro Asn
500 505 510

Glu Lys Val Leu Pro Lys His Ser Leu Leu Tyr Glu Tyr Phe Thr Val
515 520 525

Tyr Asn Glu Leu Thr Lys Val Lys Tyr Val Thr Glu Gly Met Arg Lys
530 535 540

Pro Ala Phe Leu Ser Gly Glu Gln Lys Lys Ala Ile Val Asp Leu Leu
545 550 555 560

Phe Lys Thr Asn Arg Lys Val Thr Val Lys Gln Leu Lys Glu Asp Tyr
565 570 575

Phe Lys Lys Ile Glu Cys Phe Asp Ser Val Glu Ile Ser Gly Val Glu
580 585 590

Asp Arg Phe Asn Ala Ser Leu Gly Thr Tyr His Asp Leu Leu Lys Ile
595 600 605

Ile Lys Asp Lys Asp Phe Leu Asp Asn Glu Glu Asn Glu Asp Ile Leu
610 615 620

Glu Asp Ile Val Leu Thr Leu Thr Leu Phe Glu Asp Arg Glu Met Ile

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625 630 635 640

Glu Glu Arg Leu Lys Thr Tyr Ala His Leu Phe Asp Asp Lys Val Met
645 650 655

Lys Gln Leu Lys Arg Arg Arg Tyr Thr Gly Trp Gly Arg Leu Ser Arg
660 665 670

Lys Leu Ile Asn Gly Ile Arg Asp Lys Gln Ser Gly Lys Thr Ile Leu
675 680 685

Asp Phe Leu Lys Ser Asp Gly Phe Ala Asn Arg Asn Phe Met Gln Leu
690 695 700

Ile His Asp Asp Ser Leu Thr Phe Lys Glu Asp Ile Gln Lys Ala Gln
705 710 715 720

Val Ser Gly Gln Gly Asp Ser Leu His Glu His Ile Ala Asn Leu Ala
725 730 735

Gly Ser Pro Ala Ile Lys Lys Gly Ile Leu Gln Thr Val Lys Val Val
740 745 750

Asp Glu Leu Val Lys Val Met Gly Arg His Lys Pro Glu Asn Ile Val
755 760 765

Ile Glu Met Ala Arg Glu Asn Gln Thr Thr Gln Lys Gly Gln Lys Asn
770 775 780

Ser Arg Glu Arg Met Lys Arg Ile Glu Glu Gly Ile Lys Glu Leu Gly
785 790 795 800

Ser Gln Ile Leu Lys Glu His Pro Val Glu Asn Thr Gln Leu Gln Asn
805 810 815

Glu Lys Leu Tyr Leu Tyr Tyr Leu Gln Asn Gly Arg Asp Met Tyr Val
820 825 830

Asp Gln Glu Leu Asp Ile Asn Arg Leu Ser Asp Tyr Asp Val Asp His
835 840 845

Ile Val Pro Gln Ser Phe Leu Lys Asp Asp Ser Ile Asp Asn Lys Val
850 855 860

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```
Leu Thr Arg Ser Asp Lys Asn Arg Gly Lys Ser Asp Asn Val Pro Ser
865                 870                 875                 880

Glu Glu Val Val Lys Lys Met Lys Asn Tyr Trp Arg Gln Leu Leu Asn
                885                 890                 895

Ala Lys Leu Ile Thr Gln Arg Lys Phe Asp Asn Leu Thr Lys Ala Glu
            900                 905                 910

Arg Gly Gly Leu Ser Glu Leu Asp Lys Ala Gly Phe Ile Lys Arg Gln
        915                 920                 925

Leu Val Glu Thr Arg Gln Ile Thr Lys His Val Ala Gln Ile Leu Asp
    930                 935                 940

Ser Arg Met Asn Thr Lys Tyr Asp Glu Asn Asp Lys Leu Ile Arg Glu
945                 950                 955                 960

Val Lys Val Ile Thr Leu Lys Ser Lys Leu Val Ser Asp Phe Arg Lys
                965                 970                 975

Asp Phe Gln Phe Tyr Lys Val Arg Glu Ile Asn Asn Tyr His His Ala
            980                 985                 990

His Asp Ala Tyr Leu Asn Ala Val  Val Gly Thr Ala Leu  Ile Lys Lys
        995                 1000                1005

Tyr Pro  Lys Leu Glu Ser Glu  Phe Val Tyr Gly Asp  Tyr Lys Val
    1010                1015                1020

Tyr Asp  Val Arg Lys Met Ile  Ala Lys Ser Glu Gln  Glu Ile Gly
    1025                1030                1035

Lys Ala  Thr Ala Lys Tyr Phe  Phe Tyr Ser Asn Ile  Met Asn Phe
    1040                1045                1050

Phe Lys  Thr Glu Ile Thr Leu  Ala Asn Gly Glu Ile  Arg Lys Arg
    1055                1060                1065

Pro Leu  Ile Glu Thr Asn Gly  Glu Thr Gly Glu Ile  Val Trp Asp
    1070                1075                1080
```

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Lys Gly Arg Asp Phe Ala Thr Val Arg Lys Val Leu Ser Met Pro
1085 1090 1095

Gln Val Asn Ile Val Lys Lys Thr Glu Val Gln Thr Gly Gly Phe
1100 1105 1110

Ser Lys Glu Ser Ile Leu Pro Lys Arg Asn Ser Asp Lys Leu Ile
1115 1120 1125

Ala Arg Lys Lys Asp Trp Asp Pro Lys Lys Tyr Gly Gly Phe Asp
1130 1135 1140

Ser Pro Thr Val Ala Tyr Ser Val Leu Val Val Ala Lys Val Glu
1145 1150 1155

Lys Gly Lys Ser Lys Lys Leu Lys Ser Val Lys Glu Leu Leu Gly
1160 1165 1170

Ile Thr Ile Met Glu Arg Ser Ser Phe Glu Lys Asn Pro Ile Asp
1175 1180 1185

Phe Leu Glu Ala Lys Gly Tyr Lys Glu Val Lys Lys Asp Leu Ile
1190 1195 1200

Ile Lys Leu Pro Lys Tyr Ser Leu Phe Glu Leu Glu Asn Gly Arg
1205 1210 1215

Lys Arg Met Leu Ala Ser Ala Gly Glu Leu Gln Lys Gly Asn Glu
1220 1225 1230

Leu Ala Leu Pro Ser Lys Tyr Val Asn Phe Leu Tyr Leu Ala Ser
1235 1240 1245

His Tyr Glu Lys Leu Lys Gly Ser Pro Glu Asp Asn Glu Gln Lys
1250 1255 1260

Gln Leu Phe Val Glu Gln His Lys His Tyr Leu Asp Glu Ile Ile
1265 1270 1275

Glu Gln Ile Ser Glu Phe Ser Lys Arg Val Ile Leu Ala Asp Ala
1280 1285 1290

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Asn Leu Asp Lys Val Leu Ser Ala Tyr Asn Lys His Arg Asp Lys
1295 1300 1305

Pro Ile Arg Glu Gln Ala Glu Asn Ile Ile His Leu Phe Thr Leu
1310 1315 1320

Thr Asn Leu Gly Ala Pro Ala Ala Phe Lys Tyr Phe Asp Thr Thr
1325 1330 1335

Ile Asp Arg Lys Arg Tyr Thr Ser Thr Lys Glu Val Leu Asp Ala
1340 1345 1350

Thr Leu Ile His Gln Ser Ile Thr Gly Leu Tyr Glu Thr Arg Ile
1355 1360 1365

Asp Leu Ser Gln Leu Gly Gly Asp Ser Arg Ala Asp Pro Lys Lys
1370 1375 1380

Lys Arg Lys Val His His His His His His
1385 1390

<210> 7822
<211> 1393
<212> PRT
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic polypeptide"

<400> 7822
Met Ala Pro Lys Lys Lys Arg Lys Val Asp Lys Lys Tyr Ser Ile Gly
1 5 10 15

Leu Asp Ile Gly Thr Asn Ser Val Gly Trp Ala Val Ile Thr Asp Glu
20 25 30

Tyr Lys Val Pro Ser Lys Lys Phe Lys Val Leu Gly Asn Thr Asp Arg
35 40 45

His Ser Ile Lys Lys Asn Leu Ile Gly Ala Leu Leu Phe Asp Ser Gly
50 55 60

Glu Thr Ala Glu Ala Thr Arg Leu Lys Arg Thr Ala Arg Arg Arg Tyr
65 70 75 80

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```
Thr Arg Arg Lys Asn Arg Ile Leu Tyr Leu Gln Glu Ile Phe Ser Asn
                85                  90                  95

Glu Met Ala Lys Val Asp Asp Ser Phe Phe His Arg Leu Glu Glu Ser
            100                 105                 110

Phe Leu Val Glu Glu Asp Lys Lys His Glu Arg His Pro Ile Phe Gly
        115                 120                 125

Asn Ile Val Asp Glu Val Ala Tyr His Glu Lys Tyr Pro Thr Ile Tyr
    130                 135                 140

His Leu Arg Lys Lys Leu Val Asp Ser Thr Asp Lys Ala Asp Leu Arg
145                 150                 155                 160

Leu Ile Tyr Leu Ala Leu Ala His Met Ile Lys Phe Arg Gly His Phe
                165                 170                 175

Leu Ile Glu Gly Asp Leu Asn Pro Asp Asn Ser Asp Val Asp Lys Leu
            180                 185                 190

Phe Ile Gln Leu Val Gln Thr Tyr Asn Gln Leu Phe Glu Glu Asn Pro
        195                 200                 205

Ile Asn Ala Ser Gly Val Asp Ala Lys Ala Ile Leu Ser Ala Arg Leu
    210                 215                 220

Ser Lys Ser Arg Arg Leu Glu Asn Leu Ile Ala Gln Leu Pro Gly Glu
225                 230                 235                 240

Lys Lys Asn Gly Leu Phe Gly Asn Leu Ile Ala Leu Ser Leu Gly Leu
                245                 250                 255

Thr Pro Asn Phe Lys Ser Asn Phe Asp Leu Ala Glu Asp Ala Lys Leu
            260                 265                 270

Gln Leu Ser Lys Asp Thr Tyr Asp Asp Asp Leu Asp Asn Leu Leu Ala
        275                 280                 285

Gln Ile Gly Asp Gln Tyr Ala Asp Leu Phe Leu Ala Ala Lys Asn Leu
    290                 295                 300
```

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Ser Asp Ala Ile Leu Leu Ser Asp Ile Leu Arg Val Asn Thr Glu Ile
305 310 315 320

Thr Lys Ala Pro Leu Ser Ala Ser Met Ile Lys Arg Tyr Asp Glu His
325 330 335

His Gln Asp Leu Thr Leu Leu Lys Ala Leu Val Arg Gln Gln Leu Pro
340 345 350

Glu Lys Tyr Lys Glu Ile Phe Phe Asp Gln Ser Lys Asn Gly Tyr Ala
355 360 365

Gly Tyr Ile Asp Gly Gly Ala Ser Gln Glu Glu Phe Tyr Lys Phe Ile
370 375 380

Lys Pro Ile Leu Glu Lys Met Asp Gly Thr Glu Glu Leu Leu Val Lys
385 390 395 400

Leu Asn Arg Glu Asp Leu Leu Arg Lys Gln Arg Thr Phe Asp Asn Gly
405 410 415

Ser Ile Pro His Gln Ile His Leu Gly Glu Leu His Ala Ile Leu Arg
420 425 430

Arg Gln Glu Asp Phe Tyr Pro Phe Leu Lys Asp Asn Arg Glu Lys Ile
435 440 445

Glu Lys Ile Leu Thr Phe Arg Ile Pro Tyr Tyr Val Gly Pro Leu Ala
450 455 460

Arg Gly Asn Ser Arg Phe Ala Trp Met Thr Arg Lys Ser Glu Glu Thr
465 470 475 480

Ile Thr Pro Trp Asn Phe Glu Glu Val Val Asp Lys Gly Ala Ser Ala
485 490 495

Gln Ser Phe Ile Glu Arg Met Thr Asn Phe Asp Lys Asn Leu Pro Asn
500 505 510

Glu Lys Val Leu Pro Lys His Ser Leu Leu Tyr Glu Tyr Phe Thr Val
515 520 525

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Tyr Asn Glu Leu Thr Lys Val Lys Tyr Val Thr Glu Gly Met Arg Lys
530 535 540

Pro Ala Phe Leu Ser Gly Glu Gln Lys Lys Ala Ile Val Asp Leu Leu
545 550 555 560

Phe Lys Thr Asn Arg Lys Val Thr Val Lys Gln Leu Lys Glu Asp Tyr
565 570 575

Phe Lys Lys Ile Glu Glu Phe Asp Ser Val Glu Ile Ser Gly Val Glu
580 585 590

Asp Arg Phe Asn Ala Ser Leu Gly Thr Tyr His Asp Leu Leu Lys Ile
595 600 605

Ile Lys Asp Lys Asp Phe Leu Asp Asn Glu Glu Asn Glu Asp Ile Leu
610 615 620

Glu Asp Ile Val Leu Thr Leu Thr Leu Phe Glu Asp Arg Glu Met Ile
625 630 635 640

Glu Glu Arg Leu Lys Thr Tyr Ala His Leu Phe Asp Asp Lys Val Met
645 650 655

Lys Gln Leu Lys Arg Arg Arg Tyr Thr Gly Trp Gly Arg Leu Ser Arg
660 665 670

Lys Leu Ile Asn Gly Ile Arg Asp Lys Gln Ser Gly Lys Thr Ile Leu
675 680 685

Asp Phe Leu Lys Ser Asp Gly Phe Ala Asn Arg Asn Phe Met Gln Leu
690 695 700

Ile His Asp Asp Ser Leu Thr Phe Lys Glu Asp Ile Gln Lys Ala Gln
705 710 715 720

Val Ser Gly Gln Gly Asp Ser Leu His Glu His Ile Ala Asn Leu Ala
725 730 735

Gly Ser Pro Ala Ile Lys Lys Gly Ile Leu Gln Thr Val Lys Val Val
740 745 750

Asp Glu Leu Val Lys Val Met Gly Arg His Lys Pro Glu Asn Ile Val

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```
        755                 760                 765

Ile Glu Met Ala Arg Glu Asn Gln Thr Thr Gln Lys Gly Gln Lys Asn
    770                 775                 780

Ser Arg Glu Arg Met Lys Arg Ile Glu Glu Gly Ile Lys Glu Leu Gly
785                 790                 795                 800

Ser Gln Ile Leu Lys Glu His Pro Val Glu Asn Thr Gln Leu Gln Asn
                805                 810                 815

Glu Lys Leu Tyr Leu Tyr Tyr Leu Gln Asn Gly Arg Asp Met Tyr Val
            820                 825                 830

Asp Gln Glu Leu Asp Ile Asn Arg Leu Ser Asp Tyr Asp Val Asp His
        835                 840                 845

Ile Val Pro Gln Ser Phe Leu Lys Asp Asp Ser Ile Asp Asn Lys Val
    850                 855                 860

Leu Thr Arg Ser Asp Lys Asn Arg Gly Lys Ser Asp Asn Val Pro Ser
865                 870                 875                 880

Glu Glu Val Val Lys Lys Met Lys Asn Tyr Trp Arg Gln Leu Leu Asn
                885                 890                 895

Ala Lys Leu Ile Thr Gln Arg Lys Phe Asp Asn Leu Thr Lys Ala Glu
            900                 905                 910

Arg Gly Gly Leu Ser Glu Leu Asp Lys Ala Gly Phe Ile Lys Arg Gln
        915                 920                 925

Leu Val Glu Thr Arg Gln Ile Thr Lys His Val Ala Gln Ile Leu Asp
    930                 935                 940

Ser Arg Met Asn Thr Lys Tyr Asp Glu Asn Asp Lys Leu Ile Arg Glu
945                 950                 955                 960

Val Lys Val Ile Thr Leu Lys Ser Lys Leu Val Ser Asp Phe Arg Lys
                965                 970                 975

Asp Phe Gln Phe Tyr Lys Val Arg Glu Ile Asn Asn Tyr His His Ala
            980                 985                 990
```

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```
His Asp Ala Tyr Leu Asn Ala Val  Val Gly Thr Ala Leu  Ile Lys Lys
        995                 1000                1005

Tyr Pro  Lys Leu Glu Ser Glu  Phe Val Tyr Gly Asp  Tyr Lys Val
    1010                1015                1020

Tyr Asp  Val Arg Lys Met Ile  Ala Lys Ser Glu Gln  Glu Ile Gly
    1025                1030                1035

Lys Ala  Thr Ala Lys Tyr Phe  Phe Tyr Ser Asn Ile  Met Asn Phe
    1040                1045                1050

Phe Lys  Thr Glu Ile Thr Leu  Ala Asn Gly Glu Ile  Arg Lys Arg
    1055                1060                1065

Pro Leu  Ile Glu Thr Asn Gly  Glu Thr Gly Glu Ile  Val Trp Asp
    1070                1075                1080

Lys Gly  Arg Asp Phe Ala Thr  Val Arg Lys Val Leu  Ser Met Pro
    1085                1090                1095

Gln Val  Asn Ile Val Lys Lys  Thr Glu Val Gln Thr  Gly Gly Phe
    1100                1105                1110

Ser Lys  Glu Ser Ile Leu Pro  Lys Arg Asn Ser Asp  Lys Leu Ile
    1115                1120                1125

Ala Arg  Lys Lys Asp Trp Asp  Pro Lys Lys Tyr Gly  Gly Phe Asp
    1130                1135                1140

Ser Pro  Thr Val Ala Tyr Ser  Val Leu Val Val Ala  Lys Val Glu
    1145                1150                1155

Lys Gly  Lys Ser Lys Lys Leu  Lys Ser Val Lys Glu  Leu Leu Gly
    1160                1165                1170

Ile Thr  Ile Met Glu Arg Ser  Ser Phe Glu Lys Asn  Pro Ile Asp
    1175                1180                1185

Phe Leu  Glu Ala Lys Gly Tyr  Lys Glu Val Lys Lys  Asp Leu Ile
    1190                1195                1200
```

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Ile Lys Leu Pro Lys Tyr Ser Leu Phe Glu Leu Glu Asn Gly Arg
1205 1210 1215

Lys Arg Met Leu Ala Ser Ala Gly Glu Leu Gln Lys Gly Asn Glu
1220 1225 1230

Leu Ala Leu Pro Ser Lys Tyr Val Asn Phe Leu Tyr Leu Ala Ser
1235 1240 1245

His Tyr Glu Lys Leu Lys Gly Ser Pro Glu Asp Asn Glu Gln Lys
1250 1255 1260

Gln Leu Phe Val Glu Gln His Lys His Tyr Leu Asp Glu Ile Ile
1265 1270 1275

Glu Gln Ile Ser Glu Phe Ser Lys Arg Val Ile Leu Ala Asp Ala
1280 1285 1290

Asn Leu Asp Lys Val Leu Ser Ala Tyr Asn Lys His Arg Asp Lys
1295 1300 1305

Pro Ile Arg Glu Gln Ala Glu Asn Ile Ile His Leu Phe Thr Leu
1310 1315 1320

Thr Asn Leu Gly Ala Pro Ala Ala Phe Lys Tyr Phe Asp Thr Thr
1325 1330 1335

Ile Asp Arg Lys Arg Tyr Thr Ser Thr Lys Glu Val Leu Asp Ala
1340 1345 1350

Thr Leu Ile His Gln Ser Ile Thr Gly Leu Tyr Glu Thr Arg Ile
1355 1360 1365

Asp Leu Ser Gln Leu Gly Gly Asp Ser Arg Ala Asp Pro Lys Lys
1370 1375 1380

Lys Arg Lys Val His His His His His His
1385 1390

<210> 7823
<211> 1399
<212> PRT
<213> Artificial Sequence

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<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic polypeptide"

<400> 7823

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Met Gly Ser Ser His His His His His His His His Glu Asn Leu Tyr
1               5                  10                  15

Phe Gln Gly Ser Met Asp Lys Lys Tyr Ser Ile Gly Leu Asp Ile Gly
            20                  25                  30

Thr Asn Ser Val Gly Trp Ala Val Ile Thr Asp Glu Tyr Lys Val Pro
        35                  40                  45

Ser Lys Lys Phe Lys Val Leu Gly Asn Thr Asp Arg His Ser Ile Lys
    50                  55                  60

Lys Asn Leu Ile Gly Ala Leu Leu Phe Asp Ser Gly Glu Thr Ala Glu
65                  70                  75                  80

Ala Thr Arg Leu Lys Arg Thr Ala Arg Arg Arg Tyr Thr Arg Arg Lys
                85                  90                  95

Asn Arg Ile Cys Tyr Leu Gln Glu Ile Phe Ser Asn Glu Met Ala Lys
            100                 105                 110

Val Asp Asp Ser Phe Phe His Arg Leu Glu Glu Ser Phe Leu Val Glu
        115                 120                 125

Glu Asp Lys Lys His Glu Arg His Pro Ile Phe Gly Asn Ile Val Asp
    130                 135                 140

Glu Val Ala Tyr His Glu Lys Tyr Pro Thr Ile Tyr His Leu Arg Lys
145                 150                 155                 160

Lys Leu Val Asp Ser Thr Asp Lys Ala Asp Leu Arg Leu Ile Tyr Leu
                165                 170                 175

Ala Leu Ala His Met Ile Lys Phe Arg Gly His Phe Leu Ile Glu Gly
            180                 185                 190

Asp Leu Asn Pro Asp Asn Ser Asp Val Asp Lys Leu Phe Ile Gln Leu
        195                 200                 205
```

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```
Val Gln Thr Tyr Asn Gln Leu Phe Glu Glu Asn Pro Ile Asn Ala Ser
    210                 215                 220

Gly Val Asp Ala Lys Ala Ile Leu Ser Ala Arg Leu Ser Lys Ser Arg
225                 230                 235                 240

Arg Leu Glu Asn Leu Ile Ala Gln Leu Pro Gly Glu Lys Lys Asn Gly
                245                 250                 255

Leu Phe Gly Asn Leu Ile Ala Leu Ser Leu Gly Leu Thr Pro Asn Phe
            260                 265                 270

Lys Ser Asn Phe Asp Leu Ala Glu Asp Ala Lys Leu Gln Leu Ser Lys
        275                 280                 285

Asp Thr Tyr Asp Asp Asp Leu Asp Asn Leu Leu Ala Gln Ile Gly Asp
    290                 295                 300

Gln Tyr Ala Asp Leu Phe Leu Ala Ala Lys Asn Leu Ser Asp Ala Ile
305                 310                 315                 320

Leu Leu Ser Asp Ile Leu Arg Val Asn Thr Glu Ile Thr Lys Ala Pro
                325                 330                 335

Leu Ser Ala Ser Met Ile Lys Arg Tyr Asp Glu His His Gln Asp Leu
            340                 345                 350

Thr Leu Leu Lys Ala Leu Val Arg Gln Gln Leu Pro Glu Lys Tyr Lys
        355                 360                 365

Glu Ile Phe Phe Asp Gln Ser Lys Asn Gly Tyr Ala Gly Tyr Ile Asp
    370                 375                 380

Gly Gly Ala Ser Gln Glu Glu Phe Tyr Lys Phe Ile Lys Pro Ile Leu
385                 390                 395                 400

Glu Lys Met Asp Gly Thr Glu Glu Leu Leu Val Lys Leu Asn Arg Glu
                405                 410                 415

Asp Leu Leu Arg Lys Gln Arg Thr Phe Asp Asn Gly Ser Ile Pro His
            420                 425                 430
```

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```
Gln Ile His Leu Gly Glu Leu His Ala Ile Leu Arg Arg Gln Glu Asp
        435                 440                 445

Phe Tyr Pro Phe Leu Lys Asp Asn Arg Glu Lys Ile Glu Lys Ile Leu
    450                 455                 460

Thr Phe Arg Ile Pro Tyr Tyr Val Gly Pro Leu Ala Arg Gly Asn Ser
465                 470                 475                 480

Arg Phe Ala Trp Met Thr Arg Lys Ser Glu Glu Thr Ile Thr Pro Trp
                485                 490                 495

Asn Phe Glu Glu Val Val Asp Lys Gly Ala Ser Ala Gln Ser Phe Ile
            500                 505                 510

Glu Arg Met Thr Asn Phe Asp Lys Asn Leu Pro Asn Glu Lys Val Leu
        515                 520                 525

Pro Lys His Ser Leu Leu Tyr Glu Tyr Phe Thr Val Tyr Asn Glu Leu
    530                 535                 540

Thr Lys Val Lys Tyr Val Thr Glu Gly Met Arg Lys Pro Ala Phe Leu
545                 550                 555                 560

Ser Gly Glu Gln Lys Lys Ala Ile Val Asp Leu Leu Phe Lys Thr Asn
                565                 570                 575

Arg Lys Val Thr Val Lys Gln Leu Lys Glu Asp Tyr Phe Lys Lys Ile
            580                 585                 590

Glu Cys Phe Asp Ser Val Glu Ile Ser Gly Val Glu Asp Arg Phe Asn
        595                 600                 605

Ala Ser Leu Gly Thr Tyr His Asp Leu Leu Lys Ile Ile Lys Asp Lys
    610                 615                 620

Asp Phe Leu Asp Asn Glu Glu Asn Glu Asp Ile Leu Glu Asp Ile Val
625                 630                 635                 640

Leu Thr Leu Thr Leu Phe Glu Asp Arg Glu Met Ile Glu Glu Arg Leu
                645                 650                 655
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Lys Thr Tyr Ala His Leu Phe Asp Asp Lys Val Met Lys Gln Leu Lys
660 665 670

Arg Arg Arg Tyr Thr Gly Trp Gly Arg Leu Ser Arg Lys Leu Ile Asn
675 680 685

Gly Ile Arg Asp Lys Gln Ser Gly Lys Thr Ile Leu Asp Phe Leu Lys
690 695 700

Ser Asp Gly Phe Ala Asn Arg Asn Phe Met Gln Leu Ile His Asp Asp
705 710 715 720

Ser Leu Thr Phe Lys Glu Asp Ile Gln Lys Ala Gln Val Ser Gly Gln
725 730 735

Gly Asp Ser Leu His Glu His Ile Ala Asn Leu Ala Gly Ser Pro Ala
740 745 750

Ile Lys Lys Gly Ile Leu Gln Thr Val Lys Val Val Asp Glu Leu Val
755 760 765

Lys Val Met Gly Arg His Lys Pro Glu Asn Ile Val Ile Glu Met Ala
770 775 780

Arg Glu Asn Gln Thr Thr Gln Lys Gly Gln Lys Asn Ser Arg Glu Arg
785 790 795 800

Met Lys Arg Ile Glu Glu Gly Ile Lys Glu Leu Gly Ser Gln Ile Leu
805 810 815

Lys Glu His Pro Val Glu Asn Thr Gln Leu Gln Asn Glu Lys Leu Tyr
820 825 830

Leu Tyr Tyr Leu Gln Asn Gly Arg Asp Met Tyr Val Asp Gln Glu Leu
835 840 845

Asp Ile Asn Arg Leu Ser Asp Tyr Asp Val Asp His Ile Val Pro Gln
850 855 860

Ser Phe Leu Lys Asp Asp Ser Ile Asp Asn Lys Val Leu Thr Arg Ser
865 870 875 880

Asp Lys Asn Arg Gly Lys Ser Asp Asn Val Pro Ser Glu Glu Val Val

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                885                 890                 895

Lys Lys Met Lys Asn Tyr Trp Arg Gln Leu Leu Asn Ala Lys Leu Ile
            900                 905                 910

Thr Gln Arg Lys Phe Asp Asn Leu Thr Lys Ala Glu Arg Gly Gly Leu
        915                 920                 925

Ser Glu Leu Asp Lys Ala Gly Phe Ile Lys Arg Gln Leu Val Glu Thr
    930                 935                 940

Arg Gln Ile Thr Lys His Val Ala Gln Ile Leu Asp Ser Arg Met Asn
945                 950                 955                 960

Thr Lys Tyr Asp Glu Asn Asp Lys Leu Ile Arg Glu Val Lys Val Ile
                965                 970                 975

Thr Leu Lys Ser Lys Leu Val Ser Asp Phe Arg Lys Asp Phe Gln Phe
            980                 985                 990

Tyr Lys Val Arg Glu Ile Asn Asn  Tyr His His Ala His  Asp Ala Tyr
        995                 1000                1005

Leu Asn  Ala Val Val Gly Thr  Ala Leu Ile Lys Lys  Tyr Pro Lys
    1010                1015                1020

Leu Glu  Ser Glu Phe Val Tyr  Gly Asp Tyr Lys Val  Tyr Asp Val
    1025                1030                1035

Arg Lys  Met Ile Ala Lys Ser  Glu Gln Glu Ile Gly  Lys Ala Thr
    1040                1045                1050

Ala Lys  Tyr Phe Phe Tyr Ser  Asn Ile Met Asn Phe  Phe Lys Thr
    1055                1060                1065

Glu Ile  Thr Leu Ala Asn Gly  Glu Ile Arg Lys Arg  Pro Leu Ile
    1070                1075                1080

Glu Thr  Asn Gly Glu Thr Gly  Glu Ile Val Trp Asp  Lys Gly Arg
    1085                1090                1095

Asp Phe  Ala Thr Val Arg Lys  Val Leu Ser Met Pro  Gln Val Asn
    1100                1105                1110
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Ile Val Lys Lys Thr Glu Val Gln Thr Gly Gly Phe Ser Lys Glu
1115 1120 1125

Ser Ile Leu Pro Lys Arg Asn Ser Asp Lys Leu Ile Ala Arg Lys
1130 1135 1140

Lys Asp Trp Asp Pro Lys Lys Tyr Gly Gly Phe Asp Ser Pro Thr
1145 1150 1155

Val Ala Tyr Ser Val Leu Val Val Ala Lys Val Glu Lys Gly Lys
1160 1165 1170

Ser Lys Lys Leu Lys Ser Val Lys Glu Leu Leu Gly Ile Thr Ile
1175 1180 1185

Met Glu Arg Ser Ser Phe Glu Lys Asn Pro Ile Asp Phe Leu Glu
1190 1195 1200

Ala Lys Gly Tyr Lys Glu Val Lys Lys Asp Leu Ile Ile Lys Leu
1205 1210 1215

Pro Lys Tyr Ser Leu Phe Glu Leu Glu Asn Gly Arg Lys Arg Met
1220 1225 1230

Leu Ala Ser Ala Gly Glu Leu Gln Lys Gly Asn Glu Leu Ala Leu
1235 1240 1245

Pro Ser Lys Tyr Val Asn Phe Leu Tyr Leu Ala Ser His Tyr Glu
1250 1255 1260

Lys Leu Lys Gly Ser Pro Glu Asp Asn Glu Gln Lys Gln Leu Phe
1265 1270 1275

Val Glu Gln His Lys His Tyr Leu Asp Glu Ile Ile Glu Gln Ile
1280 1285 1290

Ser Glu Phe Ser Lys Arg Val Ile Leu Ala Asp Ala Asn Leu Asp
1295 1300 1305

Lys Val Leu Ser Ala Tyr Asn Lys His Arg Asp Lys Pro Ile Arg
1310 1315 1320

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Glu Gln Ala Glu Asn Ile Ile His Leu Phe Thr Leu Thr Asn Leu
1325 1330 1335

Gly Ala Pro Ala Ala Phe Lys Tyr Phe Asp Thr Thr Ile Asp Arg
1340 1345 1350

Lys Arg Tyr Thr Ser Thr Lys Glu Val Leu Asp Ala Thr Leu Ile
1355 1360 1365

His Gln Ser Ile Thr Gly Leu Tyr Glu Thr Arg Ile Asp Leu Ser
1370 1375 1380

Gln Leu Gly Gly Asp Gly Gly Gly Ser Pro Lys Lys Lys Arg Lys
1385 1390 1395

Val

<210> 7824
<211> 1396
<212> PRT
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic polypeptide"

<400> 7824
Met Ala His His His His His His Gly Gly Ser Pro Lys Lys Lys Arg
1 5 10 15

Lys Val Asp Lys Lys Tyr Ser Ile Gly Leu Asp Ile Gly Thr Asn Ser
20 25 30

Val Gly Trp Ala Val Ile Thr Asp Glu Tyr Lys Val Pro Ser Lys Lys
35 40 45

Phe Lys Val Leu Gly Asn Thr Asp Arg His Ser Ile Lys Lys Asn Leu
50 55 60

Ile Gly Ala Leu Leu Phe Asp Ser Gly Glu Thr Ala Glu Ala Thr Arg
65 70 75 80

Leu Lys Arg Thr Ala Arg Arg Arg Tyr Thr Arg Arg Lys Asn Arg Ile

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```
                85                  90                  95

Cys Tyr Leu Gln Glu Ile Phe Ser Asn Glu Met Ala Lys Val Asp Asp
            100                 105                 110

Ser Phe Phe His Arg Leu Glu Glu Ser Phe Leu Val Glu Glu Asp Lys
        115                 120                 125

Lys His Glu Arg His Pro Ile Phe Gly Asn Ile Val Asp Glu Val Ala
    130                 135                 140

Tyr His Glu Lys Tyr Pro Thr Ile Tyr His Leu Arg Lys Lys Leu Val
145                 150                 155                 160

Asp Ser Thr Asp Lys Ala Asp Leu Arg Leu Ile Tyr Leu Ala Leu Ala
                165                 170                 175

His Met Ile Lys Phe Arg Gly His Phe Leu Ile Glu Gly Asp Leu Asn
            180                 185                 190

Pro Asp Asn Ser Asp Val Asp Lys Leu Phe Ile Gln Leu Val Gln Thr
        195                 200                 205

Tyr Asn Gln Leu Phe Glu Glu Asn Pro Ile Asn Ala Ser Gly Val Asp
    210                 215                 220

Ala Lys Ala Ile Leu Ser Ala Arg Leu Ser Lys Ser Arg Arg Leu Glu
225                 230                 235                 240

Asn Leu Ile Ala Gln Leu Pro Gly Glu Lys Lys Asn Gly Leu Phe Gly
                245                 250                 255

Asn Leu Ile Ala Leu Ser Leu Gly Leu Thr Pro Asn Phe Lys Ser Asn
            260                 265                 270

Phe Asp Leu Ala Glu Asp Ala Lys Leu Gln Leu Ser Lys Asp Thr Tyr
        275                 280                 285

Asp Asp Asp Leu Asp Asn Leu Leu Ala Gln Ile Gly Asp Gln Tyr Ala
    290                 295                 300

Asp Leu Phe Leu Ala Ala Lys Asn Leu Ser Asp Ala Ile Leu Leu Ser
305                 310                 315                 320
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Asp Ile Leu Arg Val Asn Thr Glu Ile Thr Lys Ala Pro Leu Ser Ala
325 330 335

Ser Met Ile Lys Arg Tyr Asp Glu His His Gln Asp Leu Thr Leu Leu
340 345 350

Lys Ala Leu Val Arg Gln Gln Leu Pro Glu Lys Tyr Lys Glu Ile Phe
355 360 365

Phe Asp Gln Ser Lys Asn Gly Tyr Ala Gly Tyr Ile Asp Gly Gly Ala
370 375 380

Ser Gln Glu Glu Phe Tyr Lys Phe Ile Lys Pro Ile Leu Glu Lys Met
385 390 395 400

Asp Gly Thr Glu Glu Leu Leu Val Lys Leu Asn Arg Glu Asp Leu Leu
405 410 415

Arg Lys Gln Arg Thr Phe Asp Asn Gly Ser Ile Pro His Gln Ile His
420 425 430

Leu Gly Glu Leu His Ala Ile Leu Arg Arg Gln Glu Asp Phe Tyr Pro
435 440 445

Phe Leu Lys Asp Asn Arg Glu Lys Ile Glu Lys Ile Leu Thr Phe Arg
450 455 460

Ile Pro Tyr Tyr Val Gly Pro Leu Ala Arg Gly Asn Ser Arg Phe Ala
465 470 475 480

Trp Met Thr Arg Lys Ser Glu Glu Thr Ile Thr Pro Trp Asn Phe Glu
485 490 495

Glu Val Val Asp Lys Gly Ala Ser Ala Gln Ser Phe Ile Glu Arg Met
500 505 510

Thr Asn Phe Asp Lys Asn Leu Pro Asn Glu Lys Val Leu Pro Lys His
515 520 525

Ser Leu Leu Tyr Glu Tyr Phe Thr Val Tyr Asn Glu Leu Thr Lys Val
530 535 540

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Lys Tyr Val Thr Glu Gly Met Arg Lys Pro Ala Phe Leu Ser Gly Glu
545 550 555 560

Gln Lys Lys Ala Ile Val Asp Leu Leu Phe Lys Thr Asn Arg Lys Val
565 570 575

Thr Val Lys Gln Leu Lys Glu Asp Tyr Phe Lys Lys Ile Glu Cys Phe
580 585 590

Asp Ser Val Glu Ile Ser Gly Val Glu Asp Arg Phe Asn Ala Ser Leu
595 600 605

Gly Thr Tyr His Asp Leu Leu Lys Ile Ile Lys Asp Lys Asp Phe Leu
610 615 620

Asp Asn Glu Glu Asn Glu Asp Ile Leu Glu Asp Ile Val Leu Thr Leu
625 630 635 640

Thr Leu Phe Glu Asp Arg Glu Met Ile Glu Glu Arg Leu Lys Thr Tyr
645 650 655

Ala His Leu Phe Asp Asp Lys Val Met Lys Gln Leu Lys Arg Arg Arg
660 665 670

Tyr Thr Gly Trp Gly Arg Leu Ser Arg Lys Leu Ile Asn Gly Ile Arg
675 680 685

Asp Lys Gln Ser Gly Lys Thr Ile Leu Asp Phe Leu Lys Ser Asp Gly
690 695 700

Phe Ala Asn Arg Asn Phe Met Gln Leu Ile His Asp Asp Ser Leu Thr
705 710 715 720

Phe Lys Glu Asp Ile Gln Lys Ala Gln Val Ser Gly Gln Gly Asp Ser
725 730 735

Leu His Glu His Ile Ala Asn Leu Ala Gly Ser Pro Ala Ile Lys Lys
740 745 750

Gly Ile Leu Gln Thr Val Lys Val Val Asp Glu Leu Val Lys Val Met
755 760 765

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```
Gly Arg His Lys Pro Glu Asn Ile Val Ile Glu Met Ala Arg Glu Asn
    770                 775                 780

Gln Thr Thr Gln Lys Gly Gln Lys Asn Ser Arg Glu Arg Met Lys Arg
785                 790                 795                 800

Ile Glu Glu Gly Ile Lys Glu Leu Gly Ser Gln Ile Leu Lys Glu His
                805                 810                 815

Pro Val Glu Asn Thr Gln Leu Gln Asn Glu Lys Leu Tyr Leu Tyr Tyr
            820                 825                 830

Leu Gln Asn Gly Arg Asp Met Tyr Val Asp Gln Glu Leu Asp Ile Asn
        835                 840                 845

Arg Leu Ser Asp Tyr Asp Val Asp His Ile Val Pro Gln Ser Phe Leu
    850                 855                 860

Lys Asp Asp Ser Ile Asp Asn Lys Val Leu Thr Arg Ser Asp Lys Asn
865                 870                 875                 880

Arg Gly Lys Ser Asp Asn Val Pro Ser Glu Glu Val Val Lys Lys Met
                885                 890                 895

Lys Asn Tyr Trp Arg Gln Leu Leu Asn Ala Lys Leu Ile Thr Gln Arg
            900                 905                 910

Lys Phe Asp Asn Leu Thr Lys Ala Glu Arg Gly Gly Leu Ser Glu Leu
        915                 920                 925

Asp Lys Ala Gly Phe Ile Lys Arg Gln Leu Val Glu Thr Arg Gln Ile
    930                 935                 940

Thr Lys His Val Ala Gln Ile Leu Asp Ser Arg Met Asn Thr Lys Tyr
945                 950                 955                 960

Asp Glu Asn Asp Lys Leu Ile Arg Glu Val Lys Val Ile Thr Leu Lys
                965                 970                 975

Ser Lys Leu Val Ser Asp Phe Arg Lys Asp Phe Gln Phe Tyr Lys Val
            980                 985                 990

Arg Glu Ile Asn Asn Tyr His His  Ala His Asp Ala Tyr  Leu Asn Ala
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995 1000 1005

Val Val Gly Thr Ala Leu Ile Lys Lys Tyr Pro Lys Leu Glu Ser
1010 1015 1020

Glu Phe Val Tyr Gly Asp Tyr Lys Val Tyr Asp Val Arg Lys Met
1025 1030 1035

Ile Ala Lys Ser Glu Gln Glu Ile Gly Lys Ala Thr Ala Lys Tyr
1040 1045 1050

Phe Phe Tyr Ser Asn Ile Met Asn Phe Phe Lys Thr Glu Ile Thr
1055 1060 1065

Leu Ala Asn Gly Glu Ile Arg Lys Arg Pro Leu Ile Glu Thr Asn
1070 1075 1080

Gly Glu Thr Gly Glu Ile Val Trp Asp Lys Gly Arg Asp Phe Ala
1085 1090 1095

Thr Val Arg Lys Val Leu Ser Met Pro Gln Val Asn Ile Val Lys
1100 1105 1110

Lys Thr Glu Val Gln Thr Gly Gly Phe Ser Lys Glu Ser Ile Leu
1115 1120 1125

Pro Lys Arg Asn Ser Asp Lys Leu Ile Ala Arg Lys Lys Asp Trp
1130 1135 1140

Asp Pro Lys Lys Tyr Gly Gly Phe Asp Ser Pro Thr Val Ala Tyr
1145 1150 1155

Ser Val Leu Val Val Ala Lys Val Glu Lys Gly Lys Ser Lys Lys
1160 1165 1170

Leu Lys Ser Val Lys Glu Leu Leu Gly Ile Thr Ile Met Glu Arg
1175 1180 1185

Ser Ser Phe Glu Lys Asn Pro Ile Asp Phe Leu Glu Ala Lys Gly
1190 1195 1200

Tyr Lys Glu Val Lys Lys Asp Leu Ile Ile Lys Leu Pro Lys Tyr
1205 1210 1215

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Ser Leu Phe Glu Leu Glu Asn Gly Arg Lys Arg Met Leu Ala Ser
1220 1225 1230

Ala Gly Glu Leu Gln Lys Gly Asn Glu Leu Ala Leu Pro Ser Lys
1235 1240 1245

Tyr Val Asn Phe Leu Tyr Leu Ala Ser His Tyr Glu Lys Leu Lys
1250 1255 1260

Gly Ser Pro Glu Asp Asn Glu Gln Lys Gln Leu Phe Val Glu Gln
1265 1270 1275

His Lys His Tyr Leu Asp Glu Ile Ile Glu Gln Ile Ser Glu Phe
1280 1285 1290

Ser Lys Arg Val Ile Leu Ala Asp Ala Asn Leu Asp Lys Val Leu
1295 1300 1305

Ser Ala Tyr Asn Lys His Arg Asp Lys Pro Ile Arg Glu Gln Ala
1310 1315 1320

Glu Asn Ile Ile His Leu Phe Thr Leu Thr Asn Leu Gly Ala Pro
1325 1330 1335

Ala Ala Phe Lys Tyr Phe Asp Thr Thr Ile Asp Arg Lys Arg Tyr
1340 1345 1350

Thr Ser Thr Lys Glu Val Leu Asp Ala Thr Leu Ile His Gln Ser
1355 1360 1365

Ile Thr Gly Leu Tyr Glu Thr Arg Ile Asp Leu Ser Gln Leu Gly
1370 1375 1380

Gly Asp Ser Arg Ala Asp Pro Lys Lys Lys Arg Lys Val
1385 1390 1395

<210> 7825
<211> 1386
<212> PRT
<213> Artificial Sequence

<220>
<221> source

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<223> /note="Description of Artificial Sequence: Synthetic polypeptide"

<400> 7825

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Met Ala Pro Lys Lys Lys Arg Lys Val Asp Lys Lys Tyr Ser Ile Gly
1               5                  10                  15

Leu Asp Ile Gly Thr Asn Ser Val Gly Trp Ala Val Ile Thr Asp Glu
            20                  25                  30

Tyr Lys Val Pro Ser Lys Lys Phe Lys Val Leu Gly Asn Thr Asp Arg
        35                  40                  45

His Ser Ile Lys Lys Asn Leu Ile Gly Ala Leu Leu Phe Asp Ser Gly
    50                  55                  60

Glu Thr Ala Glu Ala Thr Arg Leu Lys Arg Thr Ala Arg Arg Arg Tyr
65                  70                  75                  80

Thr Arg Arg Lys Asn Arg Ile Cys Tyr Leu Gln Glu Ile Phe Ser Asn
                85                  90                  95

Glu Met Ala Lys Val Asp Asp Ser Phe Phe His Arg Leu Glu Glu Ser
            100                 105                 110

Phe Leu Val Glu Glu Asp Lys Lys His Glu Arg His Pro Ile Phe Gly
        115                 120                 125

Asn Ile Val Asp Glu Val Ala Tyr His Glu Lys Tyr Pro Thr Ile Tyr
    130                 135                 140

His Leu Arg Lys Lys Leu Val Asp Ser Thr Asp Lys Ala Asp Leu Arg
145                 150                 155                 160

Leu Ile Tyr Leu Ala Leu Ala His Met Ile Lys Phe Arg Gly His Phe
                165                 170                 175

Leu Ile Glu Gly Asp Leu Asn Pro Asp Asn Ser Asp Val Asp Lys Leu
            180                 185                 190

Phe Ile Gln Leu Val Gln Thr Tyr Asn Gln Leu Phe Glu Glu Asn Pro
        195                 200                 205

Ile Asn Ala Ser Gly Val Asp Ala Lys Ala Ile Leu Ser Ala Arg Leu
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210 215 220

Ser Lys Ser Arg Arg Leu Glu Asn Leu Ile Ala Gln Leu Pro Gly Glu
225 230 235 240

Lys Lys Asn Gly Leu Phe Gly Asn Leu Ile Ala Leu Ser Leu Gly Leu
245 250 255

Thr Pro Asn Phe Lys Ser Asn Phe Asp Leu Ala Glu Asp Ala Lys Leu
260 265 270

Gln Leu Ser Lys Asp Thr Tyr Asp Asp Asp Leu Asp Asn Leu Leu Ala
275 280 285

Gln Ile Gly Asp Gln Tyr Ala Asp Leu Phe Leu Ala Ala Lys Asn Leu
290 295 300

Ser Asp Ala Ile Leu Leu Ser Asp Ile Leu Arg Val Asn Thr Glu Ile
305 310 315 320

Thr Lys Ala Pro Leu Ser Ala Ser Met Ile Lys Arg Tyr Asp Glu His
325 330 335

His Gln Asp Leu Thr Leu Leu Lys Ala Leu Val Arg Gln Gln Leu Pro
340 345 350

Glu Lys Tyr Lys Glu Ile Phe Phe Asp Gln Ser Lys Asn Gly Tyr Ala
355 360 365

Gly Tyr Ile Asp Gly Gly Ala Ser Gln Glu Glu Phe Tyr Lys Phe Ile
370 375 380

Lys Pro Ile Leu Glu Lys Met Asp Gly Thr Glu Glu Leu Leu Val Lys
385 390 395 400

Leu Asn Arg Glu Asp Leu Leu Arg Lys Gln Arg Thr Phe Asp Asn Gly
405 410 415

Ser Ile Pro His Gln Ile His Leu Gly Glu Leu His Ala Ile Leu Arg
420 425 430

Arg Gln Glu Asp Phe Tyr Pro Phe Leu Lys Asp Asn Arg Glu Lys Ile
435 440 445

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Glu Lys Ile Leu Thr Phe Arg Ile Pro Tyr Tyr Val Gly Pro Leu Ala
450 455 460

Arg Gly Asn Ser Arg Phe Ala Trp Met Thr Arg Lys Ser Glu Glu Thr
465 470 475 480

Ile Thr Pro Trp Asn Phe Glu Glu Val Val Asp Lys Gly Ala Ser Ala
485 490 495

Gln Ser Phe Ile Glu Arg Met Thr Asn Phe Asp Lys Asn Leu Pro Asn
500 505 510

Glu Lys Val Leu Pro Lys His Ser Leu Leu Tyr Glu Tyr Phe Thr Val
515 520 525

Tyr Asn Glu Leu Thr Lys Val Lys Tyr Val Thr Glu Gly Met Arg Lys
530 535 540

Pro Ala Phe Leu Ser Gly Glu Gln Lys Lys Ala Ile Val Asp Leu Leu
545 550 555 560

Phe Lys Thr Asn Arg Lys Val Thr Val Lys Gln Leu Lys Glu Asp Tyr
565 570 575

Phe Lys Lys Ile Glu Cys Phe Asp Ser Val Glu Ile Ser Gly Val Glu
580 585 590

Asp Arg Phe Asn Ala Ser Leu Gly Thr Tyr His Asp Leu Leu Lys Ile
595 600 605

Ile Lys Asp Lys Asp Phe Leu Asp Asn Glu Glu Asn Glu Asp Ile Leu
610 615 620

Glu Asp Ile Val Leu Thr Leu Thr Leu Phe Glu Asp Arg Glu Met Ile
625 630 635 640

Glu Glu Arg Leu Lys Thr Tyr Ala His Leu Phe Asp Asp Lys Val Met
645 650 655

Lys Gln Leu Lys Arg Arg Arg Tyr Thr Gly Trp Gly Arg Leu Ser Arg
660 665 670

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Lys Leu Ile Asn Gly Ile Arg Asp Lys Gln Ser Gly Lys Thr Ile Leu
675 680 685

Asp Phe Leu Lys Ser Asp Gly Phe Ala Asn Arg Asn Phe Met Gln Leu
690 695 700

Ile His Asp Asp Ser Leu Thr Phe Lys Glu Asp Ile Gln Lys Ala Gln
705 710 715 720

Val Ser Gly Gln Gly Asp Ser Leu His Glu His Ile Ala Asn Leu Ala
725 730 735

Gly Ser Pro Ala Ile Lys Lys Gly Ile Leu Gln Thr Val Lys Val Val
740 745 750

Asp Glu Leu Val Lys Val Met Gly Arg His Lys Pro Glu Asn Ile Val
755 760 765

Ile Glu Met Ala Arg Glu Asn Gln Thr Thr Gln Lys Gly Gln Lys Asn
770 775 780

Ser Arg Glu Arg Met Lys Arg Ile Glu Glu Gly Ile Lys Glu Leu Gly
785 790 795 800

Ser Gln Ile Leu Lys Glu His Pro Val Glu Asn Thr Gln Leu Gln Asn
805 810 815

Glu Lys Leu Tyr Leu Tyr Tyr Leu Gln Asn Gly Arg Asp Met Tyr Val
820 825 830

Asp Gln Glu Leu Asp Ile Asn Arg Leu Ser Asp Tyr Asp Val Asp His
835 840 845

Ile Val Pro Gln Ser Phe Leu Lys Asp Asp Ser Ile Asp Asn Lys Val
850 855 860

Leu Thr Arg Ser Asp Lys Asn Arg Gly Lys Ser Asp Asn Val Pro Ser
865 870 875 880

Glu Glu Val Val Lys Lys Met Lys Asn Tyr Trp Arg Gln Leu Leu Asn
885 890 895

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```
Ala Lys Leu Ile Thr Gln Arg Lys Phe Asp Asn Leu Thr Lys Ala Glu
            900                 905                 910

Arg Gly Gly Leu Ser Glu Leu Asp Lys Ala Gly Phe Ile Lys Arg Gln
        915                 920                 925

Leu Val Glu Thr Arg Gln Ile Thr Lys His Val Ala Gln Ile Leu Asp
    930                 935                 940

Ser Arg Met Asn Thr Lys Tyr Asp Glu Asn Asp Lys Leu Ile Arg Glu
945                 950                 955                 960

Val Lys Val Ile Thr Leu Lys Ser Lys Leu Val Ser Asp Phe Arg Lys
                965                 970                 975

Asp Phe Gln Phe Tyr Lys Val Arg Glu Ile Asn Asn Tyr His His Ala
            980                 985                 990

His Asp Ala Tyr Leu Asn Ala Val  Val Gly Thr Ala Leu  Ile Lys Lys
        995                 1000                1005

Tyr Pro  Lys Leu Glu Ser Glu  Phe Val Tyr Gly Asp  Tyr Lys Val
    1010                1015                1020

Tyr Asp  Val Arg Lys Met Ile  Ala Lys Ser Glu Gln  Glu Ile Gly
    1025                1030                1035

Lys Ala  Thr Ala Lys Tyr Phe  Phe Tyr Ser Asn Ile  Met Asn Phe
    1040                1045                1050

Phe Lys  Thr Glu Ile Thr Leu  Ala Asn Gly Glu Ile  Arg Lys Arg
    1055                1060                1065

Pro Leu  Ile Glu Thr Asn Gly  Glu Thr Gly Glu Ile  Val Trp Asp
    1070                1075                1080

Lys Gly  Arg Asp Phe Ala Thr  Val Arg Lys Val Leu  Ser Met Pro
    1085                1090                1095

Gln Val  Asn Ile Val Lys Lys  Thr Glu Val Gln Thr  Gly Gly Phe
    1100                1105                1110

Ser Lys  Glu Ser Ile Leu Pro  Lys Arg Asn Ser Asp  Lys Leu Ile
```

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1115 1120 1125

Ala Arg Lys Lys Asp Trp Asp Pro Lys Lys Tyr Gly Gly Phe Asp
1130 1135 1140

Ser Pro Thr Val Ala Tyr Ser Val Leu Val Val Ala Lys Val Glu
1145 1150 1155

Lys Gly Lys Ser Lys Lys Leu Lys Ser Val Lys Glu Leu Leu Gly
1160 1165 1170

Ile Thr Ile Met Glu Arg Ser Ser Phe Glu Lys Asn Pro Ile Asp
1175 1180 1185

Phe Leu Glu Ala Lys Gly Tyr Lys Glu Val Lys Lys Asp Leu Ile
1190 1195 1200

Ile Lys Leu Pro Lys Tyr Ser Leu Phe Glu Leu Glu Asn Gly Arg
1205 1210 1215

Lys Arg Met Leu Ala Ser Ala Gly Glu Leu Gln Lys Gly Asn Glu
1220 1225 1230

Leu Ala Leu Pro Ser Lys Tyr Val Asn Phe Leu Tyr Leu Ala Ser
1235 1240 1245

His Tyr Glu Lys Leu Lys Gly Ser Pro Glu Asp Asn Glu Gln Lys
1250 1255 1260

Gln Leu Phe Val Glu Gln His Lys His Tyr Leu Asp Glu Ile Ile
1265 1270 1275

Glu Gln Ile Ser Glu Phe Ser Lys Arg Val Ile Leu Ala Asp Ala
1280 1285 1290

Asn Leu Asp Lys Val Leu Ser Ala Tyr Asn Lys His Arg Asp Lys
1295 1300 1305

Pro Ile Arg Glu Gln Ala Glu Asn Ile Ile His Leu Phe Thr Leu
1310 1315 1320

Thr Asn Leu Gly Ala Pro Ala Ala Phe Lys Tyr Phe Asp Thr Thr
1325 1330 1335

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Ile Asp Arg Lys Arg Tyr Thr Ser Thr Lys Glu Val Leu Asp Ala
1340 1345 1350

Thr Leu Ile His Gln Ser Ile Thr Gly Leu Tyr Glu Thr Arg Ile
1355 1360 1365

Asp Leu Ser Gln Leu Gly Gly Asp Ser Arg Ala Asp His His His
1370 1375 1380

His His His
1385

<210> 7826
<211> 1389
<212> PRT
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic polypeptide"

<400> 7826
Met Ala His His His His His His Gly Gly Ser Asp Lys Lys Tyr Ser
1 5 10 15

Ile Gly Leu Asp Ile Gly Thr Asn Ser Val Gly Trp Ala Val Ile Thr
20 25 30

Asp Glu Tyr Lys Val Pro Ser Lys Lys Phe Lys Val Leu Gly Asn Thr
35 40 45

Asp Arg His Ser Ile Lys Lys Asn Leu Ile Gly Ala Leu Leu Phe Asp
50 55 60

Ser Gly Glu Thr Ala Glu Ala Thr Arg Leu Lys Arg Thr Ala Arg Arg
65 70 75 80

Arg Tyr Thr Arg Arg Lys Asn Arg Ile Cys Tyr Leu Gln Glu Ile Phe
85 90 95

Ser Asn Glu Met Ala Lys Val Asp Asp Ser Phe Phe His Arg Leu Glu
100 105 110

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```
Glu Ser Phe Leu Val Glu Glu Asp Lys Lys His Glu Arg His Pro Ile
        115                 120                 125

Phe Gly Asn Ile Val Asp Glu Val Ala Tyr His Glu Lys Tyr Pro Thr
    130                 135                 140

Ile Tyr His Leu Arg Lys Lys Leu Val Asp Ser Thr Asp Lys Ala Asp
145                 150                 155                 160

Leu Arg Leu Ile Tyr Leu Ala Leu Ala His Met Ile Lys Phe Arg Gly
                165                 170                 175

His Phe Leu Ile Glu Gly Asp Leu Asn Pro Asp Asn Ser Asp Val Asp
            180                 185                 190

Lys Leu Phe Ile Gln Leu Val Gln Thr Tyr Asn Gln Leu Phe Glu Glu
        195                 200                 205

Asn Pro Ile Asn Ala Ser Gly Val Asp Ala Lys Ala Ile Leu Ser Ala
    210                 215                 220

Arg Leu Ser Lys Ser Arg Arg Leu Glu Asn Leu Ile Ala Gln Leu Pro
225                 230                 235                 240

Gly Glu Lys Lys Asn Gly Leu Phe Gly Asn Leu Ile Ala Leu Ser Leu
                245                 250                 255

Gly Leu Thr Pro Asn Phe Lys Ser Asn Phe Asp Leu Ala Glu Asp Ala
            260                 265                 270

Lys Leu Gln Leu Ser Lys Asp Thr Tyr Asp Asp Asp Leu Asp Asn Leu
        275                 280                 285

Leu Ala Gln Ile Gly Asp Gln Tyr Ala Asp Leu Phe Leu Ala Ala Lys
    290                 295                 300

Asn Leu Ser Asp Ala Ile Leu Leu Ser Asp Ile Leu Arg Val Asn Thr
305                 310                 315                 320

Glu Ile Thr Lys Ala Pro Leu Ser Ala Ser Met Ile Lys Arg Tyr Asp
                325                 330                 335

Glu His His Gln Asp Leu Thr Leu Leu Lys Ala Leu Val Arg Gln Gln
```

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340 345 350

Leu Pro Glu Lys Tyr Lys Glu Ile Phe Phe Asp Gln Ser Lys Asn Gly
355 360 365

Tyr Ala Gly Tyr Ile Asp Gly Gly Ala Ser Gln Glu Glu Phe Tyr Lys
370 375 380

Phe Ile Lys Pro Ile Leu Glu Lys Met Asp Gly Thr Glu Glu Leu Leu
385 390 395 400

Val Lys Leu Asn Arg Glu Asp Leu Leu Arg Lys Gln Arg Thr Phe Asp
405 410 415

Asn Gly Ser Ile Pro His Gln Ile His Leu Gly Glu Leu His Ala Ile
420 425 430

Leu Arg Arg Gln Glu Asp Phe Tyr Pro Phe Leu Lys Asp Asn Arg Glu
435 440 445

Lys Ile Glu Lys Ile Leu Thr Phe Arg Ile Pro Tyr Tyr Val Gly Pro
450 455 460

Leu Ala Arg Gly Asn Ser Arg Phe Ala Trp Met Thr Arg Lys Ser Glu
465 470 475 480

Glu Thr Ile Thr Pro Trp Asn Phe Glu Glu Val Val Asp Lys Gly Ala
485 490 495

Ser Ala Gln Ser Phe Ile Glu Arg Met Thr Asn Phe Asp Lys Asn Leu
500 505 510

Pro Asn Glu Lys Val Leu Pro Lys His Ser Leu Leu Tyr Glu Tyr Phe
515 520 525

Thr Val Tyr Asn Glu Leu Thr Lys Val Lys Tyr Val Thr Glu Gly Met
530 535 540

Arg Lys Pro Ala Phe Leu Ser Gly Glu Gln Lys Lys Ala Ile Val Asp
545 550 555 560

Leu Leu Phe Lys Thr Asn Arg Lys Val Thr Val Lys Gln Leu Lys Glu
565 570 575

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```
Asp Tyr Phe Lys Lys Ile Glu Cys Phe Asp Ser Val Glu Ile Ser Gly
            580                 585                 590

Val Glu Asp Arg Phe Asn Ala Ser Leu Gly Thr Tyr His Asp Leu Leu
        595                 600                 605

Lys Ile Ile Lys Asp Lys Asp Phe Leu Asp Asn Glu Glu Asn Glu Asp
    610                 615                 620

Ile Leu Glu Asp Ile Val Leu Thr Leu Thr Leu Phe Glu Asp Arg Glu
625                 630                 635                 640

Met Ile Glu Glu Arg Leu Lys Thr Tyr Ala His Leu Phe Asp Asp Lys
                645                 650                 655

Val Met Lys Gln Leu Lys Arg Arg Arg Tyr Thr Gly Trp Gly Arg Leu
            660                 665                 670

Ser Arg Lys Leu Ile Asn Gly Ile Arg Asp Lys Gln Ser Gly Lys Thr
        675                 680                 685

Ile Leu Asp Phe Leu Lys Ser Asp Gly Phe Ala Asn Arg Asn Phe Met
    690                 695                 700

Gln Leu Ile His Asp Asp Ser Leu Thr Phe Lys Glu Asp Ile Gln Lys
705                 710                 715                 720

Ala Gln Val Ser Gly Gln Gly Asp Ser Leu His Glu His Ile Ala Asn
                725                 730                 735

Leu Ala Gly Ser Pro Ala Ile Lys Lys Gly Ile Leu Gln Thr Val Lys
            740                 745                 750

Val Val Asp Glu Leu Val Lys Val Met Gly Arg His Lys Pro Glu Asn
        755                 760                 765

Ile Val Ile Glu Met Ala Arg Glu Asn Gln Thr Thr Gln Lys Gly Gln
    770                 775                 780

Lys Asn Ser Arg Glu Arg Met Lys Arg Ile Glu Glu Gly Ile Lys Glu
785                 790                 795                 800
```

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```
Leu Gly Ser Gln Ile Leu Lys Glu His Pro Val Glu Asn Thr Gln Leu
                805                 810                 815

Gln Asn Glu Lys Leu Tyr Leu Tyr Tyr Leu Gln Asn Gly Arg Asp Met
            820                 825                 830

Tyr Val Asp Gln Glu Leu Asp Ile Asn Arg Leu Ser Asp Tyr Asp Val
        835                 840                 845

Asp His Ile Val Pro Gln Ser Phe Leu Lys Asp Asp Ser Ile Asp Asn
    850                 855                 860

Lys Val Leu Thr Arg Ser Asp Lys Asn Arg Gly Lys Ser Asp Asn Val
865                 870                 875                 880

Pro Ser Glu Glu Val Val Lys Lys Met Lys Asn Tyr Trp Arg Gln Leu
                885                 890                 895

Leu Asn Ala Lys Leu Ile Thr Gln Arg Lys Phe Asp Asn Leu Thr Lys
            900                 905                 910

Ala Glu Arg Gly Gly Leu Ser Glu Leu Asp Lys Ala Gly Phe Ile Lys
        915                 920                 925

Arg Gln Leu Val Glu Thr Arg Gln Ile Thr Lys His Val Ala Gln Ile
    930                 935                 940

Leu Asp Ser Arg Met Asn Thr Lys Tyr Asp Glu Asn Asp Lys Leu Ile
945                 950                 955                 960

Arg Glu Val Lys Val Ile Thr Leu Lys Ser Lys Leu Val Ser Asp Phe
                965                 970                 975

Arg Lys Asp Phe Gln Phe Tyr Lys Val Arg Glu Ile Asn Asn Tyr His
            980                 985                 990

His Ala His Asp Ala Tyr Leu Asn  Ala Val Val Gly Thr  Ala Leu Ile
        995                 1000                1005

Lys Lys  Tyr Pro Lys Leu Glu  Ser Glu Phe Val Tyr  Gly Asp Tyr
    1010                1015                1020
```

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Lys Val Tyr Asp Val Arg Lys Met Ile Ala Lys Ser Glu Gln Glu
1025 1030 1035

Ile Gly Lys Ala Thr Ala Lys Tyr Phe Phe Tyr Ser Asn Ile Met
1040 1045 1050

Asn Phe Phe Lys Thr Glu Ile Thr Leu Ala Asn Gly Glu Ile Arg
1055 1060 1065

Lys Arg Pro Leu Ile Glu Thr Asn Gly Glu Thr Gly Glu Ile Val
1070 1075 1080

Trp Asp Lys Gly Arg Asp Phe Ala Thr Val Arg Lys Val Leu Ser
1085 1090 1095

Met Pro Gln Val Asn Ile Val Lys Lys Thr Glu Val Gln Thr Gly
1100 1105 1110

Gly Phe Ser Lys Glu Ser Ile Leu Pro Lys Arg Asn Ser Asp Lys
1115 1120 1125

Leu Ile Ala Arg Lys Lys Asp Trp Asp Pro Lys Lys Tyr Gly Gly
1130 1135 1140

Phe Asp Ser Pro Thr Val Ala Tyr Ser Val Leu Val Val Ala Lys
1145 1150 1155

Val Glu Lys Gly Lys Ser Lys Lys Leu Lys Ser Val Lys Glu Leu
1160 1165 1170

Leu Gly Ile Thr Ile Met Glu Arg Ser Ser Phe Glu Lys Asn Pro
1175 1180 1185

Ile Asp Phe Leu Glu Ala Lys Gly Tyr Lys Glu Val Lys Lys Asp
1190 1195 1200

Leu Ile Ile Lys Leu Pro Lys Tyr Ser Leu Phe Glu Leu Glu Asn
1205 1210 1215

Gly Arg Lys Arg Met Leu Ala Ser Ala Gly Glu Leu Gln Lys Gly
1220 1225 1230

Asn Glu Leu Ala Leu Pro Ser Lys Tyr Val Asn Phe Leu Tyr Leu

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    1235                1240                1245

Ala Ser  His Tyr Glu Lys Leu  Lys Gly Ser Pro Glu  Asp Asn Glu
    1250                1255                1260

Gln Lys  Gln Leu Phe Val Glu  Gln His Lys His Tyr  Leu Asp Glu
    1265                1270                1275

Ile Ile  Glu Gln Ile Ser Glu  Phe Ser Lys Arg Val  Ile Leu Ala
    1280                1285                1290

Asp Ala  Asn Leu Asp Lys Val  Leu Ser Ala Tyr Asn  Lys His Arg
    1295                1300                1305

Asp Lys  Pro Ile Arg Glu Gln  Ala Glu Asn Ile Ile  His Leu Phe
    1310                1315                1320

Thr Leu  Thr Asn Leu Gly Ala  Pro Ala Ala Phe Lys  Tyr Phe Asp
    1325                1330                1335

Thr Thr  Ile Asp Arg Lys Arg  Tyr Thr Ser Thr Lys  Glu Val Leu
    1340                1345                1350

Asp Ala  Thr Leu Ile His Gln  Ser Ile Thr Gly Leu  Tyr Glu Thr
    1355                1360                1365

Arg Ile  Asp Leu Ser Gln Leu  Gly Gly Asp Ser Arg  Ala Asp Pro
    1370                1375                1380

Lys Lys  Lys Arg Lys Val
    1385


<210> 7827
<211> 1399
<212> PRT
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic
      polypeptide"

<400> 7827
Met Gly Ser Ser His His His His His His His His Glu Asn Leu Tyr
1               5                  10                  15
```

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```
Phe Gln Gly Ser Met Asp Lys Lys Tyr Ser Ile Gly Leu Asp Ile Gly
            20                  25                  30

Thr Asn Ser Val Gly Trp Ala Val Ile Thr Asp Glu Tyr Lys Val Pro
        35                  40                  45

Ser Lys Lys Phe Lys Val Leu Gly Asn Thr Asp Arg His Ser Ile Lys
    50                  55                  60

Lys Asn Leu Ile Gly Ala Leu Leu Phe Asp Ser Gly Glu Thr Ala Glu
65                  70                  75                  80

Ala Thr Arg Leu Lys Arg Thr Ala Arg Arg Arg Tyr Thr Arg Arg Lys
                85                  90                  95

Asn Arg Ile Cys Tyr Leu Gln Glu Ile Phe Ser Asn Glu Met Ala Lys
            100                 105                 110

Val Asp Asp Ser Phe Phe His Arg Leu Glu Glu Ser Phe Leu Val Glu
        115                 120                 125

Glu Asp Lys Lys His Glu Arg His Pro Ile Phe Gly Asn Ile Val Asp
    130                 135                 140

Glu Val Ala Tyr His Glu Lys Tyr Pro Thr Ile Tyr His Leu Arg Lys
145                 150                 155                 160

Lys Leu Val Asp Ser Thr Asp Lys Ala Asp Leu Arg Leu Ile Tyr Leu
                165                 170                 175

Ala Leu Ala His Met Ile Lys Phe Arg Gly His Phe Leu Ile Glu Gly
            180                 185                 190

Asp Leu Asn Pro Asp Asn Ser Asp Val Asp Lys Leu Phe Ile Gln Leu
        195                 200                 205

Val Gln Thr Tyr Asn Gln Leu Phe Glu Glu Asn Pro Ile Asn Ala Ser
    210                 215                 220

Gly Val Asp Ala Lys Ala Ile Leu Ser Ala Arg Leu Ser Lys Ser Arg
225                 230                 235                 240
```

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```
Arg Leu Glu Asn Leu Ile Ala Gln Leu Pro Gly Glu Lys Lys Asn Gly
                245                 250                 255

Leu Phe Gly Asn Leu Ile Ala Leu Ser Leu Gly Leu Thr Pro Asn Phe
            260                 265                 270

Lys Ser Asn Phe Asp Leu Ala Glu Asp Ala Lys Leu Gln Leu Ser Lys
        275                 280                 285

Asp Thr Tyr Asp Asp Asp Leu Asp Asn Leu Leu Ala Gln Ile Gly Asp
    290                 295                 300

Gln Tyr Ala Asp Leu Phe Leu Ala Ala Lys Asn Leu Ser Asp Ala Ile
305                 310                 315                 320

Leu Leu Ser Asp Ile Leu Arg Val Asn Thr Glu Ile Thr Lys Ala Pro
                325                 330                 335

Leu Ser Ala Ser Met Ile Lys Arg Tyr Asp Glu His His Gln Asp Leu
            340                 345                 350

Thr Leu Leu Lys Ala Leu Val Arg Gln Gln Leu Pro Glu Lys Tyr Lys
        355                 360                 365

Glu Ile Phe Phe Asp Gln Ser Lys Asn Gly Tyr Ala Gly Tyr Ile Asp
    370                 375                 380

Gly Gly Ala Ser Gln Glu Glu Phe Tyr Lys Phe Ile Lys Pro Ile Leu
385                 390                 395                 400

Glu Lys Met Asp Gly Thr Glu Glu Leu Leu Val Lys Leu Asn Arg Glu
                405                 410                 415

Asp Leu Leu Arg Lys Gln Arg Thr Phe Asp Asn Gly Ser Ile Pro His
            420                 425                 430

Gln Ile His Leu Gly Glu Leu His Ala Ile Leu Arg Arg Gln Glu Asp
        435                 440                 445

Phe Tyr Pro Phe Leu Lys Asp Asn Arg Glu Lys Ile Glu Lys Ile Leu
    450                 455                 460

Thr Phe Arg Ile Pro Tyr Tyr Val Gly Pro Leu Ala Arg Gly Asn Ser
```

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```
465                 470                 475                 480

Arg Phe Ala Trp Met Thr Arg Lys Ser Glu Glu Thr Ile Thr Pro Trp
                485                 490                 495

Asn Phe Glu Glu Val Val Asp Lys Gly Ala Ser Ala Gln Ser Phe Ile
            500                 505                 510

Glu Arg Met Thr Asn Phe Asp Lys Asn Leu Pro Asn Glu Lys Val Leu
        515                 520                 525

Pro Lys His Ser Leu Leu Tyr Glu Tyr Phe Thr Val Tyr Asn Glu Leu
    530                 535                 540

Thr Lys Val Lys Tyr Val Thr Glu Gly Met Arg Lys Pro Ala Phe Leu
545                 550                 555                 560

Ser Gly Glu Gln Lys Lys Ala Ile Val Asp Leu Leu Phe Lys Thr Asn
                565                 570                 575

Arg Lys Val Thr Val Lys Gln Leu Lys Glu Asp Tyr Phe Lys Lys Ile
            580                 585                 590

Glu Cys Phe Asp Ser Val Glu Ile Ser Gly Val Glu Asp Arg Phe Asn
        595                 600                 605

Ala Ser Leu Gly Thr Tyr His Asp Leu Leu Lys Ile Ile Lys Asp Lys
    610                 615                 620

Asp Phe Leu Asp Asn Glu Glu Asn Glu Asp Ile Leu Glu Asp Ile Val
625                 630                 635                 640

Leu Thr Leu Thr Leu Phe Glu Asp Arg Glu Met Ile Glu Glu Arg Leu
                645                 650                 655

Lys Thr Tyr Ala His Leu Phe Asp Asp Lys Val Met Lys Gln Leu Lys
            660                 665                 670

Arg Arg Arg Tyr Thr Gly Trp Gly Arg Leu Ser Arg Lys Leu Ile Asn
        675                 680                 685

Gly Ile Arg Asp Lys Gln Ser Gly Lys Thr Ile Leu Asp Phe Leu Lys
    690                 695                 700
```

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```
Ser Asp Gly Phe Ala Asn Arg Asn Phe Met Gln Leu Ile His Asp Asp
705                 710                 715                 720

Ser Leu Thr Phe Lys Glu Asp Ile Gln Lys Ala Gln Val Ser Gly Gln
                725                 730                 735

Gly Asp Ser Leu His Glu His Ile Ala Asn Leu Ala Gly Ser Pro Ala
            740                 745                 750

Ile Lys Lys Gly Ile Leu Gln Thr Val Lys Val Val Asp Glu Leu Val
        755                 760                 765

Lys Val Met Gly Arg His Lys Pro Glu Asn Ile Val Ile Glu Met Ala
    770                 775                 780

Arg Glu Asn Gln Thr Thr Gln Lys Gly Gln Lys Asn Ser Arg Glu Arg
785                 790                 795                 800

Met Lys Arg Ile Glu Glu Gly Ile Lys Glu Leu Gly Ser Gln Ile Leu
                805                 810                 815

Lys Glu His Pro Val Glu Asn Thr Gln Leu Gln Asn Glu Lys Leu Tyr
            820                 825                 830

Leu Tyr Tyr Leu Gln Asn Gly Arg Asp Met Tyr Val Asp Gln Glu Leu
        835                 840                 845

Asp Ile Asn Arg Leu Ser Asp Tyr Asp Val Asp His Ile Val Pro Gln
    850                 855                 860

Ser Phe Leu Lys Asp Asp Ser Ile Asp Asn Lys Val Leu Thr Arg Ser
865                 870                 875                 880

Asp Lys Asn Arg Gly Lys Ser Asp Asn Val Pro Ser Glu Glu Val Val
                885                 890                 895

Lys Lys Met Lys Asn Tyr Trp Arg Gln Leu Leu Asn Ala Lys Leu Ile
            900                 905                 910

Thr Gln Arg Lys Phe Asp Asn Leu Thr Lys Ala Glu Arg Gly Gly Leu
        915                 920                 925
```

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```
Ser Glu Leu Asp Lys Ala Gly Phe Ile Lys Arg Gln Leu Val Glu Thr
    930                 935                 940

Arg Gln Ile Thr Lys His Val Ala Gln Ile Leu Asp Ser Arg Met Asn
945                 950                 955                 960

Thr Lys Tyr Asp Glu Asn Asp Lys Leu Ile Arg Glu Val Lys Val Ile
                965                 970                 975

Thr Leu Lys Ser Lys Leu Val Ser Asp Phe Arg Lys Asp Phe Gln Phe
            980                 985                 990

Tyr Lys Val Arg Glu Ile Asn Asn  Tyr His His Ala His  Asp Ala Tyr
        995                 1000                1005

Leu Asn  Ala Val Val Gly Thr  Ala Leu Ile Lys Lys  Tyr Pro Lys
    1010                1015                1020

Leu Glu  Ser Glu Phe Val Tyr  Gly Asp Tyr Lys Val  Tyr Asp Val
    1025                1030                1035

Arg Lys  Met Ile Ala Lys Ser  Glu Gln Glu Ile Gly  Lys Ala Thr
    1040                1045                1050

Ala Lys  Tyr Phe Phe Tyr Ser  Asn Ile Met Asn Phe  Phe Lys Thr
    1055                1060                1065

Glu Ile  Thr Leu Ala Asn Gly  Glu Ile Arg Lys Arg  Pro Leu Ile
    1070                1075                1080

Glu Thr  Asn Gly Glu Thr Gly  Glu Ile Val Trp Asp  Lys Gly Arg
    1085                1090                1095

Asp Phe  Ala Thr Val Arg Lys  Val Leu Ser Met Pro  Gln Val Asn
    1100                1105                1110

Ile Val  Lys Lys Thr Glu Val  Gln Thr Gly Gly Phe  Ser Lys Glu
    1115                1120                1125

Ser Ile  Leu Pro Lys Arg Asn  Ser Asp Lys Leu Ile  Ala Arg Lys
    1130                1135                1140
```

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Lys Asp Trp Asp Pro Lys Lys Tyr Gly Gly Phe Asp Ser Pro Thr
1145 1150 1155

Val Ala Tyr Ser Val Leu Val Val Ala Lys Val Glu Lys Gly Lys
1160 1165 1170

Ser Lys Lys Leu Lys Ser Val Lys Glu Leu Leu Gly Ile Thr Ile
1175 1180 1185

Met Glu Arg Ser Ser Phe Glu Lys Asn Pro Ile Asp Phe Leu Glu
1190 1195 1200

Ala Lys Gly Tyr Lys Glu Val Lys Lys Asp Leu Ile Ile Lys Leu
1205 1210 1215

Pro Lys Tyr Ser Leu Phe Glu Leu Glu Asn Gly Arg Lys Arg Met
1220 1225 1230

Leu Ala Ser Ala Gly Glu Leu Gln Lys Gly Asn Glu Leu Ala Leu
1235 1240 1245

Pro Ser Lys Tyr Val Asn Phe Leu Tyr Leu Ala Ser His Tyr Glu
1250 1255 1260

Lys Leu Lys Gly Ser Pro Glu Asp Asn Glu Gln Lys Gln Leu Phe
1265 1270 1275

Val Glu Gln His Lys His Tyr Leu Asp Glu Ile Ile Glu Gln Ile
1280 1285 1290

Ser Glu Phe Ser Lys Arg Val Ile Leu Ala Asp Ala Asn Leu Asp
1295 1300 1305

Lys Val Leu Ser Ala Tyr Asn Lys His Arg Asp Lys Pro Ile Arg
1310 1315 1320

Glu Gln Ala Glu Asn Ile Ile His Leu Phe Thr Leu Thr Asn Leu
1325 1330 1335

Gly Ala Pro Ala Ala Phe Lys Tyr Phe Asp Thr Thr Ile Asp Arg
1340 1345 1350

Lys Arg Tyr Thr Ser Thr Lys Glu Val Leu Asp Ala Thr Leu Ile

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```
    1355                1360                1365

His Gln  Ser Ile Thr Gly Leu  Tyr Glu Thr Arg Ile  Asp Leu Ser
    1370                1375                1380

Gln Leu  Gly Gly Asp Gly Gly  Gly Ser Pro Lys Lys  Lys Arg Lys
    1385                1390                1395

Val
```

<210> 7828
<211> 1393
<212> PRT
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic polypeptide"

<400> 7828

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Met Ala Pro Lys Lys Lys Arg Lys Val Asp Lys Lys Tyr Ser Ile Gly
1               5                   10                  15

Leu Asp Ile Gly Thr Asn Ser Val Gly Trp Ala Val Ile Thr Asp Glu
            20                  25                  30

Tyr Lys Val Pro Ser Lys Lys Phe Lys Val Leu Gly Asn Thr Asp Arg
        35                  40                  45

His Ser Ile Lys Lys Asn Leu Ile Gly Ala Leu Leu Phe Asp Ser Gly
    50                  55                  60

Glu Thr Ala Glu Ala Thr Arg Leu Lys Arg Thr Ala Arg Arg Arg Tyr
65                  70                  75                  80

Thr Arg Arg Lys Asn Arg Ile Cys Tyr Leu Gln Glu Ile Phe Ser Asn
                85                  90                  95

Glu Met Ala Lys Val Asp Asp Ser Phe Phe His Arg Leu Glu Glu Ser
            100                 105                 110

Phe Leu Val Glu Glu Asp Lys Lys His Glu Arg His Pro Ile Phe Gly
        115                 120                 125
```

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Asn Ile Val Asp Glu Val Ala Tyr His Glu Lys Tyr Pro Thr Ile Tyr
130 135 140

His Leu Arg Lys Lys Leu Val Asp Ser Thr Asp Lys Ala Asp Leu Arg
145 150 155 160

Leu Ile Tyr Leu Ala Leu Ala His Met Ile Lys Phe Arg Gly His Phe
165 170 175

Leu Ile Glu Gly Asp Leu Asn Pro Asp Asn Ser Asp Val Asp Lys Leu
180 185 190

Phe Ile Gln Leu Val Gln Thr Tyr Asn Gln Leu Phe Glu Glu Asn Pro
195 200 205

Ile Asn Ala Ser Gly Val Asp Ala Lys Ala Ile Leu Ser Ala Arg Leu
210 215 220

Ser Lys Ser Arg Arg Leu Glu Asn Leu Ile Ala Gln Leu Pro Gly Glu
225 230 235 240

Lys Lys Asn Gly Leu Phe Gly Asn Leu Ile Ala Leu Ser Leu Gly Leu
245 250 255

Thr Pro Asn Phe Lys Ser Asn Phe Asp Leu Ala Glu Asp Ala Lys Leu
260 265 270

Gln Leu Ser Lys Asp Thr Tyr Asp Asp Asp Leu Asp Asn Leu Leu Ala
275 280 285

Gln Ile Gly Asp Gln Tyr Ala Asp Leu Phe Leu Ala Ala Lys Asn Leu
290 295 300

Ser Asp Ala Ile Leu Leu Ser Asp Ile Leu Arg Val Asn Thr Glu Ile
305 310 315 320

Thr Lys Ala Pro Leu Ser Ala Ser Met Ile Lys Arg Tyr Asp Glu His
325 330 335

His Gln Asp Leu Thr Leu Leu Lys Ala Leu Val Arg Gln Gln Leu Pro
340 345 350

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Glu Lys Tyr Lys Glu Ile Phe Phe Asp Gln Ser Lys Asn Gly Tyr Ala
355 360 365

Gly Tyr Ile Asp Gly Gly Ala Ser Gln Glu Glu Phe Tyr Lys Phe Ile
370 375 380

Lys Pro Ile Leu Glu Lys Met Asp Gly Thr Glu Glu Leu Leu Val Lys
385 390 395 400

Leu Asn Arg Glu Asp Leu Leu Arg Lys Gln Arg Thr Phe Asp Asn Gly
405 410 415

Ser Ile Pro His Gln Ile His Leu Gly Glu Leu His Ala Ile Leu Arg
420 425 430

Arg Gln Glu Asp Phe Tyr Pro Phe Leu Lys Asp Asn Arg Glu Lys Ile
435 440 445

Glu Lys Ile Leu Thr Phe Arg Ile Pro Tyr Tyr Val Gly Pro Leu Ala
450 455 460

Arg Gly Asn Ser Arg Phe Ala Trp Met Thr Arg Lys Ser Glu Glu Thr
465 470 475 480

Ile Thr Pro Trp Asn Phe Glu Glu Val Val Asp Lys Gly Ala Ser Ala
485 490 495

Gln Ser Phe Ile Glu Arg Met Thr Asn Phe Asp Lys Asn Leu Pro Asn
500 505 510

Glu Lys Val Leu Pro Lys His Ser Leu Leu Tyr Glu Tyr Phe Thr Val
515 520 525

Tyr Asn Glu Leu Thr Lys Val Lys Tyr Val Thr Glu Gly Met Arg Lys
530 535 540

Pro Ala Phe Leu Ser Gly Glu Gln Lys Lys Ala Ile Val Asp Leu Leu
545 550 555 560

Phe Lys Thr Asn Arg Lys Val Thr Val Lys Gln Leu Lys Glu Asp Tyr
565 570 575

Phe Lys Lys Ile Glu Cys Phe Asp Ser Val Glu Ile Ser Gly Val Glu

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580 585 590

Asp Arg Phe Asn Ala Ser Leu Gly Thr Tyr His Asp Leu Leu Lys Ile
595 600 605

Ile Lys Asp Lys Asp Phe Leu Asp Asn Glu Glu Asn Glu Asp Ile Leu
610 615 620

Glu Asp Ile Val Leu Thr Leu Thr Leu Phe Glu Asp Arg Glu Met Ile
625 630 635 640

Glu Glu Arg Leu Lys Thr Tyr Ala His Leu Phe Asp Asp Lys Val Met
645 650 655

Lys Gln Leu Lys Arg Arg Arg Tyr Thr Gly Trp Gly Arg Leu Ser Arg
660 665 670

Lys Leu Ile Asn Gly Ile Arg Asp Lys Gln Ser Gly Lys Thr Ile Leu
675 680 685

Asp Phe Leu Lys Ser Asp Gly Phe Ala Asn Arg Asn Phe Met Gln Leu
690 695 700

Ile His Asp Asp Ser Leu Thr Phe Lys Glu Asp Ile Gln Lys Ala Gln
705 710 715 720

Val Ser Gly Gln Gly Asp Ser Leu His Glu His Ile Ala Asn Leu Ala
725 730 735

Gly Ser Pro Ala Ile Lys Lys Gly Ile Leu Gln Thr Val Lys Val Val
740 745 750

Asp Glu Leu Val Lys Val Met Gly Arg His Lys Pro Glu Asn Ile Val
755 760 765

Ile Glu Met Ala Arg Glu Asn Gln Thr Thr Gln Lys Gly Gln Lys Asn
770 775 780

Ser Arg Glu Arg Met Lys Arg Ile Glu Glu Gly Ile Lys Glu Leu Gly
785 790 795 800

Ser Gln Ile Leu Lys Glu His Pro Val Glu Asn Thr Gln Leu Gln Asn
805 810 815

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```
Glu Lys Leu Tyr Leu Tyr Tyr Leu Gln Asn Gly Arg Asp Met Tyr Val
            820                 825                 830

Asp Gln Glu Leu Asp Ile Asn Arg Leu Ser Asp Tyr Asp Val Asp His
        835                 840                 845

Ile Val Pro Gln Ser Phe Leu Lys Asp Asp Ser Ile Asp Asn Ala Val
    850                 855                 860

Leu Thr Arg Ser Asp Lys Asn Arg Gly Lys Ser Asp Asn Val Pro Ser
865                 870                 875                 880

Glu Glu Val Val Lys Lys Met Lys Asn Tyr Trp Arg Gln Leu Leu Asn
                885                 890                 895

Ala Lys Leu Ile Thr Gln Arg Lys Phe Asp Asn Leu Thr Lys Ala Glu
            900                 905                 910

Arg Gly Gly Leu Ser Glu Leu Asp Lys Ala Gly Phe Ile Lys Arg Gln
        915                 920                 925

Leu Val Glu Thr Arg Gln Ile Thr Lys His Val Ala Gln Ile Leu Asp
    930                 935                 940

Ser Arg Met Asn Thr Lys Tyr Asp Glu Asn Asp Lys Leu Ile Arg Glu
945                 950                 955                 960

Val Lys Val Ile Thr Leu Lys Ser Lys Leu Val Ser Asp Phe Arg Lys
                965                 970                 975

Asp Phe Gln Phe Tyr Lys Val Arg Glu Ile Asn Asn Tyr His His Ala
            980                 985                 990

His Asp Ala Tyr Leu Asn Ala Val  Val Gly Thr Ala Leu  Ile Lys Lys
        995                 1000                1005

Tyr Pro  Lys Leu Glu Ser Glu  Phe Val Tyr Gly Asp  Tyr Lys Val
    1010                1015                1020

Tyr Asp  Val Arg Lys Met Ile  Ala Lys Ser Glu Gln  Glu Ile Gly
    1025                1030                1035
```

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```
Lys Ala  Thr Ala Lys Tyr Phe  Phe Tyr Ser Asn Ile  Met Asn Phe
    1040                1045                1050

Phe Lys  Thr Glu Ile Thr Leu  Ala Asn Gly Glu Ile  Arg Lys Arg
    1055                1060                1065

Pro Leu  Ile Glu Thr Asn Gly  Glu Thr Gly Glu Ile  Val Trp Asp
    1070                1075                1080

Lys Gly  Arg Asp Phe Ala Thr  Val Arg Lys Val Leu  Ser Met Pro
    1085                1090                1095

Gln Val  Asn Ile Val Lys Lys  Thr Glu Val Gln Thr  Gly Gly Phe
    1100                1105                1110

Ser Lys  Glu Ser Ile Leu Pro  Lys Arg Asn Ser Asp  Lys Leu Ile
    1115                1120                1125

Ala Arg  Lys Lys Asp Trp Asp  Pro Lys Lys Tyr Gly  Gly Phe Asp
    1130                1135                1140

Ser Pro  Thr Val Ala Tyr Ser  Val Leu Val Val Ala  Lys Val Glu
    1145                1150                1155

Lys Gly  Lys Ser Lys Lys Leu  Lys Ser Val Lys Glu  Leu Leu Gly
    1160                1165                1170

Ile Thr  Ile Met Glu Arg Ser  Ser Phe Glu Lys Asn  Pro Ile Asp
    1175                1180                1185

Phe Leu  Glu Ala Lys Gly Tyr  Lys Glu Val Lys Lys  Asp Leu Ile
    1190                1195                1200

Ile Lys  Leu Pro Lys Tyr Ser  Leu Phe Glu Leu Glu  Asn Gly Arg
    1205                1210                1215

Lys Arg  Met Leu Ala Ser Ala  Gly Glu Leu Gln Lys  Gly Asn Glu
    1220                1225                1230

Leu Ala  Leu Pro Ser Lys Tyr  Val Asn Phe Leu Tyr  Leu Ala Ser
    1235                1240                1245
```

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```
His Tyr  Glu Lys Leu Lys Gly  Ser Pro Glu Asp Asn  Glu Gln Lys
    1250                1255                1260

Gln Leu  Phe Val Glu Gln His  Lys His Tyr Leu Asp  Glu Ile Ile
    1265                1270                1275

Glu Gln  Ile Ser Glu Phe Ser  Lys Arg Val Ile Leu  Ala Asp Ala
    1280                1285                1290

Asn Leu  Asp Lys Val Leu Ser  Ala Tyr Asn Lys His  Arg Asp Lys
    1295                1300                1305

Pro Ile  Arg Glu Gln Ala Glu  Asn Ile Ile His Leu  Phe Thr Leu
    1310                1315                1320

Thr Asn  Leu Gly Ala Pro Ala  Ala Phe Lys Tyr Phe  Asp Thr Thr
    1325                1330                1335

Ile Asp  Arg Lys Arg Tyr Thr  Ser Thr Lys Glu Val  Leu Asp Ala
    1340                1345                1350

Thr Leu  Ile His Gln Ser Ile  Thr Gly Leu Tyr Glu  Thr Arg Ile
    1355                1360                1365

Asp Leu  Ser Gln Leu Gly Gly  Asp Ser Arg Ala Asp  Pro Lys Lys
    1370                1375                1380

Lys Arg  Lys Val His His His  His His His
    1385                1390
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<210> 7829
<211> 1393
<212> PRT
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic polypeptide"

<400> 7829

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Met Ala Pro Lys Lys Lys Arg Lys Val Asp Lys Lys Tyr Ser Ile Gly
1               5                  10                  15

Leu Asp Ile Gly Thr Asn Ser Val Gly Trp Ala Val Ile Thr Asp Glu
            20                  25                  30
```

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Tyr Lys Val Pro Ser Lys Lys Phe Lys Val Leu Gly Asn Thr Asp Arg
35 40 45

His Ser Ile Lys Lys Asn Leu Ile Gly Ala Leu Leu Phe Asp Ser Gly
50 55 60

Glu Thr Ala Glu Ala Thr Arg Leu Lys Arg Thr Ala Arg Arg Arg Tyr
65 70 75 80

Thr Arg Arg Lys Asn Arg Ile Cys Tyr Leu Gln Glu Ile Phe Ser Asn
85 90 95

Glu Met Ala Lys Val Asp Asp Ser Phe Phe His Arg Leu Glu Glu Ser
100 105 110

Phe Leu Val Glu Glu Asp Lys Lys His Glu Arg His Pro Ile Phe Gly
115 120 125

Asn Ile Val Asp Glu Val Ala Tyr His Glu Lys Tyr Pro Thr Ile Tyr
130 135 140

His Leu Arg Lys Lys Leu Val Asp Ser Thr Asp Lys Ala Asp Leu Arg
145 150 155 160

Leu Ile Tyr Leu Ala Leu Ala His Met Ile Lys Phe Arg Gly His Phe
165 170 175

Leu Ile Glu Gly Asp Leu Asn Pro Asp Asn Ser Asp Val Asp Lys Leu
180 185 190

Phe Ile Gln Leu Val Gln Thr Tyr Asn Gln Leu Phe Glu Glu Asn Pro
195 200 205

Ile Asn Ala Ser Gly Val Asp Ala Lys Ala Ile Leu Ser Ala Arg Leu
210 215 220

Ser Lys Ser Arg Arg Leu Glu Asn Leu Ile Ala Gln Leu Pro Gly Glu
225 230 235 240

Lys Lys Asn Gly Leu Phe Gly Asn Leu Ile Ala Leu Ser Leu Gly Leu
245 250 255

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Thr Pro Asn Phe Lys Ser Asn Phe Asp Leu Ala Glu Asp Ala Lys Leu
            260                 265                 270

Gln Leu Ser Lys Asp Thr Tyr Asp Asp Asp Leu Asp Asn Leu Leu Ala
        275                 280                 285

Gln Ile Gly Asp Gln Tyr Ala Asp Leu Phe Leu Ala Ala Lys Asn Leu
    290                 295                 300

Ser Asp Ala Ile Leu Leu Ser Asp Ile Leu Arg Val Asn Thr Glu Ile
305                 310                 315                 320

Thr Lys Ala Pro Leu Ser Ala Ser Met Ile Lys Arg Tyr Asp Glu His
                325                 330                 335

His Gln Asp Leu Thr Leu Leu Lys Ala Leu Val Arg Gln Gln Leu Pro
            340                 345                 350

Glu Lys Tyr Lys Glu Ile Phe Phe Asp Gln Ser Lys Asn Gly Tyr Ala
        355                 360                 365

Gly Tyr Ile Asp Gly Gly Ala Ser Gln Glu Glu Phe Tyr Lys Phe Ile
    370                 375                 380

Lys Pro Ile Leu Glu Lys Met Asp Gly Thr Glu Glu Leu Leu Val Lys
385                 390                 395                 400

Leu Asn Arg Glu Asp Leu Leu Arg Lys Gln Arg Thr Phe Asp Asn Gly
                405                 410                 415

Ser Ile Pro His Gln Ile His Leu Gly Glu Leu His Ala Ile Leu Arg
            420                 425                 430

Arg Gln Glu Asp Phe Tyr Pro Phe Leu Lys Asp Asn Arg Glu Lys Ile
        435                 440                 445

Glu Lys Ile Leu Thr Phe Arg Ile Pro Tyr Tyr Val Gly Pro Leu Ala
    450                 455                 460

Arg Gly Asn Ser Arg Phe Ala Trp Met Thr Arg Lys Ser Glu Glu Thr
465                 470                 475                 480
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Ile Thr Pro Trp Asn Phe Glu Glu Val Val Asp Lys Gly Ala Ser Ala
485 490 495

Gln Ser Phe Ile Glu Arg Met Thr Asn Phe Asp Lys Asn Leu Pro Asn
500 505 510

Glu Lys Val Leu Pro Lys His Ser Leu Leu Tyr Glu Tyr Phe Thr Val
515 520 525

Tyr Asn Glu Leu Thr Lys Val Lys Tyr Val Thr Glu Gly Met Arg Lys
530 535 540

Pro Ala Phe Leu Ser Gly Glu Gln Lys Lys Ala Ile Val Asp Leu Leu
545 550 555 560

Phe Lys Thr Asn Arg Lys Val Thr Val Lys Gln Leu Lys Glu Asp Tyr
565 570 575

Phe Lys Lys Ile Glu Cys Phe Asp Ser Val Glu Ile Ser Gly Val Glu
580 585 590

Asp Arg Phe Asn Ala Ser Leu Gly Thr Tyr His Asp Leu Leu Lys Ile
595 600 605

Ile Lys Asp Lys Asp Phe Leu Asp Asn Glu Glu Asn Glu Asp Ile Leu
610 615 620

Glu Asp Ile Val Leu Thr Leu Thr Leu Phe Glu Asp Arg Glu Met Ile
625 630 635 640

Glu Glu Arg Leu Lys Thr Tyr Ala His Leu Phe Asp Asp Lys Val Met
645 650 655

Lys Gln Leu Lys Arg Arg Arg Tyr Thr Gly Trp Gly Arg Leu Ser Arg
660 665 670

Lys Leu Ile Asn Gly Ile Arg Asp Lys Gln Ser Gly Lys Thr Ile Leu
675 680 685

Asp Phe Leu Lys Ser Asp Gly Phe Ala Asn Arg Asn Phe Met Gln Leu
690 695 700

Ile His Asp Asp Ser Leu Thr Phe Lys Glu Asp Ile Gln Lys Ala Gln

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705 710 715 720

Val Ser Gly Gln Gly Asp Ser Leu His Glu His Ile Ala Asn Leu Ala
725 730 735

Gly Ser Pro Ala Ile Lys Lys Gly Ile Leu Gln Thr Val Lys Val Val
740 745 750

Asp Glu Leu Val Lys Val Met Gly Arg His Lys Pro Glu Asn Ile Val
755 760 765

Ile Glu Met Ala Arg Glu Asn Gln Thr Thr Gln Lys Gly Gln Lys Asn
770 775 780

Ser Arg Glu Arg Met Lys Arg Ile Glu Glu Gly Ile Lys Glu Leu Gly
785 790 795 800

Ser Gln Ile Leu Lys Glu His Pro Val Glu Asn Thr Gln Leu Gln Asn
805 810 815

Glu Ala Leu Tyr Leu Tyr Tyr Leu Gln Asn Gly Arg Asp Met Tyr Val
820 825 830

Asp Gln Glu Leu Asp Ile Asn Arg Leu Ser Asp Tyr Asp Val Asp His
835 840 845

Ile Val Pro Gln Ser Phe Leu Lys Asp Asp Ser Ile Asp Asn Lys Val
850 855 860

Leu Thr Arg Ser Asp Lys Asn Arg Gly Lys Ser Asp Asn Val Pro Ser
865 870 875 880

Glu Glu Val Val Lys Lys Met Lys Asn Tyr Trp Arg Gln Leu Leu Asn
885 890 895

Ala Lys Leu Ile Thr Gln Arg Lys Phe Asp Asn Leu Thr Lys Ala Glu
900 905 910

Arg Gly Gly Leu Ser Glu Leu Asp Lys Ala Gly Phe Ile Lys Arg Gln
915 920 925

Leu Val Glu Thr Arg Gln Ile Thr Lys His Val Ala Gln Ile Leu Asp
930 935 940

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Ser Arg Met Asn Thr Lys Tyr Asp Glu Asn Asp Lys Leu Ile Arg Glu
945                 950                 955                 960

Val Lys Val Ile Thr Leu Lys Ser Lys Leu Val Ser Asp Phe Arg Lys
                965                 970                 975

Asp Phe Gln Phe Tyr Lys Val Arg Glu Ile Asn Asn Tyr His His Ala
            980                 985                 990

His Asp Ala Tyr Leu Asn Ala Val  Val Gly Thr Ala Leu  Ile Lys Lys
        995                 1000                1005

Tyr Pro  Ala Leu Glu Ser Glu  Phe Val Tyr Gly Asp  Tyr Lys Val
    1010                1015                1020

Tyr Asp  Val Arg Lys Met Ile  Ala Lys Ser Glu Gln  Glu Ile Gly
    1025                1030                1035

Lys Ala  Thr Ala Lys Tyr Phe  Phe Tyr Ser Asn Ile  Met Asn Phe
    1040                1045                1050

Phe Lys  Thr Glu Ile Thr Leu  Ala Asn Gly Glu Ile  Arg Lys Ala
    1055                1060                1065

Pro Leu  Ile Glu Thr Asn Gly  Glu Thr Gly Glu Ile  Val Trp Asp
    1070                1075                1080

Lys Gly  Arg Asp Phe Ala Thr  Val Arg Lys Val Leu  Ser Met Pro
    1085                1090                1095

Gln Val  Asn Ile Val Lys Lys  Thr Glu Val Gln Thr  Gly Gly Phe
    1100                1105                1110

Ser Lys  Glu Ser Ile Leu Pro  Lys Arg Asn Ser Asp  Lys Leu Ile
    1115                1120                1125

Ala Arg  Lys Lys Asp Trp Asp  Pro Lys Lys Tyr Gly  Gly Phe Asp
    1130                1135                1140

Ser Pro  Thr Val Ala Tyr Ser  Val Leu Val Val Ala  Lys Val Glu
    1145                1150                1155
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Lys Gly Lys Ser Lys Lys Leu Lys Ser Val Lys Glu Leu Leu Gly
1160 1165 1170

Ile Thr Ile Met Glu Arg Ser Ser Phe Glu Lys Asn Pro Ile Asp
1175 1180 1185

Phe Leu Glu Ala Lys Gly Tyr Lys Glu Val Lys Lys Asp Leu Ile
1190 1195 1200

Ile Lys Leu Pro Lys Tyr Ser Leu Phe Glu Leu Glu Asn Gly Arg
1205 1210 1215

Lys Arg Met Leu Ala Ser Ala Gly Glu Leu Gln Lys Gly Asn Glu
1220 1225 1230

Leu Ala Leu Pro Ser Lys Tyr Val Asn Phe Leu Tyr Leu Ala Ser
1235 1240 1245

His Tyr Glu Lys Leu Lys Gly Ser Pro Glu Asp Asn Glu Gln Lys
1250 1255 1260

Gln Leu Phe Val Glu Gln His Lys His Tyr Leu Asp Glu Ile Ile
1265 1270 1275

Glu Gln Ile Ser Glu Phe Ser Lys Arg Val Ile Leu Ala Asp Ala
1280 1285 1290

Asn Leu Asp Lys Val Leu Ser Ala Tyr Asn Lys His Arg Asp Lys
1295 1300 1305

Pro Ile Arg Glu Gln Ala Glu Asn Ile Ile His Leu Phe Thr Leu
1310 1315 1320

Thr Asn Leu Gly Ala Pro Ala Ala Phe Lys Tyr Phe Asp Thr Thr
1325 1330 1335

Ile Asp Arg Lys Arg Tyr Thr Ser Thr Lys Glu Val Leu Asp Ala
1340 1345 1350

Thr Leu Ile His Gln Ser Ile Thr Gly Leu Tyr Glu Thr Arg Ile
1355 1360 1365

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Asp Leu Ser Gln Leu Gly Gly Asp Ser Arg Ala Asp Pro Lys Lys
1370 1375 1380

Lys Arg Lys Val His His His His His His
1385 1390

<210> 7830
<211> 1393
<212> PRT
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic polypeptide"

<400> 7830
Met Ala Pro Lys Lys Lys Arg Lys Val Asp Lys Lys Tyr Ser Ile Gly
1 5 10 15

Leu Asp Ile Gly Thr Asn Ser Val Gly Trp Ala Val Ile Thr Asp Glu
20 25 30

Tyr Lys Val Pro Ser Lys Lys Phe Lys Val Leu Gly Asn Thr Asp Arg
35 40 45

His Ser Ile Lys Lys Asn Leu Ile Gly Ala Leu Leu Phe Asp Ser Gly
50 55 60

Glu Thr Ala Glu Ala Thr Arg Leu Lys Arg Thr Ala Arg Arg Arg Tyr
65 70 75 80

Thr Arg Arg Lys Asn Arg Ile Cys Tyr Leu Gln Glu Ile Phe Ser Asn
85 90 95

Glu Met Ala Lys Val Asp Asp Ser Phe Phe His Arg Leu Glu Glu Ser
100 105 110

Phe Leu Val Glu Glu Asp Lys Lys His Glu Arg His Pro Ile Phe Gly
115 120 125

Asn Ile Val Asp Glu Val Ala Tyr His Glu Lys Tyr Pro Thr Ile Tyr
130 135 140

His Leu Arg Lys Lys Leu Val Asp Ser Thr Asp Lys Ala Asp Leu Arg
145 150 155 160

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Leu Ile Tyr Leu Ala Leu Ala His Met Ile Lys Phe Arg Gly His Phe
165 170 175

Leu Ile Glu Gly Asp Leu Asn Pro Asp Asn Ser Asp Val Asp Lys Leu
180 185 190

Phe Ile Gln Leu Val Gln Thr Tyr Asn Gln Leu Phe Glu Glu Asn Pro
195 200 205

Ile Asn Ala Ser Gly Val Asp Ala Lys Ala Ile Leu Ser Ala Arg Leu
210 215 220

Ser Lys Ser Arg Arg Leu Glu Asn Leu Ile Ala Gln Leu Pro Gly Glu
225 230 235 240

Lys Lys Asn Gly Leu Phe Gly Asn Leu Ile Ala Leu Ser Leu Gly Leu
245 250 255

Thr Pro Asn Phe Lys Ser Asn Phe Asp Leu Ala Glu Asp Ala Lys Leu
260 265 270

Gln Leu Ser Lys Asp Thr Tyr Asp Asp Asp Leu Asp Asn Leu Leu Ala
275 280 285

Gln Ile Gly Asp Gln Tyr Ala Asp Leu Phe Leu Ala Ala Lys Asn Leu
290 295 300

Ser Asp Ala Ile Leu Leu Ser Asp Ile Leu Arg Val Asn Thr Glu Ile
305 310 315 320

Thr Lys Ala Pro Leu Ser Ala Ser Met Ile Lys Arg Tyr Asp Glu His
325 330 335

His Gln Asp Leu Thr Leu Leu Lys Ala Leu Val Arg Gln Gln Leu Pro
340 345 350

Glu Lys Tyr Lys Glu Ile Phe Phe Asp Gln Ser Lys Asn Gly Tyr Ala
355 360 365

Gly Tyr Ile Asp Gly Gly Ala Ser Gln Glu Glu Phe Tyr Lys Phe Ile
370 375 380

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```
Lys Pro Ile Leu Glu Lys Met Asp Gly Thr Glu Glu Leu Leu Val Lys
385                 390                 395                 400

Leu Asn Arg Glu Asp Leu Leu Arg Lys Gln Arg Thr Phe Asp Asn Gly
                405                 410                 415

Ser Ile Pro His Gln Ile His Leu Gly Glu Leu His Ala Ile Leu Arg
            420                 425                 430

Arg Gln Glu Asp Phe Tyr Pro Phe Leu Lys Asp Asn Arg Glu Lys Ile
        435                 440                 445

Glu Lys Ile Leu Thr Phe Arg Ile Pro Tyr Tyr Val Gly Pro Leu Ala
    450                 455                 460

Arg Gly Asn Ser Arg Phe Ala Trp Met Thr Arg Lys Ser Glu Glu Thr
465                 470                 475                 480

Ile Thr Pro Trp Asn Phe Glu Glu Val Val Asp Lys Gly Ala Ser Ala
                485                 490                 495

Gln Ser Phe Ile Glu Arg Met Thr Asn Phe Asp Lys Asn Leu Pro Asn
            500                 505                 510

Glu Lys Val Leu Pro Lys His Ser Leu Leu Tyr Glu Tyr Phe Thr Val
        515                 520                 525

Tyr Asn Glu Leu Thr Lys Val Lys Tyr Val Thr Glu Gly Met Arg Lys
    530                 535                 540

Pro Ala Phe Leu Ser Gly Glu Gln Lys Lys Ala Ile Val Asp Leu Leu
545                 550                 555                 560

Phe Lys Thr Asn Arg Lys Val Thr Val Lys Gln Leu Lys Glu Asp Tyr
                565                 570                 575

Phe Lys Lys Ile Glu Cys Phe Asp Ser Val Glu Ile Ser Gly Val Glu
            580                 585                 590

Asp Arg Phe Asn Ala Ser Leu Gly Thr Tyr His Asp Leu Leu Lys Ile
        595                 600                 605
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Ile Lys Asp Lys Asp Phe Leu Asp Asn Glu Glu Asn Glu Asp Ile Leu
610 615 620

Glu Asp Ile Val Leu Thr Leu Thr Leu Phe Glu Asp Arg Glu Met Ile
625 630 635 640

Glu Glu Arg Leu Lys Thr Tyr Ala His Leu Phe Asp Asp Lys Val Met
645 650 655

Lys Gln Leu Lys Arg Arg Arg Tyr Thr Gly Trp Gly Arg Leu Ser Arg
660 665 670

Lys Leu Ile Asn Gly Ile Arg Asp Lys Gln Ser Gly Lys Thr Ile Leu
675 680 685

Asp Phe Leu Lys Ser Asp Gly Phe Ala Asn Arg Asn Phe Met Gln Leu
690 695 700

Ile His Asp Asp Ser Leu Thr Phe Lys Glu Asp Ile Gln Lys Ala Gln
705 710 715 720

Val Ser Gly Gln Gly Asp Ser Leu His Glu His Ile Ala Asn Leu Ala
725 730 735

Gly Ser Pro Ala Ile Lys Lys Gly Ile Leu Gln Thr Val Lys Val Val
740 745 750

Asp Glu Leu Val Lys Val Met Gly Arg His Lys Pro Glu Asn Ile Val
755 760 765

Ile Glu Met Ala Arg Glu Asn Gln Thr Thr Gln Lys Gly Gln Lys Asn
770 775 780

Ser Arg Glu Arg Met Lys Arg Ile Glu Glu Gly Ile Lys Glu Leu Gly
785 790 795 800

Ser Gln Ile Leu Lys Glu His Pro Val Glu Asn Thr Gln Leu Gln Asn
805 810 815

Glu Lys Leu Tyr Leu Tyr Tyr Leu Gln Asn Gly Arg Asp Met Tyr Val
820 825 830

Asp Gln Glu Leu Asp Ile Asn Arg Leu Ser Asp Tyr Asp Val Asp His

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835 840 845

Ile Val Pro Gln Ser Phe Leu Ala Asp Asp Ser Ile Asp Asn Lys Val
850 855 860

Leu Thr Arg Ser Asp Lys Asn Arg Gly Lys Ser Asp Asn Val Pro Ser
865 870 875 880

Glu Glu Val Val Lys Lys Met Lys Asn Tyr Trp Arg Gln Leu Leu Asn
885 890 895

Ala Lys Leu Ile Thr Gln Arg Lys Phe Asp Asn Leu Thr Lys Ala Glu
900 905 910

Arg Gly Gly Leu Ser Glu Leu Asp Lys Ala Gly Phe Ile Lys Arg Gln
915 920 925

Leu Val Glu Thr Arg Gln Ile Thr Lys His Val Ala Gln Ile Leu Asp
930 935 940

Ser Arg Met Asn Thr Lys Tyr Asp Glu Asn Asp Lys Leu Ile Arg Glu
945 950 955 960

Val Lys Val Ile Thr Leu Lys Ser Lys Leu Val Ser Asp Phe Arg Lys
965 970 975

Asp Phe Gln Phe Tyr Lys Val Arg Glu Ile Asn Asn Tyr His His Ala
980 985 990

His Asp Ala Tyr Leu Asn Ala Val Val Gly Thr Ala Leu Ile Lys Lys
995 1000 1005

Tyr Pro Ala Leu Glu Ser Glu Phe Val Tyr Gly Asp Tyr Lys Val
1010 1015 1020

Tyr Asp Val Arg Lys Met Ile Ala Lys Ser Glu Gln Glu Ile Gly
1025 1030 1035

Lys Ala Thr Ala Lys Tyr Phe Phe Tyr Ser Asn Ile Met Asn Phe
1040 1045 1050

Phe Lys Thr Glu Ile Thr Leu Ala Asn Gly Glu Ile Arg Lys Ala
1055 1060 1065

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Pro Leu  Ile Glu Thr Asn Gly  Glu Thr Gly Glu Ile  Val Trp Asp
    1070                 1075                 1080

Lys Gly  Arg Asp Phe Ala Thr  Val Arg Lys Val Leu  Ser Met Pro
    1085                 1090                 1095

Gln Val  Asn Ile Val Lys Lys  Thr Glu Val Gln Thr  Gly Gly Phe
    1100                 1105                 1110

Ser Lys  Glu Ser Ile Leu Pro  Lys Arg Asn Ser Asp  Lys Leu Ile
    1115                 1120                 1125

Ala Arg  Lys Lys Asp Trp Asp  Pro Lys Lys Tyr Gly  Gly Phe Asp
    1130                 1135                 1140

Ser Pro  Thr Val Ala Tyr Ser  Val Leu Val Val Ala  Lys Val Glu
    1145                 1150                 1155

Lys Gly  Lys Ser Lys Lys Leu  Lys Ser Val Lys Glu  Leu Leu Gly
    1160                 1165                 1170

Ile Thr  Ile Met Glu Arg Ser  Ser Phe Glu Lys Asn  Pro Ile Asp
    1175                 1180                 1185

Phe Leu  Glu Ala Lys Gly Tyr  Lys Glu Val Lys Lys  Asp Leu Ile
    1190                 1195                 1200

Ile Lys  Leu Pro Lys Tyr Ser  Leu Phe Glu Leu Glu  Asn Gly Arg
    1205                 1210                 1215

Lys Arg  Met Leu Ala Ser Ala  Gly Glu Leu Gln Lys  Gly Asn Glu
    1220                 1225                 1230

Leu Ala  Leu Pro Ser Lys Tyr  Val Asn Phe Leu Tyr  Leu Ala Ser
    1235                 1240                 1245

His Tyr  Glu Lys Leu Lys Gly  Ser Pro Glu Asp Asn  Glu Gln Lys
    1250                 1255                 1260

Gln Leu  Phe Val Glu Gln His  Lys His Tyr Leu Asp  Glu Ile Ile
    1265                 1270                 1275
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Glu Gln Ile Ser Glu Phe Ser Lys Arg Val Ile Leu Ala Asp Ala
1280 1285 1290

Asn Leu Asp Lys Val Leu Ser Ala Tyr Asn Lys His Arg Asp Lys
1295 1300 1305

Pro Ile Arg Glu Gln Ala Glu Asn Ile Ile His Leu Phe Thr Leu
1310 1315 1320

Thr Asn Leu Gly Ala Pro Ala Ala Phe Lys Tyr Phe Asp Thr Thr
1325 1330 1335

Ile Asp Arg Lys Arg Tyr Thr Ser Thr Lys Glu Val Leu Asp Ala
1340 1345 1350

Thr Leu Ile His Gln Ser Ile Thr Gly Leu Tyr Glu Thr Arg Ile
1355 1360 1365

Asp Leu Ser Gln Leu Gly Gly Asp Ser Arg Ala Asp Pro Lys Lys
1370 1375 1380

Lys Arg Lys Val His His His His His His
1385 1390

<210> 7831
<211> 1393
<212> PRT
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic polypeptide"

<400> 7831
Met Ala Pro Lys Lys Lys Arg Lys Val Asp Lys Lys Tyr Ser Ile Gly
1 5 10 15

Leu Asp Ile Gly Thr Asn Ser Val Gly Trp Ala Val Ile Thr Asp Glu
20 25 30

Tyr Lys Val Pro Ser Lys Lys Phe Lys Val Leu Gly Asn Thr Asp Arg
35 40 45

His Ser Ile Lys Lys Asn Leu Ile Gly Ala Leu Leu Phe Asp Ser Gly

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    50                  55                  60

Glu Thr Ala Glu Ala Thr Arg Leu Lys Arg Thr Ala Arg Arg Arg Tyr
65                  70                  75                  80

Thr Arg Arg Lys Asn Arg Ile Cys Tyr Leu Gln Glu Ile Phe Ser Asn
                85                  90                  95

Glu Met Ala Lys Val Asp Asp Ser Phe Phe His Arg Leu Glu Glu Ser
            100                 105                 110

Phe Leu Val Glu Glu Asp Lys Lys His Glu Arg His Pro Ile Phe Gly
        115                 120                 125

Asn Ile Val Asp Glu Val Ala Tyr His Glu Lys Tyr Pro Thr Ile Tyr
    130                 135                 140

His Leu Arg Lys Lys Leu Val Asp Ser Thr Asp Lys Ala Asp Leu Arg
145                 150                 155                 160

Leu Ile Tyr Leu Ala Leu Ala His Met Ile Lys Phe Arg Gly His Phe
                165                 170                 175

Leu Ile Glu Gly Asp Leu Asn Pro Asp Asn Ser Asp Val Asp Lys Leu
            180                 185                 190

Phe Ile Gln Leu Val Gln Thr Tyr Asn Gln Leu Phe Glu Glu Asn Pro
        195                 200                 205

Ile Asn Ala Ser Gly Val Asp Ala Lys Ala Ile Leu Ser Ala Arg Leu
    210                 215                 220

Ser Lys Ser Arg Arg Leu Glu Asn Leu Ile Ala Gln Leu Pro Gly Glu
225                 230                 235                 240

Lys Lys Asn Gly Leu Phe Gly Asn Leu Ile Ala Leu Ser Leu Gly Leu
                245                 250                 255

Thr Pro Asn Phe Lys Ser Asn Phe Asp Leu Ala Glu Asp Ala Lys Leu
            260                 265                 270

Gln Leu Ser Lys Asp Thr Tyr Asp Asp Asp Leu Asp Asn Leu Leu Ala
        275                 280                 285
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Gln Ile Gly Asp Gln Tyr Ala Asp Leu Phe Leu Ala Ala Lys Asn Leu
    290                 295                 300

Ser Asp Ala Ile Leu Leu Ser Asp Ile Leu Arg Val Asn Thr Glu Ile
305                 310                 315                 320

Thr Lys Ala Pro Leu Ser Ala Ser Met Ile Lys Arg Tyr Asp Glu His
                325                 330                 335

His Gln Asp Leu Thr Leu Leu Lys Ala Leu Val Arg Gln Gln Leu Pro
            340                 345                 350

Glu Lys Tyr Lys Glu Ile Phe Phe Asp Gln Ser Lys Asn Gly Tyr Ala
        355                 360                 365

Gly Tyr Ile Asp Gly Gly Ala Ser Gln Glu Glu Phe Tyr Lys Phe Ile
    370                 375                 380

Lys Pro Ile Leu Glu Lys Met Asp Gly Thr Glu Glu Leu Leu Val Lys
385                 390                 395                 400

Leu Asn Arg Glu Asp Leu Leu Arg Lys Gln Arg Thr Phe Asp Asn Gly
                405                 410                 415

Ser Ile Pro His Gln Ile His Leu Gly Glu Leu His Ala Ile Leu Arg
            420                 425                 430

Arg Gln Glu Asp Phe Tyr Pro Phe Leu Lys Asp Asn Arg Glu Lys Ile
        435                 440                 445

Glu Lys Ile Leu Thr Phe Arg Ile Pro Tyr Tyr Val Gly Pro Leu Ala
    450                 455                 460

Arg Gly Asn Ser Arg Phe Ala Trp Met Thr Arg Lys Ser Glu Glu Thr
465                 470                 475                 480

Ile Thr Pro Trp Asn Phe Glu Glu Val Val Asp Lys Gly Ala Ser Ala
                485                 490                 495

Gln Ser Phe Ile Glu Arg Met Thr Ala Phe Asp Lys Asn Leu Pro Asn
            500                 505                 510
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Glu Lys Val Leu Pro Lys His Ser Leu Leu Tyr Glu Tyr Phe Thr Val
515 520 525

Tyr Asn Glu Leu Thr Lys Val Lys Tyr Val Thr Glu Gly Met Arg Lys
530 535 540

Pro Ala Phe Leu Ser Gly Glu Gln Lys Lys Ala Ile Val Asp Leu Leu
545 550 555 560

Phe Lys Thr Asn Arg Lys Val Thr Val Lys Gln Leu Lys Glu Asp Tyr
565 570 575

Phe Lys Lys Ile Glu Cys Phe Asp Ser Val Glu Ile Ser Gly Val Glu
580 585 590

Asp Arg Phe Asn Ala Ser Leu Gly Thr Tyr His Asp Leu Leu Lys Ile
595 600 605

Ile Lys Asp Lys Asp Phe Leu Asp Asn Glu Glu Asn Glu Asp Ile Leu
610 615 620

Glu Asp Ile Val Leu Thr Leu Thr Leu Phe Glu Asp Arg Glu Met Ile
625 630 635 640

Glu Glu Arg Leu Lys Thr Tyr Ala His Leu Phe Asp Asp Lys Val Met
645 650 655

Lys Gln Leu Lys Arg Arg Arg Tyr Thr Gly Trp Gly Ala Leu Ser Arg
660 665 670

Lys Leu Ile Asn Gly Ile Arg Asp Lys Gln Ser Gly Lys Thr Ile Leu
675 680 685

Asp Phe Leu Lys Ser Asp Gly Phe Ala Asn Arg Asn Phe Met Ala Leu
690 695 700

Ile His Asp Asp Ser Leu Thr Phe Lys Glu Asp Ile Gln Lys Ala Gln
705 710 715 720

Val Ser Gly Gln Gly Asp Ser Leu His Glu His Ile Ala Asn Leu Ala
725 730 735

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Gly Ser Pro Ala Ile Lys Lys Gly Ile Leu Gln Thr Val Lys Val Val
740 745 750

Asp Glu Leu Val Lys Val Met Gly Arg His Lys Pro Glu Asn Ile Val
755 760 765

Ile Glu Met Ala Arg Glu Asn Gln Thr Thr Gln Lys Gly Gln Lys Asn
770 775 780

Ser Arg Glu Arg Met Lys Arg Ile Glu Glu Gly Ile Lys Glu Leu Gly
785 790 795 800

Ser Gln Ile Leu Lys Glu His Pro Val Glu Asn Thr Gln Leu Gln Asn
805 810 815

Glu Lys Leu Tyr Leu Tyr Tyr Leu Gln Asn Gly Arg Asp Met Tyr Val
820 825 830

Asp Gln Glu Leu Asp Ile Asn Arg Leu Ser Asp Tyr Asp Val Asp His
835 840 845

Ile Val Pro Gln Ser Phe Leu Lys Asp Asp Ser Ile Asp Asn Lys Val
850 855 860

Leu Thr Arg Ser Asp Lys Asn Arg Gly Lys Ser Asp Asn Val Pro Ser
865 870 875 880

Glu Glu Val Val Lys Lys Met Lys Asn Tyr Trp Arg Gln Leu Leu Asn
885 890 895

Ala Lys Leu Ile Thr Gln Arg Lys Phe Asp Asn Leu Thr Lys Ala Glu
900 905 910

Arg Gly Gly Leu Ser Glu Leu Asp Lys Ala Gly Phe Ile Lys Arg Gln
915 920 925

Leu Val Glu Thr Arg Ala Ile Thr Lys His Val Ala Gln Ile Leu Asp
930 935 940

Ser Arg Met Asn Thr Lys Tyr Asp Glu Asn Asp Lys Leu Ile Arg Glu
945 950 955 960

Val Lys Val Ile Thr Leu Lys Ser Lys Leu Val Ser Asp Phe Arg Lys

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965 970 975

Asp Phe Gln Phe Tyr Lys Val Arg Glu Ile Asn Asn Tyr His His Ala
980 985 990

His Asp Ala Tyr Leu Asn Ala Val Val Gly Thr Ala Leu Ile Lys Lys
995 1000 1005

Tyr Pro Lys Leu Glu Ser Glu Phe Val Tyr Gly Asp Tyr Lys Val
1010 1015 1020

Tyr Asp Val Arg Lys Met Ile Ala Lys Ser Glu Gln Glu Ile Gly
1025 1030 1035

Lys Ala Thr Ala Lys Tyr Phe Phe Tyr Ser Asn Ile Met Asn Phe
1040 1045 1050

Phe Lys Thr Glu Ile Thr Leu Ala Asn Gly Glu Ile Arg Lys Arg
1055 1060 1065

Pro Leu Ile Glu Thr Asn Gly Glu Thr Gly Glu Ile Val Trp Asp
1070 1075 1080

Lys Gly Arg Asp Phe Ala Thr Val Arg Lys Val Leu Ser Met Pro
1085 1090 1095

Gln Val Asn Ile Val Lys Lys Thr Glu Val Gln Thr Gly Gly Phe
1100 1105 1110

Ser Lys Glu Ser Ile Leu Pro Lys Arg Asn Ser Asp Lys Leu Ile
1115 1120 1125

Ala Arg Lys Lys Asp Trp Asp Pro Lys Lys Tyr Gly Gly Phe Asp
1130 1135 1140

Ser Pro Thr Val Ala Tyr Ser Val Leu Val Val Ala Lys Val Glu
1145 1150 1155

Lys Gly Lys Ser Lys Lys Leu Lys Ser Val Lys Glu Leu Leu Gly
1160 1165 1170

Ile Thr Ile Met Glu Arg Ser Ser Phe Glu Lys Asn Pro Ile Asp
1175 1180 1185

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Phe Leu Glu Ala Lys Gly Tyr Lys Glu Val Lys Lys Asp Leu Ile
1190 1195 1200

Ile Lys Leu Pro Lys Tyr Ser Leu Phe Glu Leu Glu Asn Gly Arg
1205 1210 1215

Lys Arg Met Leu Ala Ser Ala Gly Glu Leu Gln Lys Gly Asn Glu
1220 1225 1230

Leu Ala Leu Pro Ser Lys Tyr Val Asn Phe Leu Tyr Leu Ala Ser
1235 1240 1245

His Tyr Glu Lys Leu Lys Gly Ser Pro Glu Asp Asn Glu Gln Lys
1250 1255 1260

Gln Leu Phe Val Glu Gln His Lys His Tyr Leu Asp Glu Ile Ile
1265 1270 1275

Glu Gln Ile Ser Glu Phe Ser Lys Arg Val Ile Leu Ala Asp Ala
1280 1285 1290

Asn Leu Asp Lys Val Leu Ser Ala Tyr Asn Lys His Arg Asp Lys
1295 1300 1305

Pro Ile Arg Glu Gln Ala Glu Asn Ile Ile His Leu Phe Thr Leu
1310 1315 1320

Thr Asn Leu Gly Ala Pro Ala Ala Phe Lys Tyr Phe Asp Thr Thr
1325 1330 1335

Ile Asp Arg Lys Arg Tyr Thr Ser Thr Lys Glu Val Leu Asp Ala
1340 1345 1350

Thr Leu Ile His Gln Ser Ile Thr Gly Leu Tyr Glu Thr Arg Ile
1355 1360 1365

Asp Leu Ser Gln Leu Gly Gly Asp Ser Arg Ala Asp Pro Lys Lys
1370 1375 1380

Lys Arg Lys Val His His His His His His
1385 1390