

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 first-repressor domain; ~~and,~~

a-second 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, SMTB1, 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.

~~(d)~~

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.

2.3. 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.

3.4. 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.

~~4.6.~~ The epigenetic editor of any one of claims ~~1-5~~, wherein the fusion protein further comprises a second DNMT domain.

~~5.7.~~ 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.

~~6.8.~~ The epigenetic editor of any one of claims ~~1-7-5~~, wherein the first DNMT domain is ~~thea~~ human DNMT3A domain or a human DNMT3L domain.

~~7. The epigenetic editor of claim 5, wherein the first DNMT domain is the DNMT3L domain.~~

~~8. The epigenetic editor of claim 1, wherein the first DNMT domain is a human DNMT domain.~~

~~9. The epigenetic editor of claim 8, wherein the human DNMT domain is a human DNMT3A domain.~~

~~10. The epigenetic editor of claim 8, wherein the human DNMT domain is a human DNMT3L domain.~~

~~11. The epigenetic editor of claim 1, wherein the first DNMT domain is a mouse DNMT domain.~~

~~12. The epigenetic editor of claim 11, wherein the mouse DNMT domain is a mouse DNMT3A domain.~~

~~13. The epigenetic editor of claim 11, wherein the mouse DNMT domain is a mouse DNMT3L domain.~~

~~14.9.~~ The epigenetic editor of any one of claims ~~6-84~~, wherein the first DNMT domain is a DNMT3A domain and the second DNMT domain is a DNMT3L domain, or a catalytic portion thereof.

~~15. The epigenetic editor of claim 14, wherein the first DNMT domain is a human DNMT3A domain and the second DNMT domain is a human DNMT3L domain.~~

~~16. The epigenetic editor of claim 14, wherein the first DNMT domain is a human DNMT3A domain and the second DNMT domain is a mouse DNMT3L domain.~~

~~17. The epigenetic editor of claim 14, wherein the first DNMT domain is a mouse DNMT3A domain and the second DNMT domain is a human DNMT3L domain.~~

~~18. The epigenetic editor of claim 14, wherein the first DNMT domain is a mouse DNMT3A domain and the second DNMT domain is a mouse DNMT3L domain.~~

~~19. The epigenetic editor of claim 1, wherein the first DNMT domain is a catalytic portion of a DNMT domain.~~

~~20. The epigenetic editor of claim 1, wherein the second DNMT domain is a catalytic portion of a DNMT domain.~~

~~21.10. 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.~~

~~22.—The epigenetic editor of claim 1, wherein at least one of the repressor domains 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.~~

~~23. The epigenetic editor of claim 22, wherein at least one of the repressor domains is selected from the group consisting of: SEQ ID NO: 67-595.~~

~~24. The epigenetic editor of claim 22, wherein at least one of 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.~~

~~25. The epigenetic editor of claim 1, wherein one of the repressor domains is a KRAB domain.~~

~~26. The epigenetic editor of claim 25, wherein the KRAB domain is a KOX1 KRAB domain.~~

~~27.11.~~ 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.

~~28. The epigenetic editor of claim 1, wherein the DNA binding domain comprises a zinc finger array.~~

~~29.12.~~ The epigenetic editor of claimany one of claims 1-11, wherein the DNA binding domain comprises a nucleic acid guided DNA binding domain bound to a guide polynucleotide.

30.13. The epigenetic editor of claim 2912, wherein the DNA binding domain comprises CRISPR-Cas protein bound to the guide polynucleotide.

31.14. The epigenetic editor of claim 2912 or 13, wherein the guide polynucleotide hybridizes with a target sequence.

32.15. The epigenetic editor of claim 3013 or 3114, wherein the CRISPR-Cas protein comprises a nuclease inactive Cas9 (dCas9).

33.16. The epigenetic editor of claim 3215, wherein the dCas9 is a dSpCas9.

34.17. The epigenetic editor of claim 3216, wherein the dSpCas9 is defined as SEQ ID NO: 3.

~~35. The epigenetic editor of claim 30 or 31, wherein the CRISPR-Cas protein comprises a nuclease inactive Cas12a (dCas12a).~~

~~36. The epigenetic editor of claim 30 or 31, wherein the CRISPR-Cas protein comprises a nuclease inactive CasX (dCasX).~~

37.18. 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-~~KOX1KRAB~~-the second repressor domain.

~~38. The epigenetic editor of claim 1, wherein a linker connects the domains of the fusion protein.~~

~~39. The epigenetic editor of claim 38, wherein the linker is an XTEN linker.~~

~~40. The epigenetic editor of claim 39, wherein the XTEN linker is selected from the group consisting of: XTEN-16, XTEN-18, and XTEN-80.~~

~~41. The epigenetic editor of claim 37, wherein the fusion protein comprises from N-terminus to C-terminus: DNMT3A-DNMT3L-XTEN80-dSpCas9-XTEN16-KOX1KRAB-XTEN18-the second repressor domain.~~

42.19. 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,~~comprising a fusion protein,~~ wherein the epigenetic editor ~~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, 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,

ZN354C, 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.

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

- ~~43. The epigenetic editor of claim 42, wherein at least one of the repressor domains is selected from the group consisting of: SEQ ID NO: 67-595.~~
- ~~44. The epigenetic editor of claim 42, wherein the DNA binding domain binds to a target sequence in a target chromosome comprising a target gene.~~
- ~~45. The epigenetic editor of claim 42, 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.~~
- ~~46. The epigenetic editor of claim 42, 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.~~
- ~~47. The epigenetic editor of claim 42, wherein the fusion protein further comprises a second DNMT domain.~~
- ~~48. The epigenetic editor of claim 42, 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.~~
- ~~49. The epigenetic editor of claim 48, wherein the first DNMT domain is the DNMT3A domain.~~
- ~~50. The epigenetic editor of claim 48, wherein the first DNMT domain is the DNMT3L domain.~~
- ~~51. The epigenetic editor of claim 42, wherein the first DNMT domain is a human DNMT domain.~~
- ~~52. The epigenetic editor of claim 51, wherein the first human DNMT domain is a human DNMT3A domain.~~
- ~~53. The epigenetic editor of claim 52, wherein the human DNMT domain is a human DNMT3L domain.~~
- ~~54. The epigenetic editor of claim 42, wherein the first DNMT domain is a mouse DNMT domain.~~
- ~~55. The epigenetic editor of claim 54, wherein the mouse DNMT domain is a mouse DNMT3A domain.~~
- ~~56. The epigenetic editor of claim 54, wherein the mouse DNMT domain is a mouse DNMT3L domain.~~
- ~~57. The epigenetic editor of claim 44, wherein the first DNMT domain is a DNMT3A domain and the second DNMT domain is a DNMT3L domain.~~
- ~~58. The epigenetic editor of claim 57, wherein the first DNMT domain is a human DNMT3A domain and the second DNMT domain is a human DNMT3L domain.~~

- ~~59. The epigenetic editor of claim 57, wherein the first DNMT domain is a human DNMT3A domain and the second DNMT domain is a mouse DNMT3L domain.~~
- ~~60. The epigenetic editor of claim 57, wherein the first DNMT domain is a mouse DNMT3A domain and the second DNMT domain is a human DNMT3L domain.~~
- ~~61. The epigenetic editor of claim 57, wherein the first DNMT domain is a mouse DNMT3A domain and the second DNMT domain is a mouse DNMT3L domain.~~
- ~~62. The epigenetic editor of claim 42, wherein the first DNMT domain is a catalytic portion of the DNMT domain.~~
- ~~63. The epigenetic editor of claim 42, wherein the second DNMT domain is a catalytic portion of a DNMT domain.~~
- ~~64. The epigenetic editor of claim 42, wherein the first DNMT domain and the second DNMT domain are selected from the group consisting of SEQ ID NO: 32-66.~~
- ~~65. The epigenetic editor of claim 42, wherein the DNA binding domain comprises a zinc finger motif.~~
- ~~66. The epigenetic editor of claim 42, wherein the DNA binding domain comprises a zinc finger array.~~
- ~~67. The epigenetic editor of claim 42, wherein the DNA binding domain comprises a nucleic acid-guided DNA binding domain bound to a guide polynucleotide.~~
- ~~68. The epigenetic editor of claim 67, wherein the DNA binding domain comprises CRISPR-Cas protein bound to the guide polynucleotide.~~
- ~~69. The epigenetic editor of claim 67, wherein the guide polynucleotide hybridizes with a target sequence.~~
- ~~70. The epigenetic editor of claim 68 or 69, wherein the CRISPR-Cas protein comprises a nuclease inactive Cas9 (dCas9).~~
- ~~71. The epigenetic editor of claim 70, wherein the dCas9 is a dSpCas9.~~
- ~~72. The epigenetic editor of claim 71, wherein the dSpCas9 is defined as SEQ ID NO: 3.~~
- ~~73. The epigenetic editor of claim 68 or 69, wherein the CRISPR-Cas protein comprises a nuclease inactive Cas12a (dCas12a).~~
- ~~74. The epigenetic editor of claim 68 or 69, wherein the CRISPR-Cas protein comprises a nuclease inactive CasX (dCasX).~~
- ~~75. The epigenetic editor of claim 42, wherein the fusion protein domain comprises from N-terminus to C-terminus DNMT3A-DNMT3L-dSpCas9 the repressor domain.~~
- ~~76. The epigenetic editor of claim 42, wherein a linker connects the domains of the fusion protein.~~

- ~~77. The epigenetic editor of claim 76, wherein the linker is an XTEN linker.~~
- ~~78. The epigenetic editor of claim 77, wherein the XTEN linker is selected from the group consisting of: XTEN-16, XTEN-18, and XTEN-80.~~
- ~~79. The epigenetic editor of claim 75, wherein the fusion protein comprises from N-terminus to C-terminus: DNMT3A-DNMT3L-XTEN80-dSpCas9-XTEN16-the repressor domain.~~
- ~~80. An epigenetic editor comprising a fusion protein, wherein the fusion protein comprises:~~
- ~~(a) a demethylase domain;~~
 - ~~(b) a DNA binding domain; and~~
 - ~~(c) an activator domain.~~
- ~~81. The epigenetic editor of claim 74, wherein there is increased expression of the target gene when contacted with the epigenetic editor of any of the preceding claims as compared to the target gene not contacted with the epigenetic editor.~~
- ~~82. An epigenetic editor comprising a fusion protein, wherein the fusion protein comprises:~~
- ~~(a) a DNA binding domain;~~
 - ~~(b) a repressor domain;~~
 - ~~(c) a first catalytic domain wherein the catalytic domain is selected from the group consisting of a DNMT3A catalytic domain and a DNMT3L catalytic domain; and~~
 - ~~(d) a second catalytic domain wherein the catalytic domain is selected from the group consisting of a DNMT3A catalytic domain and a DNMT3L catalytic domain,~~
- ~~wherein the first catalytic domain has less than 380 amino acids or~~
- ~~wherein the second catalytic domain has less than 380 amino acids.~~
- ~~83. 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;~~
 - ~~(c) a first repressor domain; and~~
 - ~~(d) a second repressor domain, and~~
- ~~wherein the DNA binding domain binds to a target sequence in the target chromosome and directs the epigenetic effector domain to effect a site-specific epigenetic modification in the target gene or a histone bound to the target gene in the target chromosome, thereby modifying the epigenetic state of the target gene.~~

84. ~~A method of modulating expression 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;~~
 - ~~(c) a first repressor domain; and~~
 - ~~(d) a second repressor domain; and~~
- ~~wherein the DNA binding domain binds to a target sequence in the target chromosome and directs the epigenetic effector domain to effect a site-specific epigenetic modification in the target gene or a histone bound to the target gene in the target chromosome, thereby modulating the epigenetic state of the target gene.~~
85. ~~A method of treating a disease in a subject in need thereof, the method comprising administering to the subject an epigenetic editor, wherein the epigenetic editor comprises:~~
- ~~(a) a first DNMT domain;~~
 - ~~(b) a DNA binding domain;~~
 - ~~(c) a first repressor domain; and~~
 - ~~(d) a second repressor domain;~~
- ~~wherein the DNA binding domain binds to a target sequence in the target chromosome and directs the epigenetic effector domain to effect a site-specific epigenetic modification in the target gene or a histone bound to the target gene in the target chromosome, thereby treating the disease,~~
- ~~wherein the target gene is associated with disease, and~~
- ~~wherein the site-specific epigenetic modification modulates expression of the target gene, thereby treating the disease.~~
86. ~~The method of any one of claims 83-85, wherein the site-specific epigenetic modification is within 3000 base pairs upstream or downstream of the target sequence.~~
87. ~~The method of claim 86, wherein the site-specific epigenetic modification is within 2000 base pairs upstream or downstream of the target sequence.~~
88. ~~The method of any one of claims 83-87, wherein the site-specific epigenetic modification is within 3000 base pairs upstream or downstream of an expression regulatory sequence.~~
89. ~~The method of claim 88, wherein the site-specific epigenetic modification is within 2000 base pairs upstream or downstream of the expression regulatory sequence.~~
90. ~~The method of claim 89, wherein the site-specific epigenetic modification is within 1000 base pairs upstream or downstream of the expression regulatory sequence.~~

91. ~~The method of any one of claims 83-90, comprising administering to the subject a cell comprising the epigenetic editor.~~
92. ~~The method of claim 91, wherein the cell is an allogeneic cell.~~
93. ~~The method of claim 92, wherein the cell is an autologous cell.~~
94. ~~The method of any one of claims 83-93, wherein the epigenetic modification is within a coding region of the target gene.~~
95. ~~The method of any one of claims 83-94, wherein the target gene comprises an allele associated with a disease.~~
96. ~~The method of any one of claims 83-95, wherein the fusion protein further comprises a second DNMT domain.~~
97. ~~The method of any one of claims 83-96, 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.~~
98. ~~The method of any one of claims 83-97, wherein the first DNMT domain is the DNMT3A domain.~~
99. ~~The method of any one of claims 83-98, wherein the first DNMT domain is the DNMT3L domain.~~
100. ~~The method of any one of claims 83-99, wherein the first DNMT domain is a human DNMT domain.~~
101. ~~The method of claim 100, wherein the human DNMT domain is a human DNMT3A domain.~~
102. ~~The method of claim 100, wherein the human DNMT domain is a human DNMT3L domain.~~
103. ~~The method of any one of claims 83-102, wherein the first DNMT domain is a mouse DNMT domain.~~
104. ~~The method of claim 103, wherein the mouse DNMT domain is a mouse DNMT3A domain.~~
105. ~~The method of claim 103, wherein the mouse DNMT domain is a mouse DNMT3L domain.~~
106. ~~The method of any one of claims 83-105, wherein the first DNMT domain is a DNMT3A domain and the second DNMT domain is a DNMT3L domain.~~
107. ~~The method of claim 96, wherein the first DNMT domain is a human DNMT3A domain and the second DNMT domain is a human DNMT3L domain.~~

- 108.—The method of claim 96, wherein the first DNMT domain is a human DNMT3A domain and the second DNMT domain is a mouse DNMT3L domain.
- 109.—The method of claim 96, wherein the first DNMT domain is the mouse DNMT3A domain and the second DNMT domain is a human DNMT3L domain.
- 110.—The method of claim 96, wherein the first DNMT domain is a mouse DNMT3A domain and the second DNMT domain is a mouse DNMT3L domain.
- 111.—The method of any one of claims 83-110, wherein the first DNMT domain is a catalytic portion of a DNMT domain.
- 112.—The method of any one of claims 83-111, wherein the second DNMT domain is a catalytic portion of a DNMT domain.
- 113.—The method of any one of claims 83-112, wherein the first DNMT domain and the second DNMT domain are selected from the group consisting of SEQ ID NO: 32-66.
- 114.—The method of any one of claims 83-113, wherein at least one of the repressor domains 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, SSSX2, 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.~~

115.—~~The method of claim 114 wherein at least one of the repressor domains is selected from the group consisting of: SEQ ID NO: 67-595.~~

116.—~~The method of claim 114, wherein at least one of 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.
117. ~~The method of any one of claims 83-116, wherein one of the repressor domains is a KRAB domain.~~
118. ~~The method of claim 117, wherein the KRAB domain is a KOX1 KRAB domain.~~
119. ~~The method of any one of claims 83-118, wherein the DNA binding domain comprises a zinc finger motif.~~
120. ~~The method of any one of claims 83-119, wherein the DNA binding domain comprises a zinc finger array.~~
121. ~~The method of any one of claims 83-120, wherein the DNA binding domain comprises a nucleic acid-guided DNA binding domain bound to a guide polynucleotide.~~
122. ~~The method of claim 121, wherein the DNA binding domain comprises CRISPR-Cas protein bound to the guide polynucleotide.~~
123. ~~The method of claim 121, wherein the guide polynucleotide hybridizes with a target sequence.~~
124. ~~The method of claim 122 or 123, wherein the CRISPR-Cas protein comprises a nuclease inactive Cas9 (dCas9).~~
125. ~~The method of claim 124, wherein the dCas9 is a dSpCas9.~~
126. ~~The method of claim 122 or 123, wherein the CRISPR-Cas protein comprises a nuclease inactive Cas12a (dCas12a).~~
127. ~~The epigenetic editor of claim 32, wherein the dSpCas9 is defined as SEQ ID NO: 3.~~
128. ~~The method of claim 122 or 123, wherein the CRISPR-Cas protein comprises a nuclease inactive CasX (dCasX).~~
129. ~~The method of any one of claims 83-128, wherein the fusion protein comprises from N-terminus to C-terminus DNMT3A-DNMT3L-dSpCas9-KOX1KRAB-the second repressor domain.~~
130. ~~The method of any one of claims 83-129, wherein a linker connects the domains of the fusion protein.~~
131. ~~The method of claim 130, wherein the linker is an XTEN linker.~~
132. ~~The method of claim 131, wherein the XTEN linker is selected from the group consisting of: XTEN-16, XTEN-18, and XTEN-80.~~
133. ~~The method of claim 129, wherein the fusion protein comprises from N-terminus to C-terminus DNMT3A-DNMT3L-XTEN80-dSpCas9-XTEN16-KOX1KRAB-XTEN18-the second repressor domain.~~

134. — ~~A composition for use in the treatment of a subject, the composition comprising a fusion protein, wherein the fusion protein comprises:~~

- ~~(a) a first DNMT domain;~~
- ~~(b) a DNA binding domain;~~
- ~~(c) a first repressor domain; and~~
- ~~(d) a second repressor domain.~~