

CLAIMS

WHAT IS CLAIMED IS:

1. An epigenetic editor comprising a fusion protein, wherein the fusion protein comprises:

- (a) a first DNMT domain;
- (b) a DNA binding domain; and
- (c) a repressor domain,

wherein the repressor domain is selected from the group consisting of: ZIM3, ZNF436, ZNF257, ZNF675, ZNF490, ZNF320, ZNF331, ZNF816, ZNF680, ZNF41, ZNF189, ZNF528, ZNF543, ZNF554, ZNF140, ZNF610, ZNF264, ZNF350, ZNF8, ZNF582, ZNF30, ZNF324, ZNF98, ZNF669, ZNF677, ZNF596, ZNF214, ZNF37A, ZNF34, ZNF250, ZNF547, ZNF273, ZNF354A, ZFP82, ZNF224, ZNF33A, ZNF45, ZNF175, ZNF595, ZNF184, ZNF419, ZFP28-1, ZFP28-2, ZNF18, ZNF213, ZNF394, ZFP1, ZFP14, ZNF416, ZNF557, ZNF566, ZNF729, ZIM2, ZNF254, ZNF764, ZNF785, ZNF10, CBX5, RYBP, YAF2, MGA, CBX1, SCM1, MPP8, SUMO3, HERC2, BIN1, PCGF2, TOX, FOXA1, FOXA2, IRF2BP1, IRF2BP2, IRF2BPL IRF-2BP1_2 N-terminal domain, HOXA13, HOXB13, HOXC13, HOXA11, HOXC11, HOXC10, HOXA10, HOXB9, HOXA9, ZFP28, ZN334, ZN568, ZN37A, ZN181, ZN510, ZN862, ZN140, ZN208, ZN248, ZN571, ZN699, ZN726, ZIK1, ZNF2, Z705F, ZNF14, ZN471, ZN624, ZNF84, ZNF7, ZN891, ZN337, Z705G, ZN529, ZN729, ZN419, Z705A, ZNF45, ZN302, ZN486, ZN621, ZN688, ZN33A, ZN554, ZN878, ZN772, ZN224, ZN184, ZN544, ZNF57, ZN283, ZN549, ZN211, ZN615, ZN253, ZN226, ZN730, Z585A, ZN732, ZN681, ZN667, ZN649, ZN470, ZN484, ZN431, ZN382, ZN254, ZN124, ZN607, ZN317, ZN620, ZN141, ZN584, ZN540, ZN75D, ZN555, ZN658, ZN684, RBAK, ZN829, ZN582, ZN112, ZN716, HKR1, ZN350, ZN480, ZN416, ZNF92, ZN100, ZN736, ZNF74, CBX1, ZN443, ZN195, ZN530, ZN782, ZN791, ZN331, Z354C, ZN157, ZN727, ZN550, ZN793, ZN235, ZNF8, ZN724, ZN573, ZN577, ZN789, ZN718, ZN300, ZN383, ZN429, ZN677, ZN850, ZN454, ZN257, ZN264, ZFP82, ZFP14, ZN485, ZN737, ZNF44, ZN596, ZN565, ZN543, ZFP69, SUMO1, ZNF12, ZN169, ZN433, SUMO3, ZNF98, ZN175, ZN347, ZNF25, ZN519, Z585B, ZIM3, ZN517, ZN846, ZN230, ZNF66, ZFP1, ZN713, ZN816, ZN426, ZN674, ZN627, ZNF20, Z587B, ZN316, ZN233, ZN611, ZN556, ZN234, ZN560, ZNF77, ZN682, ZN614, ZN785, ZN445, ZFP30, ZN225, ZN551, ZN610, ZN528, ZN284, ZN418, MPP8, ZN490, ZN805, Z780B, ZN763, ZN285, ZNF85, ZN223, ZNF90, ZN557, ZN425, ZN229, ZN606, ZN155, ZN222, ZN442, ZNF91, ZN135, ZN778, RYBP, ZN534, ZN586, ZN567, ZN440, ZN583, ZN441, ZNF43, CBX5, ZN589, ZNF10, ZN563, ZN561, ZN136, ZN630, ZN527, ZN333, Z324B, ZN786, ZN709, ZN792, ZN599, ZN613, ZF69B, ZN799, ZN569,

ZN564, ZN546, ZFP92, YAF2, ZN723, ZNF34, ZN439, ZFP57, ZNF19, ZN404, ZN274, CBX3, ZNF30, ZN250, ZN570, ZN675, ZN695, ZN548, ZN132, ZN738, ZN420, ZN626, ZN559, ZN460, ZN268, ZN304, ZIM2, ZN605, ZN844, SUMO5, ZN101, ZN783, ZN417, ZN182, ZN823, ZN177, ZN197, ZN717, ZN669, ZN256, ZN251, CBX4, PCGF2, CDY2, CDYL2, HERC2, ZN562, ZN461, Z324A, ZN766, ID2, TOX, ZN274, SCMH1, ZN214, CBX7, ID1, CREM, SCX, ASCL1, ZN764, SCML2, TWST1, CREB1, TERF1, ID3, CBX8, CBX4, GSX1, NKX22, ATF1, TWST2, ZNF17, TOX3, TOX4, ZMYM3, I2BP1, RHXF1, SSX2, I2BPL, ZN680, CBX1, TRI68, HXA13, PHC3, TCF24, CBX3, HXB13, HEY1, PHC2, ZNF81, FIGLA, SAM11, KMT2B, HEY2, JDP2, HXC13, ASCL4, HHEX, HERC2, GSX2, BIN1, ETV7, ASCL3, PHC1, OTP, I2BP2, VGLL2, HXA11, PDLI4, ASCL2, CDX4, ZN860, LMBL4, PDIP3, NKX25, CEBPB, ISL1, CDX2, PROP1, SIN3B, SMBT1, HXC11, HXC10, PRS6A, VSX1, NKX23, MTG16, HMX3, HMX1, KIF22, CSTF2, CEBPE, DLX2, ZMYM3, PPARG, PRIC1, UNC4, BARX2, ALX3, TCF15, TERA, VSX2, HXD12, CDX1, TCF23, ALX1, HXA10, RX, CXXC5, SCML1, NFIL3, DLX6, MTG8, CBX8, CEBPD, SEC13, FIP1, ALX4, LHX3, PRIC2, MAGI3, NELL1, PRRX1, MTG8R, RAX2, DLX3, DLX1, NKX26, NAB1, SAMD7, PITX3, WDR5, MEOX2, NAB2, DHX8, FOXA2, CBX6, EMX2, CPSF6, HXC12, KDM4B, LMBL3, PHX2A, EMX1, NC2B, DLX4, SRY, ZN777, NELL1, ZN398, GATA3, BSH, SF3B4, TEAD1, TEAD3, RGAP1, PHF1, FOXA1, GATA2, FOXO3, ZN212, IRX4, ZBED6, LHX4, SIN3A, RBBP7, NKX61, TRI68, R51A1, MB3L1, DLX5, NOTC1, TERF2, ZN282, RGS12, ZN840, SPI2B, PAX7, NKX62, ASXL2, FOXO1, GATA3, GATA1, ZMYM5, ZN783, SPI2B, LRP1, MIXL1, SGT1, LMCD1, CEBPA, GATA2, SOX14, WTIP, PRP19, CBX6, NKX11, RBBP4, DMRT2, SMCA2 and fragments thereof.

2. The epigenetic editor of claim 1, wherein at least one of the repressor domains is selected from the group consisting of: SEQ ID NO: 67-595.

3. The epigenetic editor of claim 1 or 2, wherein the DNA binding domain binds to a target sequence in a target chromosome comprising a target gene.

4. The epigenetic editor of any one of claims 1-3, wherein the repressor domain specifically binds to an epigenetic effector protein in a cell comprising a target gene and directs the epigenetic editor to the target gene to effect an epigenetic modification in a nucleotide in the target gene or a histone bound to the target gene.

5. The epigenetic editor of any one of claims 1-4, wherein the repressor domains is selected from the group consisting of: ZIM3, ZNF264, ZN577, ZN793, ZFP28, ZN627, RYBP, TOX, TOX3, TOX4, I2BP1, SCMH1, SCML2, CDYL2, CBX8, CBX5, and CBX1, and fragments thereof.

6. The epigenetic editor of any one of claims 1-5, wherein the fusion protein further comprises a second DNMT domain.

7. The epigenetic editor of any one of claims 1-6, wherein the first DNMT domain is selected from the group consisting of a DNMT3A domain, a DNMT3B domain, a DNMT3C domain, and a DNMT3L domain.

8. The epigenetic editor of any one of claims 1-7, wherein the first DNMT domain is a human DNMT3A domain or a human DNMT3L domain.

9. The epigenetic editor of any one of claims 6-8, wherein the first DNMT domain is a DNMT3A domain and the second DNMT domain is a DNMT3L domain, or a catalytic portion thereof.

10. The epigenetic editor of any one of claims 6-9, wherein the first DNMT domain and the second DNMT domain are selected from the group consisting of SEQ ID NO: 32-66.

11. The epigenetic editor of any one of claims 1-10, wherein the DNA binding domain comprises a zinc finger motif or a zinc finger array.

12. The epigenetic editor of any one of claims 1-11, wherein the DNA binding domain comprises a nucleic acid guided DNA binding domain bound to a guide polynucleotide.

13. The epigenetic editor of claim 12, wherein the DNA binding domain comprises CRISPR-Cas protein bound to the guide polynucleotide.

14. The epigenetic editor of claim 12 or 13, wherein the guide polynucleotide hybridizes with a target sequence.

15. The epigenetic editor of claim 13 or 14, wherein the CRISPR-Cas protein comprises a nuclease inactive Cas9 (dCas9).

16. The epigenetic editor of claim 15, wherein the dCas9 is a dSpCas9.

17. The epigenetic editor of claim 16, wherein the dSpCas9 is defined as SEQ ID NO: 3.

18. The epigenetic editor of any one of claims 1-17, wherein the fusion protein domain comprises from N-terminus to C-terminus DNMT3A-DNMT3L-dSpCas9-the repressor domain.

19. A method of modifying an epigenetic state of a target gene in a target chromosome, the method comprising contacting the target chromosome with an epigenetic editor, wherein the epigenetic editor comprises:

- a) a first DNMT domain;
- b) a DNA binding domain; and
- c) a repressor domain,

wherein the repressor domain is selected from the group consisting of: ZIM3, ZNF436, ZNF257, ZNF675, ZNF490, ZNF320, ZNF331, ZNF816, ZNF680, ZNF41, ZNF189, ZNF528, ZNF543, ZNF554, ZNF140, ZNF610, ZNF264, ZNF350, ZNF8, ZNF582, ZNF30,

ZNF324, ZNF98, ZNF669, ZNF677, ZNF596, ZNF214, ZNF37A, ZNF34, ZNF250, ZNF547, ZNF273, ZNF354A, ZFP82, ZNF224, ZNF33A, ZNF45, ZNF175, ZNF595, ZNF184, ZNF419, ZFP28-1, ZFP28-2, ZNF18, ZNF213, ZNF394, ZFP1, ZFP14, ZNF416, ZNF557, ZNF566, ZNF729, ZIM2, ZNF254, ZNF764, ZNF785, ZNF10, CBX5, RYBP, YAF2, MGA, CBX1, SCMH1, MPP8, SUMO3, HERC2, BIN1, PCGF2, TOX, FOXA1, FOXA2, IRF2BP1, IRF2BP2, IRF2BPL IRF-2BP1_2 N-terminal domain, HOXA13, HOXB13, HOXC13, HOXA11, HOXC11, HOXC10, HOXA10, HOXB9, HOXA9, ZFP28, ZN334, ZN568, ZN37A, ZN181, ZN510, ZN862, ZN140, ZN208, ZN248, ZN571, ZN699, ZN726, ZIK1, ZNF2, Z705F, ZNF14, ZN471, ZN624, ZNF84, ZNF7, ZN891, ZN337, Z705G, ZN529, ZN729, ZN419, Z705A, ZNF45, ZN302, ZN486, ZN621, ZN688, ZN33A, ZN554, ZN878, ZN772, ZN224, ZN184, ZN544, ZNF57, ZN283, ZN549, ZN211, ZN615, ZN253, ZN226, ZN730, Z585A, ZN732, ZN681, ZN667, ZN649, ZN470, ZN484, ZN431, ZN382, ZN254, ZN124, ZN607, ZN317, ZN620, ZN141, ZN584, ZN540, ZN75D, ZN555, ZN658, ZN684, RBAK, ZN829, ZN582, ZN112, ZN716, HKR1, ZN350, ZN480, ZN416, ZNF92, ZN100, ZN736, ZNF74, CBX1, ZN443, ZN195, ZN530, ZN782, ZN791, ZN331, Z354C, ZN157, ZN727, ZN550, ZN793, ZN235, ZNF8, ZN724, ZN573, ZN577, ZN789, ZN718, ZN300, ZN383, ZN429, ZN677, ZN850, ZN454, ZN257, ZN264, ZFP82, ZFP14, ZN485, ZN737, ZNF44, ZN596, ZN565, ZN543, ZFP69, SUMO1, ZNF12, ZN169, ZN433, SUMO3, ZNF98, ZN175, ZN347, ZNF25, ZN519, Z585B, ZIM3, ZN517, ZN846, ZN230, ZNF66, ZFP1, ZN713, ZN816, ZN426, ZN674, ZN627, ZNF20, Z587B, ZN316, ZN233, ZN611, ZN556, ZN234, ZN560, ZNF77, ZN682, ZN614, ZN785, ZN445, ZFP30, ZN225, ZN551, ZN610, ZN528, ZN284, ZN418, MPP8, ZN490, ZN805, Z780B, ZN763, ZN285, ZNF85, ZN223, ZNF90, ZN557, ZN425, ZN229, ZN606, ZN155, ZN222, ZN442, ZNF91, ZN135, ZN778, RYBP, ZN534, ZN586, ZN567, ZN440, ZN583, ZN441, ZNF43, CBX5, ZN589, ZNF10, ZN563, ZN561, ZN136, ZN630, ZN527, ZN333, Z324B, ZN786, ZN709, ZN792, ZN599, ZN613, ZF69B, ZN799, ZN569, ZN564, ZN546, ZFP92, YAF2, ZN723, ZNF34, ZN439, ZFP57, ZNF19, ZN404, ZN274, CBX3, ZNF30, ZN250, ZN570, ZN675, ZN695, ZN548, ZN132, ZN738, ZN420, ZN626, ZN559, ZN460, ZN268, ZN304, ZIM2, ZN605, ZN844, SUMO5, ZN101, ZN783, ZN417, ZN182, ZN823, ZN177, ZN197, ZN717, ZN669, ZN256, ZN251, CBX4, PCGF2, CDY2, CDYL2, HERC2, ZN562, ZN461, Z324A, ZN766, ID2, TOX, ZN274, SCMH1, ZN214, CBX7, ID1, CREM, SCX, ASCL1, ZN764, SCML2, TWST1, CREB1, TERF1, ID3, CBX8, CBX4, GSX1, NKX22, ATF1, TWST2, ZNF17, TOX3, TOX4, ZMYM3, I2BP1, RHXF1, SSX2, I2BPL, ZN680, CBX1, TRI68, HXA13, PHC3, TCF24, CBX3, HXB13, HEY1, PHC2, ZNF81, FIGLA, SAM11, KMT2B,

HEY2, JDP2, HXC13, ASCL4, HHEX, HERC2, GSX2, BIN1, ETV7, ASCL3, PHC1, OTP, I2BP2, VGLL2, HXA11, PDLI4, ASCL2, CDX4, ZN860, LMBL4, PDIP3, NKX25, CEBPB, ISL1, CDX2, PROP1, SIN3B, SMBT1, HXC11, HXC10, PRS6A, VSX1, NKX23, MTG16, HMX3, HMX1, KIF22, CSTF2, CEBPE, DLX2, ZMYM3, PPARG, PRIC1, UNC4, BARX2, ALX3, TCF15, TERA, VSX2, HXD12, CDX1, TCF23, ALX1, HXA10, RX, CXXC5, SCML1, NFIL3, DLX6, MTG8, CBX8, CEBPD, SEC13, FIP1, ALX4, LHX3, PRIC2, MAGI3, NELL1, PRRX1, MTG8R, RAX2, DLX3, DLX1, NKX26, NAB1, SAMD7, PITX3, WDR5, MEOX2, NAB2, DHX8, FOXA2, CBX6, EMX2, CPSF6, HXC12, KDM4B, LMBL3, PHX2A, EMX1, NC2B, DLX4, SRY, ZN777, NELL1, ZN398, GATA3, BSH, SF3B4, TEAD1, TEAD3, RGAP1, PHF1, FOXA1, GATA2, FOXO3, ZN212, IRX4, ZBED6, LHX4, SIN3A, RBBP7, NKX61, TRI68, R51A1, MB3L1, DLX5, NOTC1, TERF2, ZN282, RGS12, ZN840, SPI2B, PAX7, NKX62, ASXL2, FOXO1, GATA3, GATA1, ZMYM5, ZN783, SPI2B, LRP1, MIXL1, SGT1, LMCD1, CEBPA, GATA2, SOX14, WTIP, PRP19, CBX6, NKX11, RBBP4, DMRT2, SMCA2 and fragments thereof.

20. Use of an epigenetic editor in the manufacture of a medicament for a treatment of a disease in a subject, wherein the epigenetic editor comprises:

- d) a first DNMT domain;
- e) a DNA binding domain; and
- f) a repressor domain,

wherein the repressor domain is selected from the group consisting of: ZIM3, ZNF436, ZNF257, ZNF675, ZNF490, ZNF320, ZNF331, ZNF816, ZNF680, ZNF41, ZNF189, ZNF528, ZNF543, ZNF554, ZNF140, ZNF610, ZNF264, ZNF350, ZNF8, ZNF582, ZNF30, ZNF324, ZNF98, ZNF669, ZNF677, ZNF596, ZNF214, ZNF37A, ZNF34, ZNF250, ZNF547, ZNF273, ZNF354A, ZFP82, ZNF224, ZNF33A, ZNF45, ZNF175, ZNF595, ZNF184, ZNF419, ZFP28-1, ZFP28-2, ZNF18, ZNF213, ZNF394, ZFP1, ZFP14, ZNF416, ZNF557, ZNF566, ZNF729, ZIM2, ZNF254, ZNF764, ZNF785, ZNF10, CBX5, RYBP, YAF2, MGA, CBX1, SCMH1, MPP8, SUMO3, HERC2, BIN1, PCGF2, TOX, FOXA1, FOXA2, IRF2BP1, IRF2BP2, IRF2BPL IRF-2BP1_2 N-terminal domain, HOXA13, HOXB13, HOXC13, HOXA11, HOXC11, HOXC10, HOXA10, HOXB9, HOXA9, ZFP28, ZN334, ZN568, ZN37A, ZN181, ZN510, ZN862, ZN140, ZN208, ZN248, ZN571, ZN699, ZN726, ZIK1, ZNF2, Z705F, ZNF14, ZN471, ZN624, ZNF84, ZNF7, ZN891, ZN337, Z705G, ZN529, ZN729, ZN419, Z705A, ZNF45, ZN302, ZN486, ZN621, ZN688, ZN33A, ZN554, ZN878, ZN772, ZN224, ZN184, ZN544, ZNF57, ZN283, ZN549, ZN211, ZN615, ZN253, ZN226, ZN730, Z585A, ZN732, ZN681, ZN667, ZN649, ZN470, ZN484, ZN431,

ZN382, ZN254, ZN124, ZN607, ZN317, ZN620, ZN141, ZN584, ZN540, ZN75D, ZN555, ZN658, ZN684, RBAK, ZN829, ZN582, ZN112, ZN716, HKR1, ZN350, ZN480, ZN416, ZNF92, ZN100, ZN736, ZNF74, CBX1, ZN443, ZN195, ZN530, ZN782, ZN791, ZN331, Z354C, ZN157, ZN727, ZN550, ZN793, ZN235, ZNF8, ZN724, ZN573, ZN577, ZN789, ZN718, ZN300, ZN383, ZN429, ZN677, ZN850, ZN454, ZN257, ZN264, ZFP82, ZFP14, ZN485, ZN737, ZNF44, ZN596, ZN565, ZN543, ZFP69, SUMO1, ZNF12, ZN169, ZN433, SUMO3, ZNF98, ZN175, ZN347, ZNF25, ZN519, Z585B, ZIM3, ZN517, ZN846, ZN230, ZNF66, ZFP1, ZN713, ZN816, ZN426, ZN674, ZN627, ZNF20, Z587B, ZN316, ZN233, ZN611, ZN556, ZN234, ZN560, ZNF77, ZN682, ZN614, ZN785, ZN445, ZFP30, ZN225, ZN551, ZN610, ZN528, ZN284, ZN418, MPP8, ZN490, ZN805, Z780B, ZN763, ZN285, ZNF85, ZN223, ZNF90, ZN557, ZN425, ZN229, ZN606, ZN155, ZN222, ZN442, ZNF91, ZN135, ZN778, RYBP, ZN534, ZN586, ZN567, ZN440, ZN583, ZN441, ZNF43, CBX5, ZN589, ZNF10, ZN563, ZN561, ZN136, ZN630, ZN527, ZN333, Z324B, ZN786, ZN709, ZN792, ZN599, ZN613, ZF69B, ZN799, ZN569, ZN564, ZN546, ZFP92, YAF2, ZN723, ZNF34, ZN439, ZFP57, ZNF19, ZN404, ZN274, CBX3, ZNF30, ZN250, ZN570, ZN675, ZN695, ZN548, ZN132, ZN738, ZN420, ZN626, ZN559, ZN460, ZN268, ZN304, ZIM2, ZN605, ZN844, SUMO5, ZN101, ZN783, ZN417, ZN182, ZN823, ZN177, ZN197, ZN717, ZN669, ZN256, ZN251, CBX4, PCGF2, CDY2, CDYL2, HERC2, ZN562, ZN461, Z324A, ZN766, ID2, TOX, ZN274, SCM1, ZN214, CBX7, ID1, CREM, SCX, ASCL1, ZN764, SCML2, TWST1, CREB1, TERF1, ID3, CBX8, CBX4, GSX1, NKX22, ATF1, TWST2, ZNF17, TOX3, TOX4, ZMYM3, I2BP1, RHXF1, SSX2, I2BPL, ZN680, CBX1, TRI68, HXA13, PHC3, TCF24, CBX3, HXB13, HEY1, PHC2, ZNF81, FIGLA, SAM11, KMT2B, HEY2, JDP2, HXC13, ASCL4, HHEX, HERC2, GSX2, BIN1, ETV7, ASCL3, PHC1, OTP, I2BP2, VGLL2, HXA11, PDLI4, ASCL2, CDX4, ZN860, LMBL4, PDIP3, NKX25, CEBPB, ISL1, CDX2, PROP1, SIN3B, SMBT1, HXC11, HXC10, PRS6A, VSX1, NKX23, MTG16, HMX3, HMX1, KIF22, CSTF2, CEBPE, DLX2, ZMYM3, PPARG, PRIC1, UNC4, BARX2, ALX3, TCF15, TERA, VSX2, HXD12, CDX1, TCF23, ALX1, HXA10, RX, CXXC5, SCML1, NFIL3, DLX6, MTG8, CBX8, CEBPD, SEC13, FIP1, ALX4, LHX3, PRIC2, MAGI3, NELL1, PRRX1, MTG8R, RAX2, DLX3, DLX1, NKX26, NAB1, SAMD7, PITX3, WDR5, MEOX2, NAB2, DHX8, FOXA2, CBX6, EMX2, CPSF6, HXC12, KDM4B, LMBL3, PHX2A, EMX1, NC2B, DLX4, SRY, ZN777, NELL1, ZN398, GATA3, BSH, SF3B4, TEAD1, TEAD3, RGAP1, PHF1, FOXA1, GATA2, FOXO3, ZN212, IRX4, ZBED6, LHX4, SIN3A, RBBP7, NKX61, TRI68, R51A1, MB3L1, DLX5, NOTC1, TERF2, ZN282, RGS12, ZN840, SPI2B, PAX7, NKX62, ASXL2, FOXO1, GATA3, GATA1,

ZMYM5, ZN783, SPI2B, LRP1, MIXL1, SGT1, LMCD1, CEBPA, GATA2, SOX14, WTIP, PRP19, CBX6, NKX11, RBBP4, DMRT2, SMCA2 and fragments thereof.

21. An epigenetic editor of claim 1 for use in therapy.