

CLAIMS

What is claimed is:

1. A genetically modified cell comprising a genomic modification within exon 2
5 or exon 3 of an endogenous *CISH* gene, wherein the *CISH* gene is modified following cleavage by a zinc finger nuclease, wherein the zinc finger nuclease comprises a zinc finger protein comprising 6 zinc finger domains each comprising a recognition helix region, wherein the zinc finger protein comprises the recognition helix regions of the proteins designated SBS#59488, SBS #59489, SBS#59440, SBS #59441,
10 SBS#59558, SBS#59557, SBS#59581 or SBS#59580 ordered as shown in a single row of the table below:

SBS #	Design					
	F1	F2	F3	F4	F5	F6
59488	RSDHLSQ (SEQ ID NO:2)	QNATRTK (SEQ ID NO:3)	RSDNLSE (SEQ ID NO:4)	KRCNLRC (SEQ ID NO:5)	DRSTRTK (SEQ ID NO:6)	RRDNLHS (SEQ ID NO:7)
59489	GHTSLKR (SEQ ID NO:8)	TSGHLSR (SEQ ID NO:9)	RSDNLAR (SEQ ID NO:10)	QNVSRPR (SEQ ID NO:11)	TSGHLSR (SEQ ID NO:9)	QSGHLSR (SEQ ID NO:12)
59440	RWQYLPT (SEQ ID NO:13)	DRSALAR (SEQ ID NO:14)	RSDNLAR (SEQ ID NO:10)	DRSNLTR (SEQ ID NO:15)	QSGNLAR (SEQ ID NO:16)	ATCCLAH (SEQ ID NO:17)
59441	RSDDLTR (SEQ ID NO:18)	QAATLSR (SEQ ID NO:19)	RSDHLSA (SEQ ID NO:20)	DRSDLSR (SEQ ID NO:21)	RSDDLTR (SEQ ID NO:18)	DRSHLAR (SEQ ID NO:22)
59558	QSGDLTR (SEQ ID NO:23)	QSGNLHV (SEQ ID NO:24)	QSGHLAR (SEQ ID NO:25)	NRYDLMT (SEQ ID NO:26)	RSDSLLR (SEQ ID NO:27)	CREYRGK (SEQ ID NO:28)
59557	QSSHLTR (SEQ ID NO:29)	QSSDLTR (SEQ ID NO:30)	QSGNLAR (SEQ ID NO:16)	RLDILQQ (SEQ ID NO:31)	RSDNLST (SEQ ID NO:32)	DNSYLPR (SEQ ID NO:33)
59581	DRSNLSR (SEQ ID NO:34)	LRQDLKR (SEQ ID NO:35)	RSDNLST (SEQ ID NO:32)	DNSNRIN (SEQ ID NO:36)	QSSDLR (SEQ ID NO:37)	WKWNLRA (SEQ ID NO:38)
59580	RSDSLLR (SEQ ID NO:27)	CREYRGK (SEQ ID NO:28)	QSGHLAR (SEQ ID NO:25)	QKGTIGE (SEQ ID NO:39)	RSDNLST (SEQ ID NO:32)	QSGHLSR (SEQ ID NO:12)

2. The genetically modified cell of claim 1, wherein:
15 (i) the genomic modification is selected from the group consisting of insertions and/or deletions; and/or.

(ii) one or more transgenes is/are integrated into the *CISH* gene.

3. The genetically modified cell of claim 2, wherein the transgene encodes a chimeric antigen receptor (CAR), an immunomodulating factor, an engineered or exogenous T cell receptor (TCR).
- 5 4. The genetically modified cell of claim 3, wherein the engineered TCR is an antibody-coupled T-cell receptors (ACTR).
5. The genetically modified cell of claim 1 or 2 or a cell descended therefrom, wherein the cell is selected from the group consisting of a hematopoietic stem cell, a T effector cell and a T regulatory cell.
- 10 6. A zinc finger protein comprising 6 zinc finger domains each comprising a recognition helix region, wherein the zinc finger protein comprises the recognition helix regions of the proteins designated SBS#59488, SBS#59489, SBS#59440, SBS#59441, SBS#59558, SBS#59557, SBS#59581 or SBS#59580 ordered as shown in a single row of the table below:

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7. A fusion protein comprising the zinc finger protein of claim 6 and a wild-type or engineered cleavage domain or wild-type or engineered cleavage half-domain.

8. A polynucleotide encoding one or more proteins of claim 6 or claim 7.

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9. An isolated cell comprising one or more proteins of claim 6 or claim 7 and/or one or more polynucleotides of claim 8.

10. The isolated cell of claim 9 or a cell descended therefrom, wherein the cell is selected from the group consisting of a T effector cell, a T regulatory cell and a hematopoietic stem cell.

11. A kit comprising one or more proteins of claim 6 or claim 7, one or more polynucleotides of claim 8 and/or one or more isolated cells of claim 9 or claim 10.

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12. A method of generating a genetically modified cell according to any one of claims 1 to 3, the method comprising introducing, into the cell, one or more polynucleotides encoding one or more nucleases comprising a DNA-binding domain that binds to target site in exon 2 or exon 3 of the *CISH* gene, wherein the one or more nucleases bind to and cleave the *CISH* gene, thereby genetically modifying the cell, wherein at least one of the one or more nucleases is a zinc finger protein comprising 6 zinc finger domains each comprising a recognition helix region, wherein the zinc finger protein comprises the recognition helix regions of the proteins designated SBS#59488, SBS#59489, SBS#59440, SBS#59441, SBS#59558, SBS#59557, SBS#59581 or SBS#59580 ordered as shown in a single row of the table below:

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13. The method of claim 12, wherein the genetically modified cell comprises a transgene that is integrated into the *CISH* gene and expressed in the cell.

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14. A population of genetically modified cells according to any of claims 1 to 5 or cell descended therefrom.