# **Supplementary Information**

#### Inhibition of base editors with anti-deaminases derived from viruses

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Supplementary Figure 1. Base editing of RmA3Bctd-, mA3CDA1- and SsA3Bctd-CBE with Ades.Supplementary Figure 2. Immunoblots of A3-CBEs in the presence or absence of corresponding Ades.

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Supplementary Table 2. Primers used for genotyping in this study.



Supplementary Figure 1. Base editing of RmA3Bctd-, mA3CDA1- and SsA3Bctd-CBE with Ades. a Schematic representation of RmA3Bctd-, mA3CDA1- and SsA3Bctd-CBE. nCas9, D10A. b-d Base editing of these three CBEs in the presence or absence of the Ade1 and Ade2 at EMX1-1, FANCF and RNF2 site. Values and error bars reflect the mean  $\pm$  s.e.m. and n=3 biologically independent experiments. All *p* values were calculated by two-sided t tests. \**p* < 0.05, \*\**p* < 0.01. Source data are provided as a Source Data file.



**Supplementary Figure 2.** Immunoblots of A3-CBEs in the presence or absence of corresponding Ades. Tubulin was used as a loading control. The western blot experiments were repeated three times independently with similar results.



**Supplementary Figure 3.** Base editing of A3-CBE chimeras. **a** Amino acid sequence alignment of A3A, A3Bctd and A3Gctd. Alignment was performed with NCBI COBALT and rendered using Jalview. The L1 and L7 are shown in red rectangle. **b** Schematic representation of A3-CBE chimeras by exchanging L1 and L7 among A3A, A3Bctd and A3Gctd. nCas9, D10A. **c** Base editing of A3-CBE chimeras in the presence or absence of the Ade1 and Ade1 at FANCF site. **d** Heat map showing summary of C-to-T editing frequencies on each base for these A3-CBE chimeras at FANCF site. Values and error bars reflect the mean  $\pm$  s.e.m. and n=3 biologically independent experiments. Source data are provided as a Source Data file.



**Supplementary Figure 4.** Ade1 and Ade2 relocalized A3Bctd- and A3A-CBEs. Representative images of HEK293T cells expressing the indicated A3-CBE-mCherry constructs alone or in combination with Ade-EGFP constructs. The immunofluorescence microscopy experiments were repeated three times independently with similar results.



**Supplementary Figure 5.** *In vitro* deaminase activity assay of A3A and A3Bctd. TBE-urea PAGE analysis of A3A (**a**) and A3Bctd (**b**) deaminase activity in the presence of Ade1 or Ade2 (product percentage indicated below each lane). The experiment was repeated three times independently with similar results.



**Supplementary Figure 6.** Base editing of rA1-, eAID-, eCDA1-CBE and ABE8e with Ades. **a** Schematic representation of rA1-, eAID-, eCDA1-CBE and ABE8e. nCas9, D10A. **b** Base editing of these four BEs in the presence or absence of the Ade1-Ade4 at EMX1-1 site. Values and error bars reflect the mean  $\pm$  s.e.m. and n=3 biologically independent experiments. Source data are provided as a Source Data file.



**Supplementary Figure 7.** Comparison of base editing characteristics by rA1-, A3B- and A3Bctd-CBE. **a** Schematic representation of rA1-, A3B- and A3Bctd-CBE. nCas9, D10A. **b-c** Summary of C-to-T editing frequencies induced by rA1-, A3B- and A3Bctd-CBE systems on each cytosine at seven target sites. **d** Summary of average C-to-T editing frequencies induced by rA1-, A3B- and A3Bctd-CBE systems at seven target sites in (**b**) and (**c**). The center line indicates the median, and the bottom and top lines of the box represent the minima and maxima, respectively. **e** Heat map showing summary of C-to-T editing frequencies on each base for rA1-, A3B- and A3Bctd-CBE. **f** Base editing of A3Bctd-CBE in the presence or absence of the Ade1 and Ade2 at seven sites. Values and error bars reflect the mean  $\pm$  s.e.m. and n=3 biologically independent experiments. Source data are provided as a Source Data file.



**Supplementary Figure 8.** C-to-G base editing by rA1 variants-, A3A variants-, and A3Bctd variants-CGBEs. **a-d** Bar plots showing the base editing frequencies induced by rA1 variants-, A3A variants-, and A3Bctd variants-CGBEs at RNF2, ABE site7, ABE site8 and HEK site2. Target C, red. Plasmids expressing CGBE, sgRNA, and Ade (1:1:1) were co-transfected into HEK293T cells. Values and error bars reflect the mean  $\pm$  s.e.m. and n=3 biologically independent experiments. Source data are provided as a Source Data file.



**Supplementary Figure 9.** Evaluation of on-target and off-target editing by A3A- and A3Bctd-CBE in HEK site4. **a** On-target editing frequencies of A3A and A3Bctd-CBE in the presence or absence of the AcrIIC1 (as a negative control), AcrIIA5, Ade1 and Ade2 at HEK site4. **b** The Cas9-dependent OT editing frequencies of A3A and A3Bctd-CBE in the presence or absence of the AcrIIC1 (as a negative control), AcrIIA5, Ade1 and Ade2 at OT1-OT3 sites. **c** The Cas9-independent OT editing frequencies of A3A and A3Bctd-CBE in the presence or absence of the AcrIIC1 (as a negative control), AcrIIA5, Ade1 and Ade2 at OT1-OT3 sites. **c** The Cas9-independent OT editing frequencies of A3A and A3Bctd-CBE in the presence or absence of the AcrIIC1 (as a negative control), AcrIIA5, Ade1 and Ade2 at Sa site5, site6, site 14 and site17. Values and error bars reflect the mean  $\pm$  s.e.m. and n=3 biologically independent experiments. All *p* values were calculated by two-sided t tests. \**p* < 0.05, \*\**p* < 0.01, \*\*\**p* < 0.001, \*\*\*\**p* < 0.0001. Source data are provided as a Source Data file.



**Supplementary Figure 10.** Evaluation of on-target and off-target editing by A3G-CBE in EMX1-1. **a** On-target editing frequencies of A3G-CBE in the presence or absence of the Ade3 and Ade4 at EMX1-1 site. **b** The Cas9-dependent OT editing frequencies of A3G-CBE in the presence or absence of the Ade3 and Ade4 at EMX1-1 OT1 and OT2 site. **c** The Cas9-independent OT editing frequencies of A3G-CBE in the presence or absence of the Ade3 and Ade4 at Sa site5, site6, site14 and site17. Values and error bars reflect the mean  $\pm$  s.e.m. and n=3 biologically independent experiments. All *p* values were calculated by two-sided t tests. \**p* < 0.05, \*\**p* < 0.01, \*\*\**p* < 0.001, \*\*\*\**p* < 0.0001. Source data are provided as a Source Data file.



**Supplementary Figure 11.** Ade2 moderately narrowed the C-to-T editing window of A3A-CBE. **a-f** Frequencies of single C-to-T conversions using A3A-CBE in the presence or absence of Ade2 at six target sites. Values and error bars reflect the mean  $\pm$  s.e.m. and n=3 biologically independent experiments. Source data are provided as a Source Data file.



Supplementary Figure 12. Base editing of A3A- and A3Bctd-CBE with both Acr and Ade. a-b Base editing of A3A- and A3Bctd-CBE in the presence or absence of the AcrIIA5 alone, Ade1 alone, Ade2 alone, Ade1+AcrIIA5 and Ade2+AcrIIA5 at EMX1-1 and FANCF site. Values and error bars reflect the mean  $\pm$  s.e.m. and n=3 biologically independent experiments. Source data are provided as a Source Data file.

Target site	Sequence (5'-3')	
EMX1-1	GAGTCCGAGCAGAAGAAGAAGGG	
FANCF	GGAATCCCTTCTGCAGCACCTGG	
EMX1-2	TGCCCCTCCCTGGCCCAGG	
RNF2	GTCATCTTAGTCATTACCTGAGG	
ABE site7	GAATACTAAGCATAGACTCCAGG	
ABE site7	GTAAACAAAGCATAGACTGAGGG	
HEK site2	GAACACAAAGCATAGACTGCGGG	
HEK site4	GGCACTGCGGCTGGAGGTGGGGG	
EMX1-1 OT1	GAGTCTAAGCAGAAGAAGAAGAAG	
EMX1-1 OT2	GAATCCAAGCAGAAGAAGAAGAAG	
HEK site4 OT1	GACACTGCAGCTGGAGGTGGGG	
HEK site4 OT2	HEK site4 OT2 GGCACGACGGCTGGAGGTGGGGG	
HEK site4 OT3	EK site4 OT3 GGCATCACGGCTGGAGGTGGAGG	
Sa site5	TCTGCTTCTCCAGCCCTGGCCTGGGT	
Sa site6	GATGTTCCAATCAGTACGCAGAGAGT	
Sa site14	GGCCTCCGTATCACTCTCTGACTGGGGT	
Sa site17	GGTCGTAGCCAGTCCGAACCCCGGAGT	

Supplementary Table 1. Target sites used in this study. Target sequence (black), PAM region (green).

Primers	Sequence (5'-3')	Product size	Target sites
		(bp)	
EMX1-F:	CCTTCTGTGAATGTTAGACCCA	520	EMX1-1,
EMX1-R:	TGCTTGTCCCTCTGTCAATG		EMX1-2
FANCF-F:	ATCTGCTCTCCCTCCACTAA	483	FANCF
FANCF-R:	GGCCTGGAAGTTCGCTAAT		
RNF2-F:	GTCTTCCTTGGTGCCTTATCA	524	RNF2
RNF2-R:	TGGTGGGACACATACATTCAG		
AS7-F:	CATCTTCTCCGCAGACAGAAATA	465	ABE site7
AS7-R:	TCCTGCCCTTAGGTCAAATAAC		
AS8-F:	CATACTTAAAGTAAAGCAGAAGGAATAACAGTGC	225	ABE site8
AS8-R:	GAAGTTTCATTCCACTATAGAACTGGTTCTG		
HS2-F:	GGACGTCTGCCCAATATGTAA	455	HEK site2
HS2-R:	GCATTAATCCACAGCAACACC		
HS4-F:	CCCTTCAAGATGGCTGACAA	230	HEK site4
HS4-R:	TTTCAACCCGAACGGAGAC		
E-OT1-F:	GCTTCTTGTTCTTTGGCTTTCT	476	EMX1-1 OT1
E-OT1-R:	AGGGTATAGTTGAGGTGGGATA		
E-OT2-F:	CATCTTCTGCTGGTTCCGATTA	407	EMX1-1 OT2
E-OT2-R:	GATCAGGGCGAGATTAGAGTTG		
H-OT1-F:	CAGTGGCTCATCCCTGTAATTC	407	HEK site4 OT1
H-OT1-R:	CCACACAAATCCAAACAAAGG		
H-OT2-F:	GGTTGCCTTTCTCCTTGGT	403	HEK site4 OT2
H-OT2-R:	GTCCAGATTCTCTGGTGTGTG		
H-OT3-F:	GTATCCTGTTATCTGTTGCTGAAATG	409	HEK site4 OT3
H-OT3-R:	CAGGTGTGGAAGAGAAATGAAATG		
Sa5-F:	ATGTGGGCTGCCTAGAAAGG	297	Sa site5
Sa5-R:	CCCAGCCAAACTTGTCAACC		
Sa6-F:	TAGGATGCCCTACATCTGCTCTC	278	Sa site6
Sa6-R:	CGGAAAAGCGATCCAGGTGC		
Sa14-F:	CCCACAGACTAGCCAAGAAAC	401	Sa site14
Sa14-R:	CCTTCTCTTGAACCAACTCCTATAC		
Sa17-F:	GGCTGTCTTGGGATGTTTCT	271	Sa site17
Sa17-R:	GGCCAGTGGAGGATCTTTATTAG		

Supplementary Table 2. Primers used for genotyping in this study.

#### Supplementary sequence

### A3A:

MEASPASGPRHLMDPHIFTSNFNNGIGRHKTYLCYEVERLDNGTSVKMDQHRGFLHNQA KNLLCGFYGRHAELRFLDLVPSLQLDPAQIYRVTWFISWSPCFSWGCAGEVRAFLQENTH VRLRIFAARIYDYDPLYKEALQMLRDAGAQVSIMTYDEFKHCWDTFVDHQGCPFQPWDG LDEHSQALSGRLRAILQNQGN

### A3B:

MNPQIRNPMERMYRDTFYDNFENEPILYGRSYTWLCYEVKIKRGRSNLLWDTGVFRGQV YFKPQYHAEMCFLSWFCGNQLPAYKCFQITWFVSWTPCPDCVAKLAEFLSEHPNVTLTIS AARLYYYWERDYRRALCRLSQAGARVKIMDYEEFAYCWENFVYNEGQQFMPWYKFDE NYAFLHRTLKEILRYLMDPDTFTFNFNNDPLVLRRRQTYLCYEVERLDNGTWVLMDQHM GFLCNEAKNLLCGFYGRHAELRFLDLVPSLQLDPAQIYRVTWFISWSPCFSWGCAGEVRA FLQENTHVRLRIFAARIYDYDPLYKEALQMLRDAGAQVSIMTYDEFEYCWDTFVYRQGC PFQPWDGLEEHSQALSGRLRAILQNQGN

### A3Bctd:

MDPDTFTFNFNNDPLVLRRRQTYLCYEVERLDNGTWVLMDQHMGFLCNEAKNLLCGFY GRHAELRFLDLVPSLQLDPAQIYRVTWFISWSPCFSWGCAGEVRAFLQENTHVRLRIFAAR IYDYDPLYKEALQMLRDAGAQVSIMTYDEFEYCWDTFVYRQGCPFQPWDGLEEHSQALS GRLRAILQNQGN

## A3G:

MKPHFRNTVERMYRDTFSYNFYNRPILSRRNTVWLCYEVKTKGPSRPPLDAKIFRGQVYS ELKYHPEMRFFHWFSKWRKLHRDQEYEVTWYISWSPCTKCTRDMATFLAEDPKVTLTIF VARLYYFWDPDYQEALRSLCQKRDGPRATMKIMNYDEFQHCWSKFVYSQRELFEPWNN LPKYYILLHIMLGEILRHSMDPPTFTFNFNNEPWVRGRHETYLCYEVERMHNDTWVLLN QRRGFLCNQAPHKHGFLEGRHAELCFLDVIPFWKLDLDQDYRVTCFTSWSPCFSCAQEM AKFISKNKHVSLCIFTARIYDDQGRCQEGLRTLAEAGAKISIMTYSEFKHCWDTFVDHQGC PFQPWDGLDEHSQDLSGRLRAILQNQEN

## A3Gctd:

MDPPTFTFNFNNEPWVRGRHETYLCYEVERMHNDTWVLLNQRRGFLCNQAPHKHGFLE GRHAELCFLDVIPFWKLDLDQDYRVTCFTSWSPCFSCAQEMAKFISKNKHVSLCIFTARIY DDQGRCQEGLRTLAEAGAKISIMTYSEFKHCWDTFVDHQGCPFQPWDGLDEHSQDLSGR LRAILQNQEN

## Ade1 (EBV-BORF2):

MATTSHVEHELLSKLIDELKVKANSDPEADVLAGRLLHRLKAESVTHTVAEYLEVFSDKF YDEEFFQMHRDELETRVSAFAQSPAYERIVSSGYLSALRYYDTYLYVGRSGKQESVQHFY MRLAGFCASTTCLYAGLRAALQRARPEIESDMEVFDYYFEHLTSQTVCCSTPFMRFAGVE NSTLASCILTTPDLSSEWDVTQALYRHLGRYLFQRAGVGVGVTGAGQDGKHISLLMRMIN SHVEYHNYGCKRPVSVAAYMEPWHSQIFKFLETKLPENHERCPGIFTGLFVPELFFKLFRD TPWSDWYLFDPKDAGDLERLYGEEFEREYYRLVTAGKFCGRVSIKSLMFSIVNCAVKAGS PFILLKEACNAHFWRDLQGEAMNAANLCAEVLQPSRKSVATCNLANICLPRCLVNAPLAV RAQRADTQGDELLLALPRLSVTLPGEGAVGDGFSLARLRDATQCATFVVACSILQGSPTYD SRDMASMGLGVQGLADVFADLGWQYTDPPSRSLNKEIFEHMYFTALCTSSLIGLHTRKIF PGFKQSKYAGGWFHWHDWAGTDLSIPREIWSRLSERIVRDGLFNSQFIALMPTSGCAQVT GCSDAFYPFYANASTKVTNKEEALRPNRSFWRHVRLDDREALNLVGGRVSCLPEALRQR YLRFQTAFDYNQEDLIQMSRDRAPFVDQSQSHSLFLREEDAARASTLANLLVRSYELGLK TIMYYCRIEKAADLGVMECKASAALSVPREEQNERSPAEQMPPRPMEPAQVAGPVDIMSK GPGEGPGGWCVPGGLEVCYKYRQLFSEDDLLETDGFTERACESCQ

## Ade2 (KSHV-ORF61):

MSVRTFCQVHLGAVPPERRGSQVSAGQLSDFDMCAQSLIDFLKVRVGWDVRANAMAGR LWHQIMEARCPATLKQYLGIFRGVLGHRVESFIQKNIDALEDMLCAYRRSKAYEDTLNCG YLSAVRLYDTYVLRTMGTEPVYESVAQMFMRVSVFVACQCLEHECLYWLARDLIEDAKS VSEMAIVEYVFGYLAAQHVCCATPILRSAGVEGGQLASCFILQPSMMNEPGTLDALYHD MSPLLASKSGVGLDVTSFSHQKNIASCLKLVDAQVHYFNDNNIRPVGASAYMELWHSQIC DFLNAKLPENPDRCHSLFQGVCIPTLFFRMYEKDPSKLWYLFDPATAPNLIKLYGAAFDNE YERLVRAGKYVSCMPLKSMMFTLIHTIIKTGSPYVLLKEALNEHHWTDTQGMAINCSNLC AEIVQLPGRNTSVCNLANICLPKCLRTVESARVGTTDANRPFFCFEALGDAVRVAVLVINA CILGGSHPTPGVERGQKERSMGIGVQGLADVFAELGYGYLDAESAELDKNIFQSMYYTAV ETSHNLVLEGQGVPFHGWEVSNFAKGRFHWQTWEGEDASFVPRHRWDALGKSIAEHGIF NSQFLAVMPTAGTSQVTGYAESVYPFFANISSKVTNKEEVLRPNVTFFKKVLPDDLRVVRQ YGGDVSTFPKHHRERYRVFLTAFDYCPFKLLDRARARAPFVDQSQSMSFFLKEDRVRNAS YLRDLLLHGYRLGLKTLMYYCRVQKQSSLTALQCLADPGSPPHSGMKQDGAWLPGPKNP EEESCAADPECLVCQ

#### Ade3 (HIV-1-Vif):

MENRWQVMIVWQVDRMRIRTWKSLVKHHMYVSGKARGWFYRHHYESPHPRISSEVHIP LGDARLVITTYWGLHTGERDWHLGQGVSIEWRKKRYSTQVDPELADQLIHLYYFDCFSD SAIRKALLGHIVSPRCEYQAGHNKVGSLQYLALAALITPKKIKPPLPSVTKLTEDRWNKPQ KTKGHRGSHTMNGH

#### Ade4 (SIVmac239-Vif):

MEEEKRWIAVPTWRIPERLERWHSLIKYLKYKTKDLQKVCYVPHFKVGWAWWTCSRVIF PLQEGSHLEVQGYWHLTPEKGWLSTYAVRITWYSKNFWTDVTPNYADILLHSTYFPCFTA GEVRRAIRGEQLLSCCRFPRAHKYQVPSLQYLALKVVSDVRSQGENPTWKQWRRDNRR GLRMAKQNSRGDKQRGGKPPTKGANFPGLAKVLGILA

#### Ade5 (HSV-1-ICP6):

MASRPAASSPVEARAPVGGQEAGGPSAATQGEAAGAPLAHGHHVYCQRVNGVMVLSDK TPGSASYRISDSNFVQCGSNCTMIIDGDVVRGRPQDPGAAASPAPFVAVTNIGAGSDGGTA VVAFGGTPRRSAGTSTGTQTADVPTEALGGPPPPPRFTLGGGCCSCRDTRRRSAVFGGEGD PVGPAEFVSDDRSSDSDSDDSEDTDSETLSHASSDVSGGATYDDALDSDSSSDDSLQIDG PVCRPWSNDTAPLDVCPGTPGPGADAGGPSAVDPHAPTPEAGAGLAADPAVARDDAEGL SDPRPRLGTGTAYPVPLELTPENAEAVARFLGDAVNREPALMLEYFCRCAREETKRVPPRTF GSPPRLTEDDFGLLNYALVEMQRLCLDVPPVPPNAYMPYYLREYVTRLVNGFKPLVSRSA RLYRILGVLVHLRIRTREASFEEWLRSKEVALDFGLTERLREHEAQLVILAQALDHYDCLIH STPHTLVERGLQSALKYEEFYLKRFGGHYMESVFQMYTRIAGFLACRATRGMRHIALGRE GSWWEMFKFFFHRLYDHQIVPSTPAMLNLGTRNYYTSSCYLVNPQATTNKATLRAITSNV SAILARNGGIGLCVQAFNDSGPGTASVMPALKVLDSLVAAHNKESARPTGACVYLEPWHT DVRAVLRMKGVLAGEEAQRCDNIFSALWMPDLFFKRLIRHLDGEKNVTWTLFDRDTSMS LADFHGEEFEKLYQHLEVMGFGEQIPIQELAYGIVRSAATTGSPFVMFKDAVNRHYIYDTQ GAAIAGSNLCTEIVHPASKRSSGVCNLGSVNLARCVSRQTFDFGRLRDAVQACVLMVNIM IDSTLQPTPQCTRGNDNLRSMGIGMQGLHTACLKLGLDLESAEFQDLNKHIAEVMLLSAM KTSNALCVRGARPFNHFKRSMYRAGRFHWERFPDARPRYEGEWEMLRQSMMKHGLRN SQFVALMPTAASAQISDVSEGFAPLFTNLFSKVTRDGETLRPNTLLLKELERTFSGKRLLEV MDSLDAKQWSVAQALPCLEPTHPLRRFKTAFDYDQKLLIDLCADRAPYVDHSQSMTLYV TEKADGTLPASTLVRLLVHAYKRGLKTGMYYCKVRKATNSGVFGGDDNIVCMSCAL

#### Ade6 (EV71-2C):

MSASWLKKFNDMANAAKGLEWISSKISKFIDWLKEKIIPAAREKVEFLNNLKQLPLLENQI SNLEQSAASQEDLEAMFGNVSYLAHFCRKFQPLYATEAKRVYALEKRMNNYMQFKSKHR IEPVCLIIRGSPGTGKSLATGIIARAIADKYHSSVYSLPPDPDHFDGYKQQVVMVMDDLCQ NPDGKDISLFCQMVSTVDFIPPMASLEEKGVSFTSKFVIASTNSSNIIVPTVSDSDAIRRRFY MDCDIEVTDSYKTDLGRLDAGRAAKLCSENNTANFKRCSPLVCGKAIQLRDRKSKVRYS VDTVVSELIREYNNRSAIGNTIEALFQ

### Ade7 (HBV-HBx):

MAARLCCQLDPARDVLCLRPVGAESRGRPLAGPLGALPPASPPVLPTDHGAHLSLRGLPV CAFSSAGPCALRFTSARRMETTVNAHRNLPKVLHKRTLGLSAMSTTDLEAYFKDCVFNE WEELGEEVRLKVFVLGGCRHKLVCSPAPCNFFTSA

## AcrIIC1:

MANKTYKIGKNAGYDGCGLCLAAISENEAIKVKYLRDICPDYDGDDKAEDWLRWGTDS RVKAAALEMEQYAYTSVGMASCWEFVEL

#### AcrIIA5:

MAYGKSRYNSYRKRSFNRSNKQRREYAQEMDRLEKAFENLDGWYLSSMKDSAYKDFGK YEIRLSNHSADNKYHDLENGRLIVNIKASKLNFVDIIENKLDKIIEKIDKLDLDKYRFINATN LEHDIKCYYKGFKTKKEVI

#### **Raw Images for Supplementary Figure 2**



**Raw Images for Supplementary Figure 5a** 



**Raw Images for Supplementary Figure 5b** 

