

Supplemental Figure S1: Amino acid sequences of dCas9- and MCP-fusion proteins.**D3L-dCas9**

NLS (SV40): aa 2–9

3X Flag: aa 15–36

D3L human DNMT3L (NP_787063): aa 47–432

dCas9 (D10A,H840A): aa 453–1820

NLS (Neoplasmin): aa 1846–1861

MPKKKRKVGSGGSDYKDHGDYKDHIDYKDDDDKGGGSGGGSGTMAAIPALDPEAEPMDV
 ILVGSELSSSVSPGTGRDLIAYEVKANQRNIEDICICCGSLQVHTQHPLFEGGICAPCKDKF
 LDALFLYDDDDGYQSYCSICCSGETLLICGNPDCTRCYCFECVDSL VGPGTSGKVHAMSNNWVCY
 LCLPSSRSGLLQRRRKWRSQ LKAFYDRESENPLEMFETVPVWRRQPVRVLSLFEDIKKELTSL
 GFLESGSDPGQLKHVVVDVTDTVRKDVEEWGPFDLVYGATPPLGHTCDRPPSWYLFQFHRL LQY
 ARPKPGSPRPFFWMFVDNLVLNKEDLDVASR FLEMEPVTIPDVHGGSLQNAVRVWSNIPAIRS
 RHWALVSEEELSLLAQNKQSSKLA AKWPTKLVKNCFLPLREYFKYFSTELTSSLSTGGSGGSG
 GSGGSGGSGRPMDDKYSIGLAIGTNSVGWAVITDEYKVPSKKFKVLGNTDRHSIKKNLIGALL
 FDSGETAEATRLKRTARRRYTRRKNRICYLQEIFS NEMAKVDDSFHRLEESFLVEEDKKHER
 HPFIGNIVDEVAYHEKYPTIYHLRKKLVDSTDKADLR LIYLALAHMIKFRGHFLIEGDLNPDN
 SDVDKLF IQLVQTYNQLF EENPINASGVDAKAILSARLSKSRLENLIAQLPGEKKNGLFGLN
 IALSGLTPNFKSNFDLAEDAKLQLSKD TYDDDLNLLAQIGDQYADLFLAAKNLSDAILLSD
 ILRVNTEITKAPLSASMIKRYDEHHQDLTLLKALVRQQLPEKYKEIFFDQSKNGYAGYIDGGA
 SQEEFYKFIKPILEKMDGTEELLVKLNREDLLRKQRTFDNGSIPHQIHLGELHAILRRQEDFY
 PFLKDNREKIEKILTFRIPIYYVGPLARGNSRF AWMTRKSEETITPWNFEVVDKGASAQSFIE
 RMTNFDKNLPNEKVL PKHSLLYEYFTVYNELTKVKYVTEGMRKPAFLSGEQKKAIVDLLFKTN
 RKVTVKQLKEDYFKKIECFDSVEISGVEDRFNASLGTYHDL LKIIKDKDFLDNEENEDILEDI
 VLTLT LTFEDREMIEERLKYAHLFDDKVMKQLKRRRYTGWGRLSRKLINGIRDKQSGKTILDF
 LKSDGFANRNFMQLIHDDSLTFKEDIQKAQVSGQGDSLHEHIANLAGSPA IKKGILQTVKVVD
 ELVKVMGRHKPENIVIEMARENQTTQKGQKNSRERMKRIEEGIKELGSQILKEHPVENTQLQN
 EKLYLYYLQNGRDMYVDQELDINRLSDYDVDAIVPQSFLKDDSIDNKVLTRSDKNRGKSDNVP
 SEEVVKMKKNYWRQLLNAKLITQRKFDNLTKAERGGLSELDKAGFIKRQLVETRQITKHVAQI
 LDSRMNTKYDENDKLIREVKVITLKS KLVSDFRKDFQFYKVREINNYHHAHDAYLNAVVG TAL
 IKKYPKLESEFVYG DYKVYDVRKMI AKSEQEIGKATAKYFFYSNIMNFFKTEITLANGEIRKR
 PLIETNGETGEIVWDKGRDFATVRKVL SMPQVNIVKKTEVQTGGFSKESILPKRNSDKLIARK
 KDWDPKKYGGFDSPTVAYSVLVVAKEK GKSKKLKSVKELLGITIMERSSSF EKNPIDFLEAKG
 YKEVKKDLIIKLPKYSLFEL ENGRKRLASAGELQGNELALPSKYVNFLYLASHYEKLKGSP
 EDNEQKQLFVEQHKHYLDEII EQISEFSKRVLADANLDKVL SAYNKH RDKPIREQAENIIHL
 FTLTNLGAPAAFKYFDTTIDRKRYTSTKEVLDATLIHQSI TGLYETRIDLSQLGGDGGSGGSG
 GSGGSGGSASGGGSGGGSKRPAATKKAGQAKKKGGSGSGATNFSLLKQA

dCas9-D3L

NLS (SV40): aa 2-9

3X Flag: aa 15-36

dCas9 (D10A,H840A): aa 65-1432

D3L human DNMT3L (NP_787063): aa 1450-1835

NLS (Neoplasmin): aa 1845-1860

MPKKKRKVGSGGSDYKDHDGDYKDHDIDYKDDDDKGGGSGGGSGTGSGSGSGSGSGSGSGSGR
PMDKKYSIGLAIGTNSVGWAVITDEYKVPSKKFKVLGNTDRHSIKKNLIGALLFDSGETAEAT
RLKRTARRRYTRRKNRICYLQEIFSNEMAKVDDSFHRLEESFLVEEDKKHERHPIFGNIVDE
VAYHEKYPTIYHLRKKLVDSTKADLRLIYLALAHMIKFRGHFLIEGDLNPDNSDVKLFIQL
VQTYNQLFEEPNINASGVDAKAILSARLSKSRLENLIAQLPGEKKNGLFGNLIASLSGLTPN
FKSNFDLAEDAKLQLSKDITYDDDLNLLAQIGDQYADLFLAAKNLSDAILLSDILRVNTEITK
APLSASMIKRYDEHHQDLTLLKALVRQQLPEKYKEIFFDQSKNGYAGYIDGGASQEEFYKFIK
PILEKMDGTEELLVKLNREDLLRKQRTFDNGSIPHQIHLGELHAILRRQEDFYFPLKDNREKI
EKILTFRIPYYVGPLARGNSRFAMWTRKSEETITPWNFEEVVDKGASASQSFIERMTNFDKNLP
NEKVLPHKSHLLYEYFTVYNELTKVKYVTEGMRKPAFLSGEQKKAIVDLLFKTNRKVTVKQLKE
DYFKKIECFDSVEISGVEDRFNASLGTYHDLKIIKDKDFLDNEENEDILEDIVLTLTLFEDR
EMIEERLKTYAHLFDDKVMKQLKRRRYTGWGRLSRKLINGIRDKQSGKTILDFLKSDGFANRN
FMQLIHDDSLTFKEDIQKAQVSGQGDSLHEHIANLAGSPAIAKKGILQTVKVVDELVKVMGRHK
PENIVIAMARENQTTQKGQKNSRERMKRIEEGIKELGSQILKEHPVENTQLQNEKLYLYYLQN
GRDMYVDQELDINRLSDYDVAIVPQSFLKDDSIDNKVLTRSDKNRGKSDNVPSEEVVKMKMN
YWRQLLNAKLITQRKFDNLTKAERGGLSELDKAGFIKRQLVETRQITKHVAQILDSRMNTKYD
ENDKLIREVKVITLKSCLVSDFRKDFQFYKVREINNYHHAHDAYLNAVVGITALIKKYPKLESE
FVYGDYKVYDVRKMIKSEQEIGKATAKYFFYSNIMNFFKTEITLANGEIRKRPLIETNGETG
EIVWDKGRDFATVRKVLSPQVNIVKKTEVQTGGFSKESILPKRNSDKLIARKKDWDPKKYGG
FDSPTVAYSVLVVAKEKGSKKLKSVKELLGITIMERSSSFENPIDFLEAKGYKEVKKDLII
KLPKYSLELENGRKRMLASAGELQKGNELALPSKYVNFLYLASHYEKLKGSPEDEQKQLFV
EQHKHYLDEIIEQISEFSKRVILADANLDKVL SAYNKHDKPIREQAENIIHLFTLTNLGAPA
AFKYFDTTIDRKRYTSTKEVLDTLIHQSIITGLYETRIDLSQLGGDGGSGSGSGSGSGSGSAS
MAAIPALDPEAEPSMDVILVGSSSELSSSVSPGTGRDLIAYEVKANQRNIEDICICCGSLQVHT
QHPLFEGGICAPCKDKFLDALFLYDDGYQSYCSICCSGETLLICGNPDCTRCYCFECVDSL
V
GPGTSGKVHAMSNNVCYLCLPSSRSGLLQRRRKWRSQKAFYDRESENPLEMFETVPVWRRQP
VRVLSLFDIEKKELTSLGFLESGSDPGQLKHVVDVTDTVRKDVEEWGPFDLVYGATPPLGHTC
DRPPSWYLFQFHRLQYARPKGSPGPFWMFVDNLVLNKKEDLDVASRFLEMEPVTTIPDVHGG
SLQNAVRVWSNIPAIRSRHWALVSEELSLLAQNKQSSKLAQWPTKLQKNCFLPLREYFKYF
STELTSSLSGGSGGGSKRPAATKKAGQAKKKKGGSGSGATNFSLLKQAGDVEENPGPAAA

2xMCP-KRAB

2xMCP: aa 1-236

KRAB (NP_056209.2, aa12-85): aa 241-312

MASNFTQFVLVDNGGTGDVTVAPSNFANGIAEWISSNSRSQAYKVTC SVRQSSAQNRKYTIKV
EVPKGAWRSYLNMELTIP IFATNSDCELIVKAMQGLLKDGNPIPSAIAANS GIYAMASNFTQF
VLVDNGGTGDVTVAPSNFANGIAEWISSNSRSQAYKVTC SVRQSSAQNRKYTIKVEVPKGAWR
SYLNMELTIP IFATNSDCELIVKAMQGLLKDGNPIPSAIAANS GIYADSRM **VTFKDVFDFT**R
EEWKLLDTAQQIVYRNVMLENYKNLVSLGYQLTKPDVILRLEKGEEPWLVEREIHQETHP

2xMCP-Ezh2

2xMCP

Ezh2 (NP_031997.2, aa 1-746)

MASNFTQFVLVDNGGTGDVTVAPSNFANGIAEWISSNSRSQAYKVTC~~SVRQSSAQNRKYTIKV~~
EVPKGAWRSYLNMELTIPIFATNSDCELIVKAMQGLLKDG~~NPIPSAIAANS~~GIYAMASNFTQF
VLVDNGGTGDVTVAPSNFANGIAEWISSNSRSQAYKVTC~~SVRQSSAQNRKYTIKVEVPKGAWR~~
SYLNMELTIPIFATNSDCELIVKAMQGLLKDG~~NPIPSAIAANS~~GIYADSRGGGSGGGSGTMGQ
TGKKSEKGPVCWRKRVKSEYMRLRQLKRFRRADDEVKTMFSSNRQKILERTETLNQEWKQRRIQ
PVHIMTSVSSLRGTRECSVTSDLDFPAQVIPLKTLNAVASVPIMYSWSPLOQNF~~MVEDETVLH~~
NIPYMGDEVLDQDGTFFIEELIKNYDGKVHGDRECGFINDEIFVELVNALGQYNDDDDDDDDGDD
PDEREEKQKDLEDNRDDKETCPPRKFPADKIFEAISSMFPDKGTAEELKEKYKELTEQQLPGA
LPPECTPNIDGPNAKSVQREQSLHSFHTLFCRRCFKYDCFLHPFHATPNTYKRKNTETALDNK
PCGPQCYQHLEGAKEFAAALTAERIKTPPKRPGGRRRGRLPNNSSRPSTPTISVLESKDTDS
REAGTETGGENNDKEEEEKKDETSSSSEANSRCQTPIKMKPNIEPPENVEWSGAEASMFRVLI
GTYYDNFCAIARLIGTKTCRQVYEFVRVKESSIIAPVPTEDVDTPPRKKKRKHLWAAHCRKIQ
LKKDGSSNHVYNYQPCDHPRQPCDSSCPCVIAQNFCEKFCQCSSECQNRFPGCRCKAQCNTKQ
CPCYLAVRECDPDLCLTCGAADHWDSKNVSCKNCSIQRGSKKHL~~LLAPSDVAGWGIFIKDPVQ~~
KNEFISEYCGEIIISQDEADRRGKVYDKYMCSFLFNLNNDFFVVDATRKG~~NKIRFANHSVNPNCY~~
AKVMMVNGDHRIGIFAKRAIQTGEELFFDYRYSQADALKYVGIEREMEIP