

## Supplementary Materials for

### Improved base excision repair inhibition and bacteriophage Mu Gam protein yields C:G-to-T:A base editors with higher efficiency and product purity

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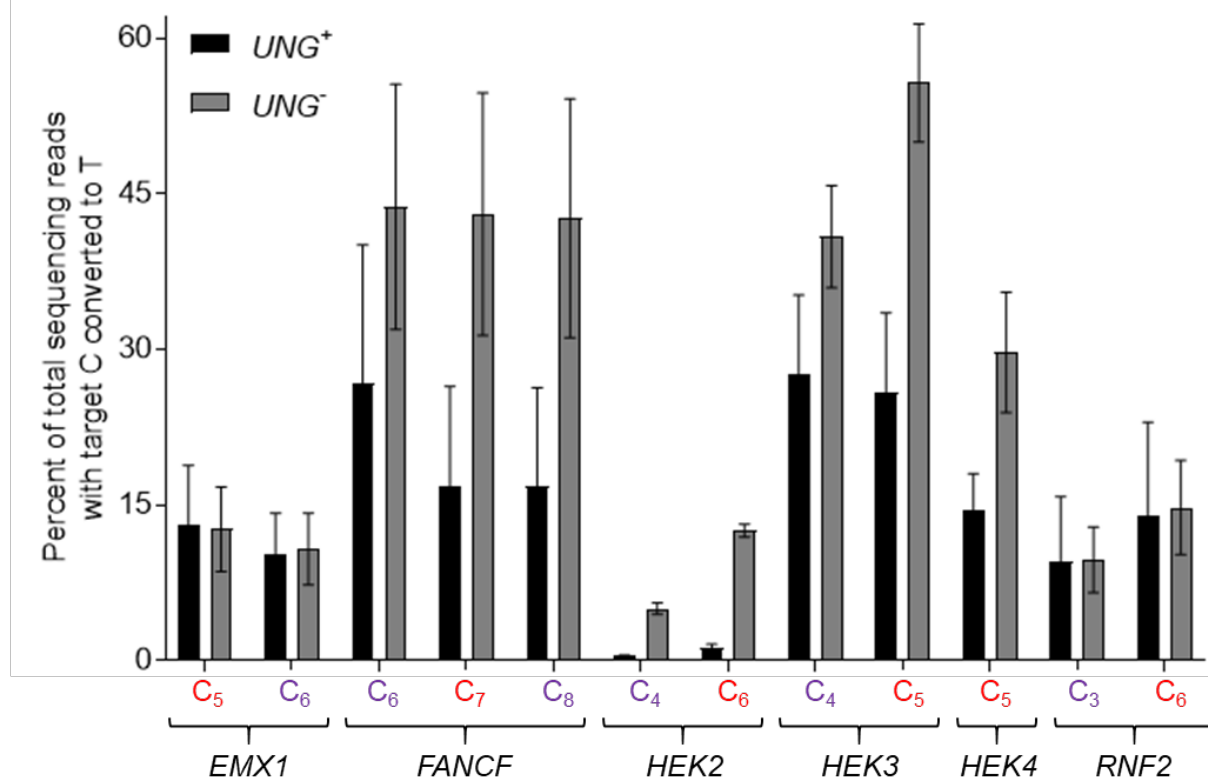
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## SUPPLEMENTARY FIGURES

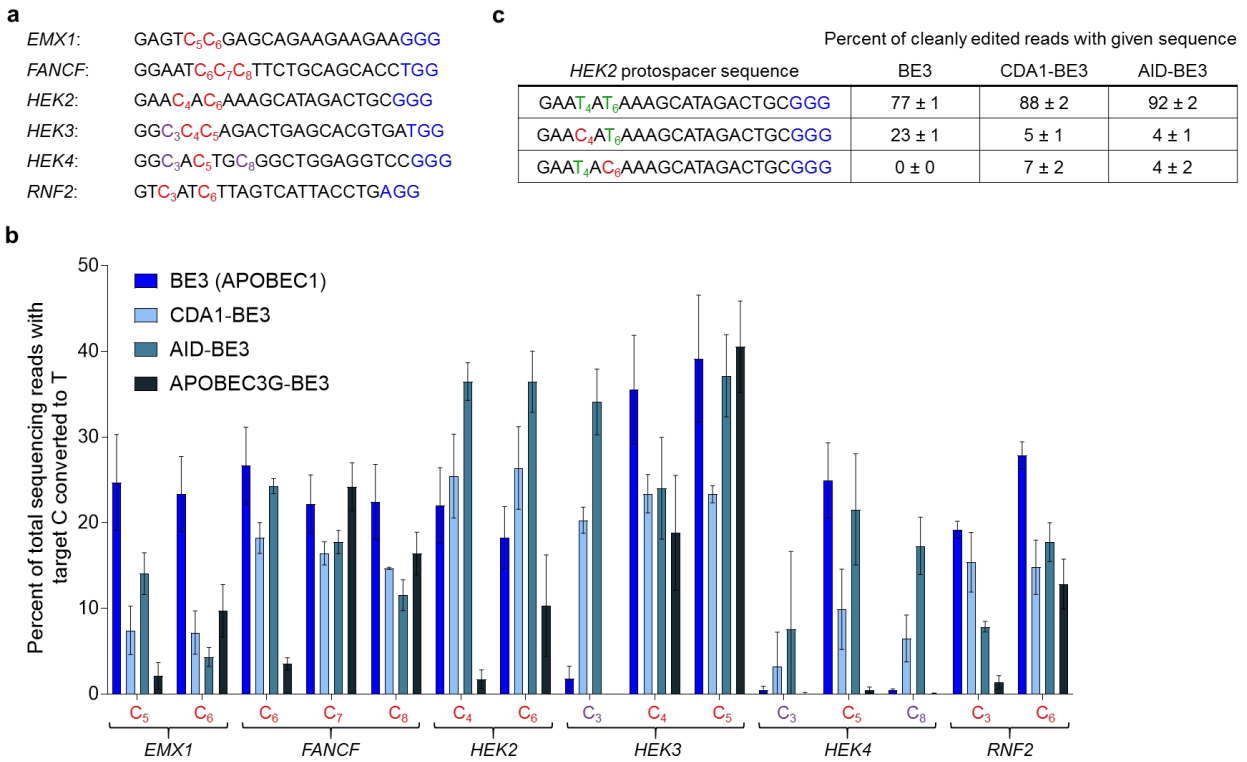
**a**

EMX1: GAGT<sub>C<sub>5</sub>C<sub>6</sub></sub>GAGCAGAAGAAGAAGGG  
 FANCF: GGAAT<sub>C<sub>6</sub>C<sub>7</sub>C<sub>8</sub></sub>TTCTGCAGCACCTGG  
 HEK2: GAAC<sub>C<sub>4</sub>A</sub>C<sub>6</sub>AAAGCATAGACTGCGGG  
 HEK3: GGCC<sub>C<sub>4</sub>C<sub>5</sub></sub>AGACTGAGCACGTGATGG  
 HEK4: GGCA<sub>C<sub>5</sub></sub>TGCGGCTGGAGGTCCGGG  
 RNF2: GTC<sub>C<sub>3</sub>A</sub>T<sub>C<sub>6</sub></sub>TTAGTCATTACCTGAGG

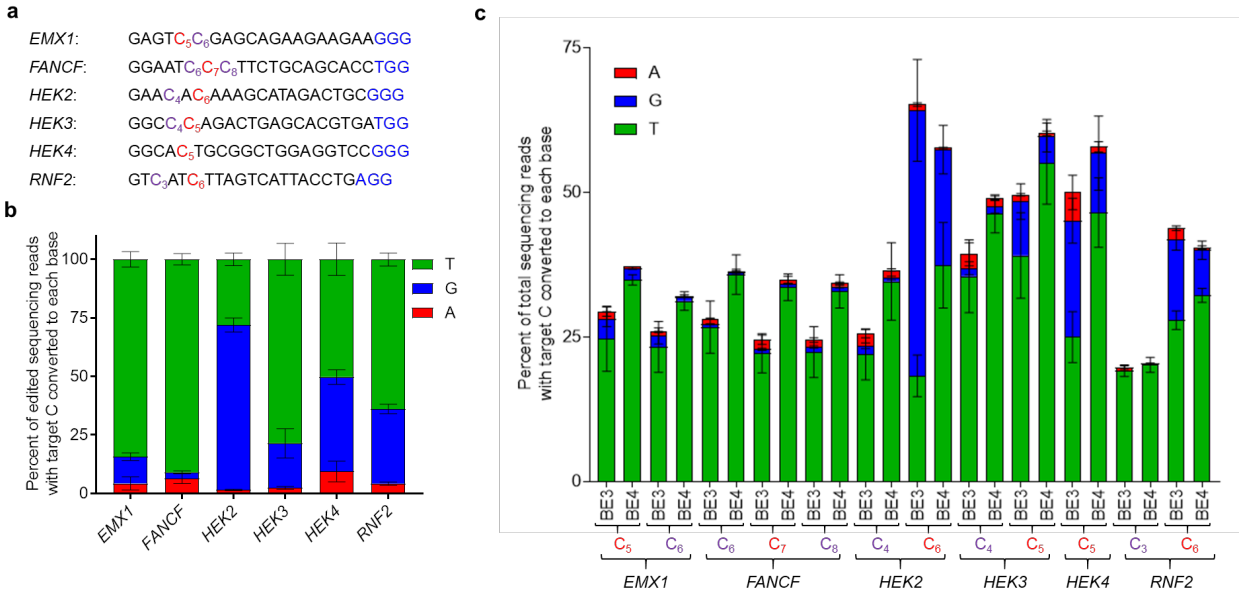
**b**



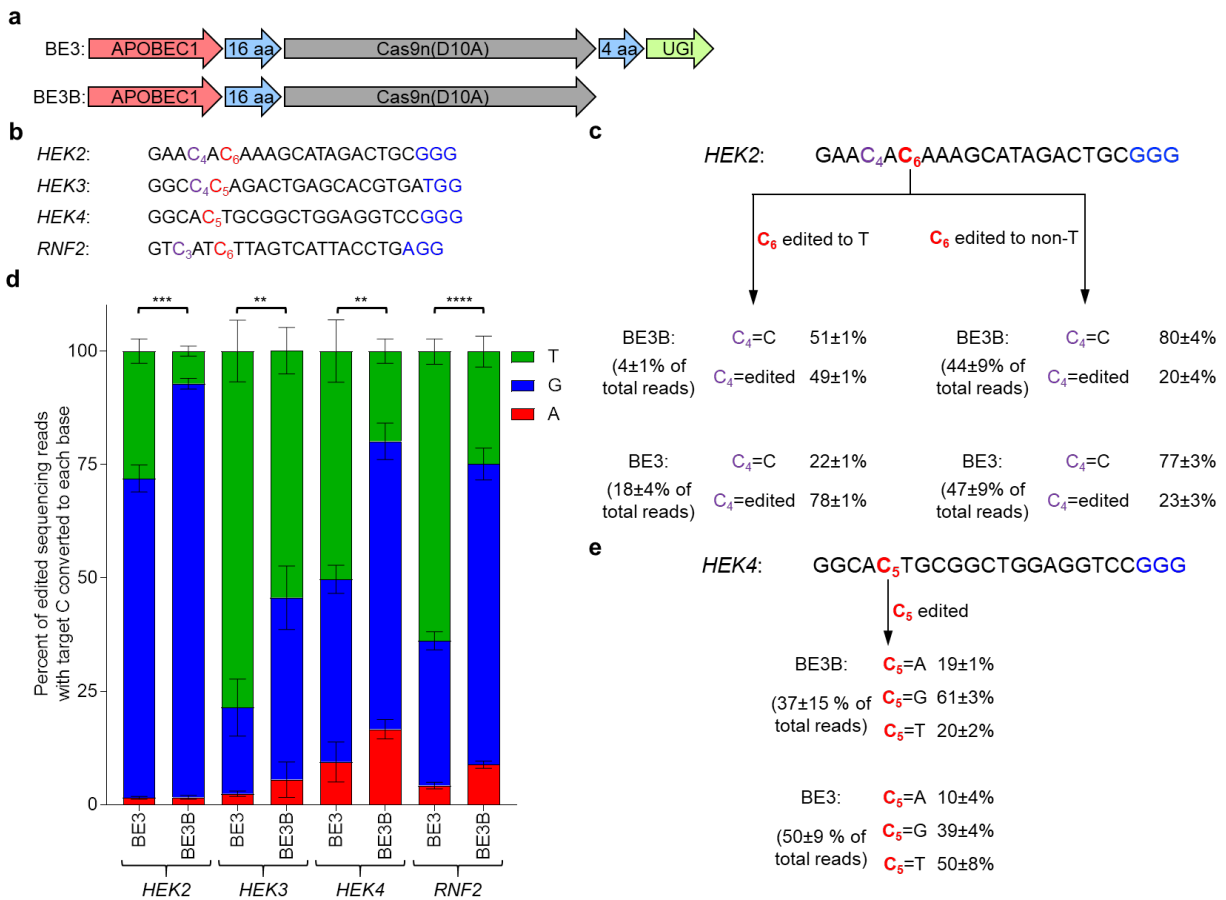
**Figure S1.** Base editing efficiencies in *UNG* knockout cells. (a) Protospacer and PAM (blue) sequences of genomic loci studied, with target Cs shown in red and purple. (b) HAP1 (*UNG*<sup>+</sup>) and HAP1 *UNG*<sup>-</sup> cells were treated with BE3 as described in the Methods. C-to-T base editing efficiencies are shown.



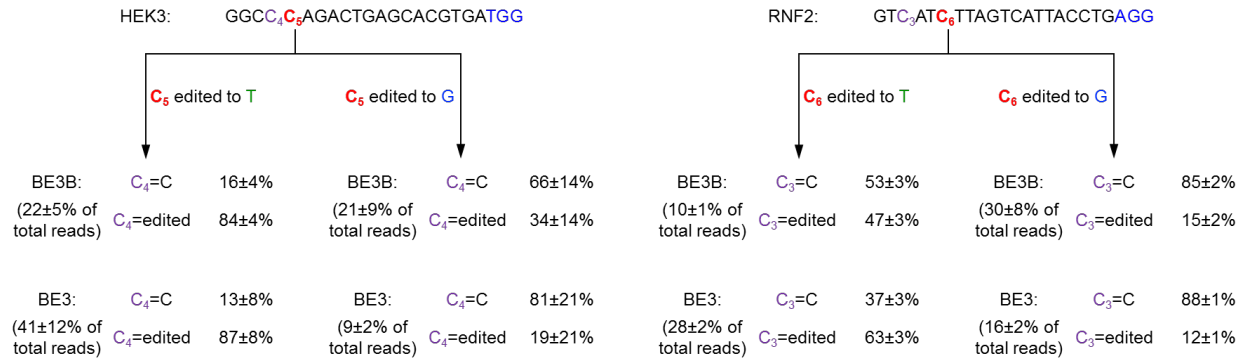
**Figure S2.** CDA1-BE3 and AID-BE3 edit Cs following target Gs more efficiently than BE3. **(a)** Protospacer and PAM (blue) sequences of genomic loci studied, with target Cs edited by BE3, CDA1-BE3, and AID-BE3 shown in red, and target Cs (following Gs) edited by CDA1-BE3 and AID-BE3 only shown in purple. **(b)** HEK293T cells were treated with BE3, CDA1-BE3, AID-BE3, or APOBEC3G-BE3 as described in the Methods. C-to-T base editing efficiencies are shown. **(c)** Individual DNA sequencing reads from HEK293T cells that were treated with BE3, CDA1-BE3, or AID-BE3 targeting the *HEK2* locus were binned according to the sequence of the protospacer and analyzed, revealing that > 85% of sequencing reads that have clean C to T edits by CDA1-BE3 and AID-BE3 have both Cs edited to T (Figure S1c).



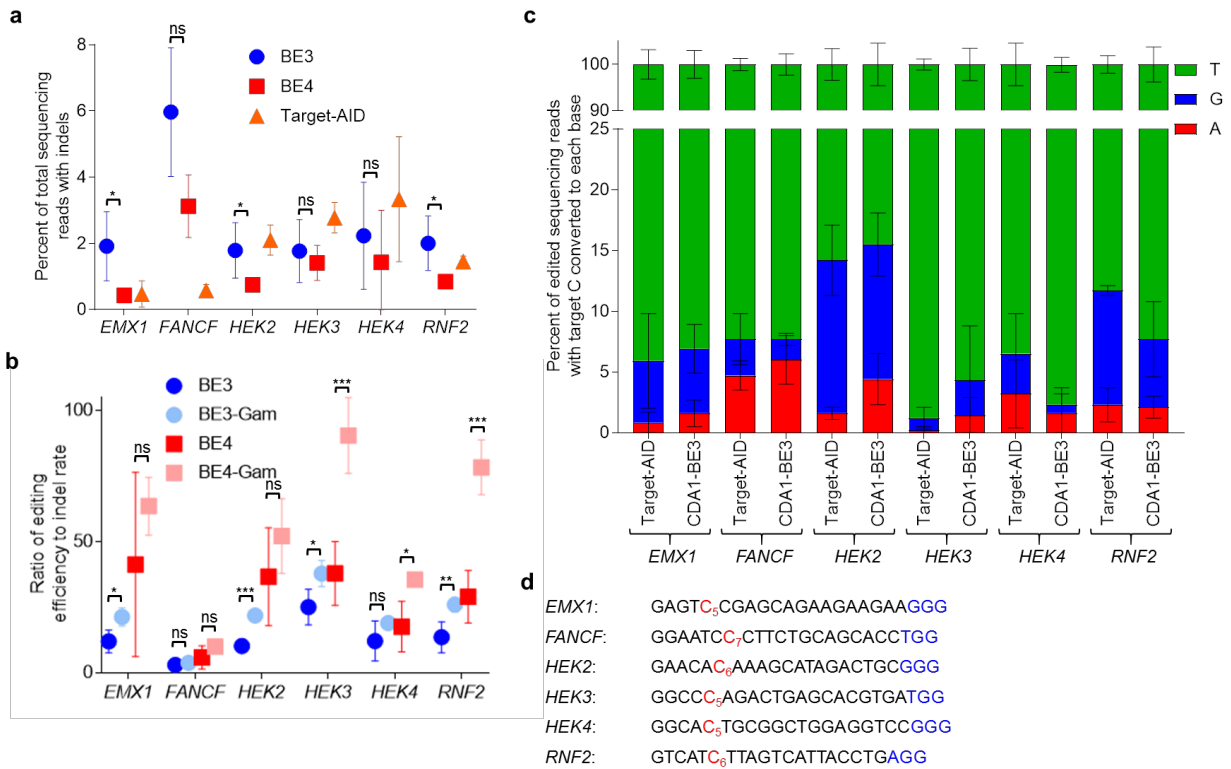
**Figure S3.** Uneven editing in sites with multiple editable Cs results in lower product purity. (a) Protospacers and PAM (blue) sequences of genomic loci studied, with the target Cs in (c) shown in purple and red, and target Cs in (b) shown in red. (b, c) HEK293T cells were treated with BE3 or BE4 as described in the Methods. The product distribution among edited DNA sequencing reads (reads in which the target C is mutated) is shown. C to non-T editing is more frequent when editing efficiencies are unequal for two Cs within the same locus. Values and error bars reflect the mean and s.d. of three independent biological replicates performed on different days.



**Figure S4.** Base editing of multiple Cs results in higher base editing product purity. **(a)** Architectures of BE3 and BE3B. **(b)** Protospacers and PAM (blue) sequences of genomic loci studied, with the target Cs that are investigated in (b) shown in red. **(c)** The HTS reads from HEK293T cells that were treated with BE3 or BE3B (which lacks UGI) targeting the *HEK2* locus were binned according to the identity of the primary target C at position 6. The resulting reads were then analyzed for the identity of the base at the secondary target C at position 4. C<sub>6</sub> is more likely to be incorrectly edited to a non-T when there is only a single editing event in that read. **(d)** HEK293T cells were treated with BE3 or BE3B (which lacks UGI) as described in the Methods. The product distribution among edited DNA sequencing reads (reads in which the target C is mutated) is shown. **(e)** The distribution of edited reads with A, G, and T at C<sub>5</sub> in cells treated with BE3 or BE3B targeting the *HEK4* locus (a site with only a single editable C) show that single G:U mismatches are processed via UNG-initiated base excision repair to give a mixture of products. Values and error bars reflect the mean and s.d. of three independent biological replicates performed on different days; \*\* $P < 0.01$ , \*\*\* $P < 0.001$ , \*\*\*\* $P < 0.0001$  by two-tailed Student's *t*-test.

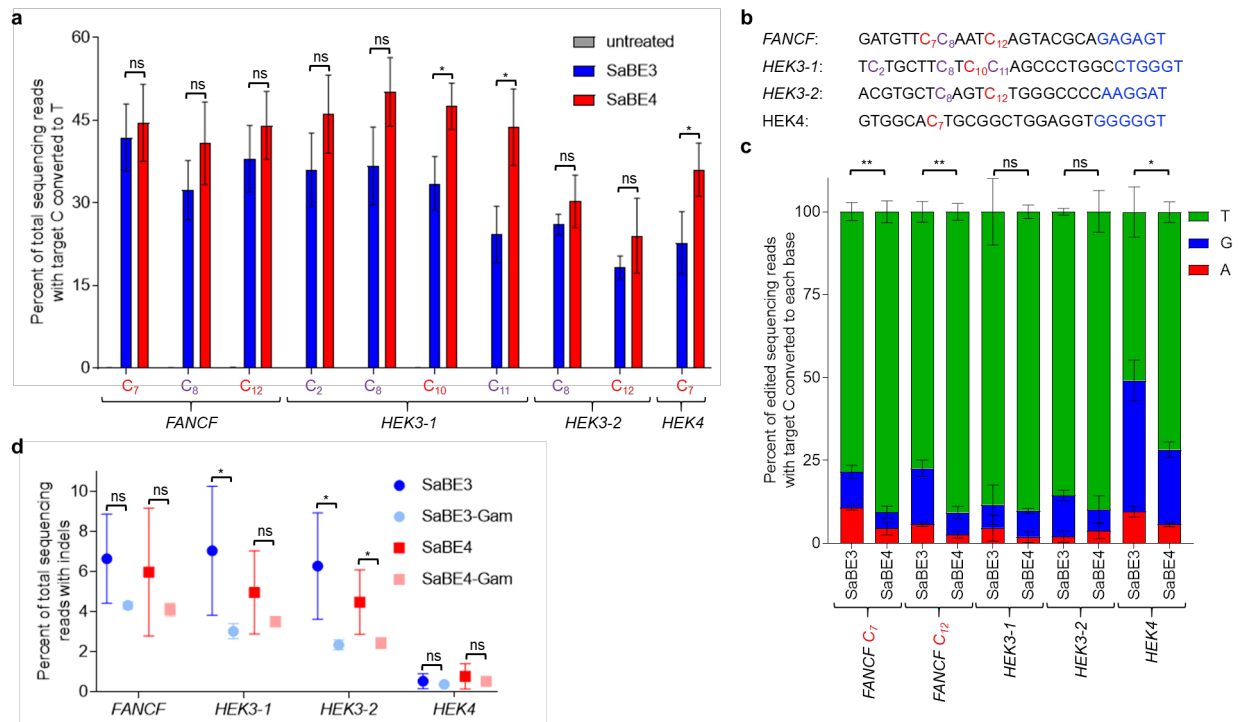


**Figure S5.** Base editing of multiple Cs results in higher base editing product purity at the *HEK3* and *RNF2* loci. DNA sequencing reads from HEK293T cells treated with BE3 or BE3B (without UGI) targeting the *HEK3* and *RNF2* loci were separated according to the identity of the base at the primary target C position (in red). The four groups of sequencing reads were then interrogated for the identity of the base at the secondary target C position (in purple). For BE3, when the primary target C (in red) is incorrectly edited to G, the secondary target C is more likely to remain C. Conversely, when the primary target C (in red) is converted to T, the secondary target C is more likely to also be edited to a T in the same sequencing read. These observations suggest that base editing product purity is impaired when only a single uracil intermediate is generated, perhaps reflecting more facile processing by UNG. Values and error bars reflect the mean and s.d. of three independent biological replicates performed on different days.



**Figure S6.** BE4 induces lower indel frequencies than BE3, and Target-AID exhibits similar product purities as CDA1-BE3. **(a)** HEK293T cells were treated with BE3, BE4, or Target-AID as described in the Methods. Frequency of indel formation (see Methods) is shown. **(b)** HEK293T cells were treated with BE3, BE3-Gam, BE4, or BE4-Gam as described in the Methods. The ratio of editing efficiency to indel rate is calculated by dividing the percent of total sequencing reads in which the target C (shown in red in Fig. 5b) is converted to T by the frequency of indel formation (see Methods). **(c)** HEK293T cells were treated with CDA1-BE3 or Target-AID as described in the Methods. The product distribution among edited DNA sequencing reads (reads in which the target C is mutated) is shown. **(d)** Protospacers and PAM (blue) sequences of genomic loci studied, with the target Cs that are investigated in (c) shown in red. Values and error bars reflect the mean and s.d. of three independent biological replicates performed on different days, except values and error bars of BE4 reflect the mean and s.d. of nine independent biological replicates performed on different days by two different researchers; ns:  $P \geq 0.05$ , \* $P < 0.05$ , \*\* $P < 0.01$ , \*\*\* $P < 0.001$  by two-tailed Student's *t*-test.





**Figure S7.** SaBE4 exhibits increased base editing yields and product purities compared to SaBE3. **(a)** HEK293T cells were treated with SaBE3 or SaBE4 as described in the Methods. The percentage of total DNA sequencing reads with Ts at the target positions indicated are shown. **(b)** Protospacers and PAM (blue) sequences of genomic loci studied, with the target Cs in (a) shown in purple and red, with target Cs that are investigated in (c) shown in red. **(c)** The product distribution among edited DNA sequencing reads (reads in which the target C is mutated) is shown. **(d)** Frequency of indel formation (see Methods) is shown. Values and error bars of SaBE3-Gam and SaBE4-Gam reflect the mean and s.d. of three independent biological replicates performed on different days. Values and error bars of SaBE3 and SaBE4 reflect the mean and s.d. of six independent biological replicates performed on different days by two different researchers; ns:  $P \geq 0.05$ , \* $P < 0.05$ , \*\* $P < 0.01$  by two-tailed Student's  $t$ -test.



**Table S2.** Base editing outcomes from treatment with BE3, CDA1-BE3, AID-BE3, or APOBEC3G-BE3 at the *FANCF* locus. The sequence of the protospacer is shown at the top, with the PAM in blue and the target bases in red with a subscripted number indicating their positions within the protospacer. Underneath the sequence are the percentages of total sequencing reads with the corresponding base. Cells were treated as described in the Methods. Values shown are from one representative experiment.

<i>FANCF</i>		G	G	A	A	T	C <sub>6</sub>	C <sub>7</sub>	C <sub>8</sub>	T	T	C <sub>11</sub>	T	G	C	A	G	C	A	C	C	T	G	G	
untreated	A	0.1	0.0	100.0	100.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	100.0	0.0	0.0	100.0	0.0	0.0	0.0	0.0	0.0	0.0
	C	0.0	0.0	0.0	0.0	0.0	100.0	100.0	100.0	0.0	0.0	100.0	0.0	0.0	100.0	0.0	0.0	100.0	0.0	100.0	100.0	0.0	0.0	0.0	0.0
	G	99.9	100.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	100.0	0.0	0.0	100.0	0.0	0.0	0.0	0.0	0.0	0.0	100.0	100.0
	T	0.0	0.0	0.0	0.0	100.0	0.0	0.0	0.0	100.0	100.0	0.0	100.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	100.0	0.0	0.0
BE3	A	0.0	0.1	100.0	100.0	0.0	1.0	1.4	1.4	0.0	0.0	0.2	0.0	0.0	0.0	100.0	0.0	0.0	100.0	0.0	0.0	0.0	0.0	0.0	0.0
	C	0.0	0.0	0.0	0.0	0.0	70.7	75.0	74.4	0.0	0.0	88.8	0.0	0.0	99.9	0.0	0.0	100.0	0.0	100.0	99.9	0.0	0.0	0.0	0.0
	G	100.0	99.9	0.0	0.0	0.0	0.4	0.8	0.9	0.0	0.0	0.1	0.0	100.0	0.0	0.0	100.0	0.0	0.0	0.0	0.0	0.0	0.0	99.9	100.0
	T	0.0	0.0	0.0	0.0	100.0	28.0	22.9	23.4	100.0	100.0	10.9	100.0	0.0	0.1	0.0	0.0	0.0	0.0	0.0	0.0	0.1	100.0	0.0	0.0
CDA1-BE3	A	0.1	0.1	100.0	100.0	0.0	0.3	0.6	0.3	0.0	0.0	0.0	0.0	0.1	0.0	100.0	0.1	0.0	100.0	0.0	0.0	0.0	0.1	0.1	0.1
	C	0.0	0.0	0.0	0.0	0.0	82.4	83.5	84.7	0.0	0.0	97.3	0.0	0.0	99.6	0.0	0.0	99.8	0.0	100.0	100.0	0.0	0.0	0.0	0.0
	G	99.9	99.9	0.0	0.0	0.0	0.1	0.3	0.2	0.0	0.0	0.0	0.0	99.9	0.0	0.0	99.9	0.0	0.0	0.0	0.0	0.0	0.0	99.9	99.9
	T	0.0	0.0	0.0	0.0	100.0	17.2	15.6	14.7	99.9	100.0	2.6	100.0	0.0	0.3	0.0	0.0	0.2	0.0	0.0	0.0	0.0	100.0	0.0	0.0
AID-BE3	A	0.0	0.0	99.9	99.9	0.1	0.2	0.6	0.3	0.0	0.0	0.0	0.0	0.1	0.0	99.9	0.1	0.1	100.0	0.0	0.0	0.0	0.1	0.1	0.1
	C	0.0	0.0	0.0	0.0	0.0	73.8	80.3	86.6	0.0	0.0	96.7	0.0	0.0	98.8	0.0	0.0	97.0	0.0	99.9	100.0	0.0	0.0	0.0	0.0
	G	99.9	99.9	0.0	0.0	0.0	0.8	0.5	0.4	0.0	0.0	0.0	0.0	99.9	0.0	0.0	99.9	0.0	0.0	0.0	0.0	0.0	0.0	99.9	99.9
	T	0.0	0.0	0.0	0.0	99.9	25.2	18.6	12.7	100.0	100.0	3.2	100.0	0.0	1.2	0.0	0.0	2.9	0.0	0.1	0.0	0.0	100.0	0.0	0.0
APOBEC3G-BE3	A	0.0	0.0	100.0	100.0	0.0	0.0	2.3	1.7	0.0	0.0	0.0	0.0	0.0	0.0	100.0	0.1	0.0	100.0	0.0	0.0	0.0	0.0	0.0	0.1
	C	0.0	0.0	0.0	0.0	0.0	96.1	66.3	68.3	0.0	0.0	99.6	0.0	0.0	99.9	0.0	0.0	100.0	0.0	100.0	100.0	0.0	0.0	0.0	0.0
	G	100.0	99.9	0.0	0.0	0.0	0.3	1.6	10.8	0.0	0.0	0.0	0.0	100.0	0.0	0.0	99.9	0.0	0.0	0.0	0.0	0.0	0.0	100.0	99.9
	T	0.0	0.0	0.0	0.0	100.0	3.6	27.2	19.2	100.0	100.0	0.1	100.0	0.0	0.1	0.0	0.0	0.0	0.0	0.0	0.0	0.0	100.0	0.0	0.0

**Table S3.** Base editing outcomes from treatment with BE3, CDA1-BE3, AID-BE3, or APOBEC3G-BE3 at the *HEK2* locus. The sequence of the protospacer is shown at the top, with the PAM in blue and the target bases in red with a subscripted number indicating their positions within the protospacer. Underneath the sequence are the percentages of total sequencing reads with the corresponding base. Cells were treated as described in the Methods. Values shown are from one representative experiment.

<i>HEK2</i>		G	A	A	C <sub>4</sub>	A	C <sub>6</sub>	A	A	A	G	C <sub>11</sub>	A	T	A	G	A	C	T	G	C	G	G	G	
untreated	A	0.0	100.0	100.0	0.0	100.0	0.0	100.0	100.0	100.0	0.0	0.0	100.0	0.0	100.0	0.0	100.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0
	C	0.0	0.0	0.0	100.0	0.0	99.9	0.0	0.0	0.0	0.0	100.0	0.0	0.0	0.0	0.0	0.0	100.0	0.0	0.0	0.0	99.9	0.0	0.0	0.0
	G	100.0	0.0	0.0	0.0	0.0	0.1	0.0	0.0	0.0	0.0	100.0	0.0	0.0	0.0	0.0	100.0	0.0	0.0	0.0	100.0	0.0	99.9	100.0	100.0
	T	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	100.0	0.0	0.0	0.0	0.0	100.0	0.0	0.0	0.1	0.0	0.0	0.0
BE3	A	0.1	100.0	100.0	1.3	99.9	0.7	100.0	100.0	100.0	0.0	0.0	100.0	0.0	100.0	0.0	100.0	0.1	0.0	0.0	0.0	0.0	0.0	0.0	0.0
	C	0.0	0.0	0.0	80.5	0.0	48.5	0.0	0.0	0.0	0.0	99.9	0.0	0.0	0.0	0.0	0.0	99.7	0.0	0.0	0.0	100.0	0.0	0.0	0.0
	G	99.9	0.0	0.0	0.9	0.1	36.0	0.0	0.0	0.0	100.0	0.0	0.0	0.0	0.0	0.0	100.0	0.0	0.0	0.0	100.0	0.0	100.0	99.9	100.0
	T	0.0	0.0	0.0	17.2	0.0	14.8	0.0	0.0	0.0	0.0	0.1	0.0	100.0	0.0	0.0	0.0	0.2	100.0	0.0	0.0	0.0	0.0	0.0	0.0
CDA1-BE3	A	0.0	99.9	99.9	9.6	99.9	1.8	100.0	100.0	100.0	0.0	0.2	100.0	0.0	100.0	0.0	100.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0
	C	0.0	0.0	0.0	70.3	0.0	73.5	0.0	0.0	0.0	0.0	90.7	0.0	0.0	0.0	0.0	0.0	100.0	0.0	0.0	99.9	0.0	0.0	0.0	0.0
	G	100.0	0.0	0.1	0.3	0.1	3.5	0.0	0.0	0.0	100.0	0.3	0.0	0.0	0.0	0.0	100.0	0.0	0.0	0.0	100.0	0.0	100.0	100.0	100.0
	T	0.0	0.0	0.0	19.8	0.0	21.2	0.0	0.0	0.0	0.0	8.8	0.0	100.0	0.0	0.0	0.0	0.0	100.0	0.0	0.0	0.1	0.0	0.0	0.0
AID-BE3	A	0.0	99.9	99.9	6.9	99.9	1.2	100.0	100.0	100.0	0.0	0.2	100.0	0.0	100.0	0.0	100.0	0.1	0.0	0.0	0.0	0.0	0.0	0.0	0.0
	C	0.0	0.0	0.0	54.5	0.0	52.4	0.0	0.0	0.0	0.0	83.8	0.0	0.0	0.0	0.0	0.0	99.7	0.0	0.0	99.8	0.0	0.0	0.0	0.0
	G	99.9	0.0	0.1	0.7	0.1	6.1	0.0	0.0	0.0	99.9	0.6	0.0	0.0	0.0	0.0	100.0	0.0	0.0	100.0	0.0	100.0	100.0	100.0	
	T	0.1	0.1	0.0	37.9	0.0	40.3	0.0	0.0	0.0	0.1	15.5	0.0	100.0	0.0	0.0	0.0	0.2	99.9	0.0	0.2	0.0	0.0	0.0	0.0
APOBEC3G-BE3	A	0.0	100.0	100.0	0.1	100.0	0.1	100.0	100.0	100.0	0.0	0.0	100.0	0.0	100.0	0.0	100.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0
	C	0.0	0.0	0.0	97.8	0.0	80.3	0.0	0.0	0.0	0.0	99.9	0.0	0.0	0.0	0.0	0.0	100.0	0.0	0.0	99.9	0.0	0.0	0.0	0.0
	G	100.0	0.0	0.0	0.1	0.0	5.9	0.0	0.0	0.0	100.0	0.0	0.0	0.0	0.0	0.0	100.0	0.0	0.0	100.0	0.0	100.0	100.0	100.0	
	T	0.0	0.0	0.0	2.0	0.0	13.7	0.0	0.0	0.0	0.0	0.0	0.0	100.0	0.0	0.0	0.0	0.0	100.0	0.0	0.1	0.0	0.0	0.0	0.0

**Table S4.** Base editing outcomes from treatment with BE3, CDA1-BE3, AID-BE3, or APOBEC3G-BE3 at the *HEK3* locus. The sequence of the protospacer is shown at the top, with the PAM in blue and the target bases in red with a subscripted number indicating their positions within the protospacer. Underneath the sequence are the percentages of total sequencing reads with the corresponding base. Cells were treated as described in the Methods. Values shown are from one representative experiment.

<i>HEK3</i>		G	G	C <sub>3</sub>	C <sub>4</sub>	C <sub>5</sub>	A	G	A	C <sub>6</sub>	T	G	A	G	C	A	C	G	T	G	A	T	G	G	
untreated	A	0.0	0.1	0.0	0.0	0.0	99.9	0.0	100.0	0.0	0.0	0.0	99.9	0.0	0.0	99.9	0.0	0.0	0.0	0.0	99.9	0.0	0.0	0.0	0.1
	C	0.0	0.0	100.0	99.9	99.9	0.0	0.0	0.0	100.0	0.0	0.0	0.0	0.0	100.0	0.0	100.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0
	G	100.0	99.9	0.0	0.0	0.0	0.0	100.0	0.0	0.0	0.0	99.9	0.0	99.9	0.0	0.0	0.0	99.9	0.0	100.0	0.0	0.0	100.0	99.9	
	T	0.0	0.0	0.0	0.0	0.1	0.0	0.0	0.0	0.0	100.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	100.0	0.0	0.0	100.0	0.0	
BE3	A	0.0	0.0	0.0	0.8	1.1	100.0	0.0	100.0	0.4	0.0	0.0	100.0	0.2	0.0	100.0	0.0	0.0	0.0	0.0	0.0	0.0	100.0	0.0	0.0
	C	0.0	0.0	98.6	67.4	58.1	0.0	0.0	0.0	98.3	0.0	0.0	0.0	0.0	100.0	0.0	99.7	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0
	G	100.0	100.0	0.0	0.4	8.9	0.0	100.0	0.0	0.6	0.0	100.0	0.0	99.8	0.0	0.0	0.0	100.0	0.0	100.0	0.0	100.0	0.0	99.9	100.0
	T	0.0	0.0	1.3	31.4	31.9	0.0	0.0	0.0	0.7	100.0	0.0	0.0	0.0	0.0	0.0	0.3	0.0	100.0	0.0	0.0	0.0	100.0	0.1	0.0
CDA1-BE3	A	0.1	0.0	0.8	0.6	0.0	100.0	0.0	99.9	0.4	0.0	0.0	99.9	0.0	0.0	100.0	0.0	0.0	0.0	0.0	0.0	99.9	0.0	0.1	0.1
	C	0.0	0.0	79.4	73.6	73.4	0.0	0.0	0.0	91.0	0.0	0.0	0.0	0.0	99.9	0.0	100.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0
	G	99.9	100.0	0.0	0.0	2.1	0.0	100.0	0.0	0.3	0.0	99.9	0.0	100.0	0.0	0.0	0.0	99.9	0.0	99.9	0.1	0.0	99.9	99.9	
	T	0.1	0.0	19.8	25.9	24.4	0.0	0.0	0.0	8.3	100.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	99.9	0.0	0.0	100.0	0.0	0.0	
AID-BE3	A	0.1	0.3	1.0	0.7	0.3	99.9	0.0	100.0	1.6	0.0	0.0	100.0	0.0	0.0	100.0	0.0	0.0	0.0	0.0	0.0	100.0	0.0	0.0	0.0
	C	0.0	0.0	63.9	75.4	60.2	0.0	0.0	0.0	86.6	0.0	0.0	0.0	0.0	98.9	0.0	99.8	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0
	G	99.8	99.7	0.1	0.4	1.0	0.0	100.0	0.0	1.2	0.0	100.0	0.0	100.0	0.0	0.0	0.0	100.0	0.0	100.0	0.0	100.0	0.0	100.0	99.9
	T	0.0	0.0	35.0	23.5	38.5	0.0	0.0	0.0	10.6	100.0	0.0	0.0	0.0	1.1	0.0	0.2	0.0	100.0	0.0	0.0	100.0	0.0	0.0	0.0
APOBEC3G-BE3	A	0.0	0.0	0.0	0.6	3.1	100.0	0.0	100.0	0.0	0.0	0.0	100.0	0.0	0.0	100.0	0.0	0.0	0.0	0.0	100.0	0.0	0.0	0.0	0.0
	C	0.0	0.0	99.9	86.7	33.9	0.0	0.0	0.0	100.0	0.0	0.0	0.0	0.0	100.0	0.0	100.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0
	G	100.0	99.9	0.0	1.4	28.6	0.0	100.0	0.0	0.0	0.0	100.0	0.0	100.0	0.0	0.0	0.0	100.0	0.0	100.0	0.0	100.0	0.0	100.0	100.0
	T	0.0	0.0	0.0	11.3	34.4	0.0	0.0	0.0	0.0	100.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	100.0	0.0	0.0	100.0	0.0	0.0	0.0

**Table S5.** Base editing outcomes from treatment with BE3, CDA1-BE3, AID-BE3, or APOBEC3G-BE3 at the *HEK4* locus. The sequence of the protospacer is shown at the top, with the PAM in blue and the target bases in red with a subscripted number indicating their positions within the protospacer. Underneath the sequence are the percentages of total sequencing reads with the corresponding base. Cells were treated as described in the Methods. Values shown are from one representative experiment.

<i>HEK4</i>		G	G	C <sub>2</sub>	A	C <sub>5</sub>	T	G	C <sub>6</sub>	G	G	C	T	G	G	A	G	G	T	G	G	G	G	G	
untreated	A	0.0	0.1	0.0	100.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0
	C	0.0	0.0	100.0	0.0	100.0	0.0	0.0	99.9	0.0	0.0	100.0	0.0	0.0	0.0	0.1	0.0	0.0	0.2	0.0	0.0	0.0	0.0	0.0	0.0
	G	99.9	99.9	0.0	0.0	0.0	0.0	100.0	0.0	100.0	100.0	0.0	0.0	0.0	100.0	100.0	0.0	100.0	100.0	0.4	99.9	99.9	100.0	99.9	99.9
	T	0.0	0.0	0.0	0.0	0.0	100.0	0.0	0.0	0.0	0.0	0.0	100.0	0.0	0.0	0.0	0.0	0.0	0.0	99.5	0.1	0.0	0.0	0.0	0.0
BE3	A	0.1	0.0	0.1	99.9	8.4	0.1	0.0	0.1	0.0	0.1	0.0	0.0	0.0	0.0	0.0	99.8	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0
	C	0.0	0.0	99.0	0.0	41.9	0.0	0.0	99.3	0.0	0.0	99.8	0.0	0.0	0.0	0.1	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0
	G	99.9	99.9	0.0	0.0	24.5	0.0	100.0	0.0	0.0	100.0	99.9	0.0	0.0	100.0	100.0	0.1	100.0	100.0	0.0	100.0	100.0	0.0	100.0	100.0
	T	0.0	0.0	0.9	0.0	25.2	99.9	0.0	0.5	0.0	0.0	0.2	100.0	0.0	0.0	0.0	0.0	0.0	0.0	100.0	0.0	0.0	100.0	0.0	0.0
CDA1-BE3	A	0.2	0.1	0.5	100.0	0.5	0.0	0.0	0.2	0.0	0.0	0.1	0.0	0.0	0.0	0.0	99.9	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0
	C	0.0	0.0	91.3	0.0	87.5	0.0	0.0	93.4	0.0	0.0	97.0	0.0	0.0	0.0	0.1	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0
	G	99.8	99.9	0.3	0.0	0.0	0.0	100.0	0.1	100.0	100.0	0.0	0.0	0.0	100.0	100.0	0.0	100.0	100.0	0.0	100.0	100.0	0.0	100.0	100.0
	T	0.0	0.0	7.8	0.0	12.0	100.0	0.0	6.3	0.0	0.0	2.9	100.0	0.0	0.0	0.0	0.0	0.0	0.0	99.9	0.0	0.0	0.0	0.0	0.0
AID-BE3	A	0.3	0.4	0.3	100.0	0.9	0.0	0.0	0.9	0.0	0.0	0.1	0.0	0.0	0.0	0.0	99.8	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0
	C	0.0	0.0	81.5	0.0	71.3	0.0	0.0	80.7	0.0	0.0	97.9	0.1	0.0	0.0	0.2	0.0	0.0	0.0	0.1	0.0	0.0	0.0	0.0	0.0
	G	99.7	99.6	0.1	0.0	0.7	0.0	100.0	0.1	100.0	100.0	0.0	0.0	0.0	99.9	100.0	0.0	100.0	100.0	0.2	99.9	100.0	100.0	100.0	99.9
	T	0.0	0.0	18.0	0.0	27.1	100.0	0.0	18.3	0.0	0.0	2.0	99.9	0.0	0.0	0.0	0.0	0.0	0.0	99.8	0.0	0.0	0.0	0.0	0.1
APOBEC3G-BE3	A	0.1	0.0	0.0	99.9	0.1	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	99.7	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0
	C	0.0	0.0	99.9	0.0	99.4	0.0	0.0	99.9	0.0	0.0	100.0	0.0	0.0	0.0	0.2	0.0	0.0	0.0	0.1	0.0	0.0	0.0	0.0	0.0
	G	99.9	99.9	0.0	0.0	0.4	0.0	99.9	0.1	100.0	99.9	0.0	0.0	99.9	100.0	0.1	100.0	99.9	0.0	99.9	100.0	100.0	100.0	100.0	99.9
	T	0.0	0.0	0.0	0.0	0.2	99.9	0.0	0.1	0.0	0.1	0.0	99.9	0.1	0.0	0.0	0.0	0.1	99.9	0.0	0.0	0.0	0.0	0.0	0.1

**Table S6.** Base editing outcomes from treatment with BE3, CDA1-BE3, AID-BE3, or APOBEC3G-BE3 at the *RNF2* locus. The sequence of the protospacer is shown at the top, with the PAM in blue and the target bases in red with a subscripted number indicating their positions within the protospacer. Underneath the sequence are the percentages of total sequencing reads with the corresponding base. Cells were treated as described in the Methods. Values shown are from one representative experiment.

<i>RNF2</i>	G	T	C <sub>5</sub>	A	T	C <sub>6</sub>	T	T	A	G	T	C <sub>12</sub>	G	T	T	A	C	C	T	G	A	G	G	
untreated	A	0.0	0.0	0.0	100.0	0.0	0.0	0.0	100.0	0.0	0.0	0.0	100.0	0.0	0.0	100.0	0.0	0.0	0.0	0.0	100.0	0.0	0.0	0.0
	C	0.0	0.0	99.9	0.0	0.0	99.9	0.0	0.0	0.0	0.0	100.0	0.0	0.0	0.0	0.0	100.0	100.0	0.0	0.0	0.0	0.0	0.0	0.0
	G	100.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	100.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	100.0	0.0	100.0	100.0
	T	0.0	100.0	0.1	0.0	100.0	0.0	100.0	100.0	0.0	0.0	100.0	0.0	0.0	100.0	100.0	0.0	0.0	0.0	100.0	0.0	0.0	0.0	0.0
BE3	A	0.0	0.0	0.3	99.9	0.1	1.6	0.1	0.0	100.0	0.0	0.0	0.1	100.0	0.0	0.0	100.0	0.0	0.0	0.0	0.0	100.0	0.0	0.0
	C	0.0	0.0	81.1	0.0	0.0	59.7	0.0	0.0	0.0	0.0	96.6	0.0	0.0	0.0	0.0	99.9	99.9	0.0	0.0	0.0	0.0	0.0	0.0
	G	99.9	0.0	0.0	0.0	0.0	12.6	0.0	0.0	0.0	100.0	0.0	0.1	0.0	0.0	0.0	0.0	0.0	0.0	0.0	99.9	0.0	99.9	100.0
	T	0.0	100.0	18.6	0.0	99.9	26.1	99.9	100.0	0.0	0.0	100.0	3.3	0.0	100.0	100.0	0.0	0.0	0.1	100.0	0.0	0.0	0.0	0.0
CDA1-BE3	A	0.0	0.0	0.3	100.0	0.0	0.3	0.0	0.0	100.0	0.0	0.0	0.0	100.0	0.0	0.0	100.0	0.0	0.0	0.0	0.0	100.0	0.0	0.0
	C	0.0	0.0	88.1	0.0	0.0	87.8	0.0	0.0	0.0	0.0	99.1	0.0	0.0	0.0	0.0	99.9	99.9	0.0	0.0	0.0	0.0	0.0	0.0
	G	100.0	0.0	0.0	0.0	0.0	0.4	0.0	0.0	0.0	100.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	100.0	0.0	100.0	100.0
	T	0.0	100.0	11.6	0.0	100.0	11.5	100.0	100.0	0.0	0.0	100.0	0.9	0.0	100.0	100.0	0.0	0.1	0.1	100.0	0.0	0.0	0.0	0.0
AID-BE3	A	0.0	0.0	0.1	100.0	0.1	0.1	0.0	0.0	100.0	0.0	0.0	0.0	100.0	0.0	0.0	100.0	0.0	0.0	0.0	0.0	100.0	0.0	0.0
	C	0.0	0.0	92.7	0.0	0.0	81.5	0.0	0.0	0.0	0.0	99.8	0.0	0.0	0.0	0.0	98.7	99.8	0.0	0.0	0.0	0.0	0.0	0.0
	G	100.0	0.0	0.0	0.0	0.0	3.2	0.0	0.0	0.0	99.9	0.0	0.0	0.0	0.0	0.0	0.1	0.0	0.0	0.0	99.9	0.0	99.9	100.0
	T	0.0	100.0	7.2	0.0	99.9	15.2	100.0	100.0	0.0	0.0	100.0	0.1	0.0	100.0	100.0	0.0	1.2	0.2	100.0	0.0	0.0	0.0	0.0
APOBEC3G-BE3	A	0.0	0.0	0.0	100.0	0.0	0.0	0.0	0.0	100.0	0.0	0.0	0.0	100.0	0.0	0.0	100.0	0.0	0.0	0.0	0.0	100.0	0.0	0.0
	C	0.0	0.0	98.2	0.0	0.0	82.8	0.0	0.0	0.0	0.0	99.6	0.0	0.0	0.0	0.0	99.8	99.8	0.0	0.0	0.0	0.0	0.0	0.0
	G	100.0	0.0	0.0	0.0	0.0	3.4	0.0	0.0	0.0	99.9	0.0	0.1	0.0	0.0	0.0	0.0	0.0	0.0	0.0	99.9	0.0	100.0	100.0
	T	0.0	100.0	1.8	0.0	100.0	13.8	100.0	100.0	0.0	0.0	100.0	0.2	0.0	100.0	100.0	0.0	0.2	0.2	100.0	0.0	0.0	0.0	0.0

## SUPPLEMENTARY NOTES

**Note S1.** Python script to detect linkage disequilibrium in base editing outcomes at target sites with multiple target cytidines. An example script is shown here for a single target site (RNF2). Multiple variables were altered for each site including: indir, outdir, 7 nucleotide sequences used to define the protospacer as well as the position within the protospacer with the highest frequency of base editing byproducts.

```
%matplotlib inline
import numpy as np
import scipy as sp
import matplotlib as mpl
import matplotlib.cm as cm
import matplotlib.pyplot as plt
import pandas as pd
pd.set_option('display.width', 500)
pd.set_option('display.max_columns', 100)
pd.set_option('display.notebook_repr_html', True)
import seaborn as sns
sns.set_style("whitegrid")
sns.set_context("poster")
import requests
import time from bs4
import BeautifulSoup
import regex
import re
import os
from Bio import SeqIO
import Bio
from Bio import motifs
#BE processivity analysis, RNF2
site='_RNF2'
indir='/Users/michaelpacker/Desktop/Liu_Lab/MiSeqData/ACK060717/fastq/RNF2/'
outdir='/Users/michaelpacker/Desktop/Liu_Lab/MiSeqData/ACK060717/fastq/RNF2/'
filenames=os.listdir(indir)
for i in range(len(filenames)):
    seqs={}
    if filenames[i][-5:]=='fastq':
        for record in SeqIO.parse(indir+filenames[i], "fastq") :
            #split prior to spacer window
            split1=record.seq.tostring().split('CTTGGCA')
            if len(split1)==2:
                #take second item in first split, and split again at the sequence right after the protospacer and take first item
                split2=split1[1].split('AGGTGTT')[0]
                #keep only 20 basepair long protospacers
                if (len(split2)==20) & (split2.find('N')== -1):
                    seqs[record.id]=split2
            #generate dataframe with protospacer sequence column and identity of the nucleotide at the position within the protospacer with the highest frequency of editing byproducts ("DirtyPosition")
            frame=pd.DataFrame({'Spacer':seqs.values(), 'DirtyPosition':[x[5] for x in seqs.values()]}, index=seqs.keys())
            #generate a biopython motif for all the protospacer sequences
            MotifAll=motifs.create(frame.Spacer.values)
            #generate a biopython motif for all protospacer sequences with (A,C,G,T) at the DirtyPosition if no sequences have an (A,C,G,T) at the DirtyPosition save a placeholder motif with a single polyA sequence
            if len(frame[frame.DirtyPosition=='A'])>0:
```



```

        MotifA=motifs.create(frame[frame.DirtyPosition=='A'].Spacer.values)
    else:
        MotifA=motifs.create(['A'*20])
    if len(frame[frame.DirtyPosition=='C'])>0:
        MotifC=motifs.create(frame[frame.DirtyPosition=='C'].Spacer.values)
    else:
        MotifC=motifs.create(['A'*20])
    if len(frame[frame.DirtyPosition=='G'])>0:
        MotifG=motifs.create(frame[frame.DirtyPosition=='G'].Spacer.values)
    else:
        MotifG=motifs.create(['A'*20])
    if len(frame[frame.DirtyPosition=='T'])>0:
        MotifT=motifs.create(frame[frame.DirtyPosition=='T'].Spacer.values)
    else:
        MotifT=motifs.create(['A'*20])
    #Save motif counts in 10 DataFrames for the 4 groups and the total pool of sequences (both raw and normalized for each)
    a=pd.DataFrame(MotifA.counts, index=['A'+str(s) for s in range(20)])
    A=pd.DataFrame(MotifA.counts.normalize(), index=['A'+str(s) for s in range(20)])
    c=pd.DataFrame(MotifC.counts, index=['C'+str(s) for s in range(20)])
    C=pd.DataFrame(MotifC.counts.normalize(), index=['C'+str(s) for s in range(20)])
    g=pd.DataFrame(MotifG.counts, index=['G'+str(s) for s in range(20)])
    G=pd.DataFrame(MotifG.counts.normalize(), index=['G'+str(s) for s in range(20)])
    t=pd.DataFrame(MotifT.counts, index=['T'+str(s) for s in range(20)])
    T=pd.DataFrame(MotifT.counts.normalize(), index=['T'+str(s) for s in range(20)])
    All=pd.DataFrame(MotifAll.counts, index=['All'+str(s) for s in range(20)])
    ALL=pd.DataFrame(MotifAll.counts.normalize(), index=['All'+str(s) for s in range(20)])
    #export csv files for the motif counts (both raw and normalized)
    All.append(a).append(c).append(g).append(t).to_csv(outdir+filenames[i].strip('.fastq')+'RawMotifs.csv')
    ALL.append(A).append(C).append(G).append(T).to_csv(outdir+filenames[i].strip('.fastq')+'NormalizedMotifs.csv')
    #export csv file with abundance of each unique protospacer sequence
    Counts=pd.DataFrame(seqs.items(), columns=['ID', 'Window']).groupby('Window').count().sort('ID', ascending=False)
    Counts.to_csv(outdir+filenames[i].strip('.fastq')+'.csv')

```

## SUPPLEMENTARY SEQUENCES

*Amino Acid Sequences of CDA1-BE3, AID-BE3, BE3-Gam, SaBE3-Gam, BE4, BE4-Gam, SaBE4, and SaBE4-Gam*

### **CDA1-BE3:**

MTDAEYVRIHEKLDIYTFKKQFFNNKKS VSHRCYVLFELKRRGERRACFWGYAVNKPQSGTERGIHAEIF  
SIRKVEEYLRDNPQGFTINWYSSWSPCADCAEKILEWYNQELRGNGHTLKIWACKLYYEKNARNQIGLW  
NLRDNGVGLNVMVSEHYQCCRKIFIQSSHNQLNENRWLEKTLKRAEKRRSELSIMIQVKILHTTKSPAVSG  
SETPGTSESATPESDKKYSIGLAIGTNSVGWAVITDEYKVPSPKFKVLGNTDRHSIKKNLIGALLFDSGETA  
EATRLKRTARRRYTRRKNRICYLQEIFS NEMAKVDDSFHRL EESFLVEEDKKHERHPIFGNIVDEVAYHE  
KYPTIYHLRKKLVDSTDKADLRILIYALAHMIKFRGHFLIEGDLNPDNSDVDFKLFQILVQTYNQLFEENPINA  
SGVDAKAILSARLSKSRLENLIAQLPGEKKNGLFGNLIASLGLTPNFKSNFDLAEDAKLQLSKD TYDDDL  
DNLLAQIGDQYADLFLAAKNLSDAILLSDILRVNTEITKAPLSASMIKRYDEHHQDLTLLKALVRQQLPEKYK  
EIFFDQSKNGYAGYIDGGASQEEFYKFIKPILEKMDGTEELLVKNLREDLLRKQRTFDNGSIPHQIHLGELH  
AILRRQEDFYFPLKDNREKIEKILTFRIPYYVGPLARGNSRFAMTRKSEETITPWNFEVVDKGASAQSF  
ERMTNFDKNLPNEKVLPHKSLLYEYFTVYNELTKVKYVTEGMRKPAFLSGEQKKAIVDLLFKTNRKVTVK  
QLKEDYFKKIECFDSVEISGVEDRFNASLGT YHDLLKIIKDKDFLDNEENEDILEDIVLTLTLFEDREMIERL  
KTYAHLFDKVMKQLKRRRYTGWGRLSRKLINGIRDKQSGKTILDFLKSDGFANRNFMQLIHDDSLTFKE  
DIKQAQVSGQDLSLHEHIANLAGSPAIKKILQTVKVVDELVKVMGRHHPENIVIAMARENQTTQKGQKN  
SRERMKRIEEGKELGSQILKEHPVENTQLQNEKLYLYLQNGRDMYVDQELDINRLSDYDVHIVPQSFL  
KDDSIDNKVLTRSDKNRGKSDNVPSEEVVKKMKNYWRQLLNAKLITQRKFDNLTKAERGGLSLKDAGFI  
KRQLVETRQITKHVAQILDSRMNTKYDENDKLIREVKVITLKS KLVSDFRKDFQFYK VREINNYHHAHDAYL  
NAVVG TALIKKYPKLESEFVYGDYKVYDVRKMIKSEQEIGKATAKYFFYSNIMNFFKTEITLANGEIRKRPL  
IETNGETGEIVWDKGRDFATVRKVL SMPQVNIVKKTEVQTGGFSKESILPKRNSDKLIARKKDWDPKKYG  
GFDSPTVAYSVLVVAKVEKGKSKKLSVKELLGITIMERS SFEKNPIDFLEAKGYKEVKKDLI IKLPKYSLFE  
LENGRKRMLASAGELQKGNELALPSKYVNFLYLASHYEKLGSPEDNEQKQLFVEQHKHYLDEIIEQISEF  
SKRVILADANLDKVL SAYNKHRDKPIREQAENIIHLFTLTNLGAPAAF KYFDTTIDRKRYTSTKEVLDATLIH  
QSITGLYETRIDLSQLGGDSGGSTNLSDIIEKETGKQLVIQESILMLPEEVEEVIGNKPESDILVHTAYDEST  
DENVMLLTS DAPEYKPWALVIQDSNGENKIKMLSGGSPKKKRKV

### **AID-BE3:**

MDSLLMNRKFLYQFKNVRWAKGRRETYLCYVVKRRDSATSFSLDFGYLRNKNKGCHVELLFLRYISDWD  
LDPGRCYRVTWFTSWSPCYDCARHVADFLRGPNLSLRIFTARLYFCEDRKAEPGLRRLHRAGVQIAI  
MTFKDYFYCWNTFVENHERTFKAWEGLHENS VRLSRQLR RILLPLYEVDDL RDAFRTLGLSGSETPGTS  
ESATPESDKKYSIGLAIGTNSVGWAVITDEYKVPSPKFKVLGNTDRHSIKKNLIGALLFDSGETAEATRLKR  
TARRRYTRRKNRICYLQEIFS NEMAKVDDSFHRL EESFLVEEDKKHERHPIFGNIVDEVAYHEKYPTIYHL  
RKKLVDSTDKADLRILIYALAHMIKFRGHFLIEGDLNPDNSDVDFKLFQILVQTYNQLFEENPINASGVDAKAI  
LSARLSKSRLENLIAQLPGEKKNGLFGNLIASLGLTPNFKSNFDLAEDAKLQLSKD TYDDDLNLLAQIG  
DQYADLFLAAKNLSDAILLSDILRVNTEITKAPLSASMIKRYDEHHQDLTLLKALVRQQLPEKYKEIFFDQSK  
NGYAGYIDGGASQEEFYKFIKPILEKMDGTEELLVKNLREDLLRKQRTFDNGSIPHQIHLGELHAILRRQED  
FYPFLKDNREKIEKILTFRIPYYVGPLARGNSRFAMTRKSEETITPWNFEVVDKGASAQSFIERMTNFD  
KNLPNEKVLPHKSLLYEYFTVYNELTKVKYVTEGMRKPAFLSGEQKKAIVDLLFKTNRKVTVKQLKEDYFK  
KIECFDSVEISGVEDRFNASLGT YHDLLKIIKDKDFLDNEENEDILEDIVLTLTLFEDREMIERLKYAHLFD  
DKVMKQLKRRRYTGWGRLSRKLINGIRDKQSGKTILDFLKSDGFANRNFMQLIHDDSLTFKEDIKQAQVS  
GQGDSLHEHIANLAGSPAIKKILQTVKVVDELVKVMGRHHPENIVIAMARENQTTQKGQKNRERMKRI  
EEGKELGSQILKEHPVENTQLQNEKLYLYLQNGRDMYVDQELDINRLSDYDVHIVPQSFLKDDSIDNK  
VLTRSDKNRGKSDNVPSEEVVKKMKNYWRQLLNAKLITQRKFDNLTKAERGGLSLKDAGFIKRQLVETR  
QITKHVAQILDSRMNTKYDENDKLIREVKVITLKS KLVSDFRKDFQFYK VREINNYHHAHDAYLNAVVG TAL  
IKKYPKLESEFVYGDYKVYDVRKMIKSEQEIGKATAKYFFYSNIMNFFKTEITLANGEIRKRPLIETNGETG  
EIVWDKGRDFATVRKVL SMPQVNIVKKTEVQTGGFSKESILPKRNSDKLIARKKDWDPKKYGGFDSPTVA  
YSVLVVAKVEKGKSKKLSVKELLGITIMERS SFEKNPIDFLEAKGYKEVKKDLI IKLPKYSLFELENGRKR  
MLASAGELQKGNELALPSKYVNFLYLASHYEKLGSPEDNEQKQLFVEQHKHYLDEIIEQISEFSKRVLADA  
NLDKVL SAYNKHRDKPIREQAENIIHLFTLTNLGAPAAF KYFDTTIDRKRYTSTKEVLDATLIHQSITGLYET  
RIDLSQLGGDSGGSTNLSDIIEKETGKQLVIQESILMLPEEVEEVIGNKPESDILVHTAYDESTDENVMLLTS  
DAPEYKPWALVIQDSNGENKIKMLSGGSPKKKRKV

### **BE3-Gam:**

MAKPAKRIKSAAAAYVPQNRDAVITDIKRIGDLQREASRLETEMNDIAEITEKFAARIAPIKTDIETLSKGVQ  
GWCEANRDELTTNGGKVKTANLVTGDVSWRVRPPSVSIRGMDAVMETLERLGLQRFIRTKQEINKEAILLE  
PKAVAGVAGITVKSIEDFSIIPFEQEAGISGSETPGTSESATPESSESSTGPVAVDPTLRRRIEPHEFEVFF  
DPRELKRETCCLLYEINWGGRRHSIWRHTSQNTNKHVEVNFIEKFTTERRYFCPNTRCSITWFLSWSPCGECS  
RAITEFLSRYPHVTLFIYIARLYHHADPRNRQGLRDLISSGVTIQIMTEQESGYCWRNFVNYSNEAHP  
RYPHLWVRLYVLELYCIILGLPPCLNLRKQPQLTFFTIALQSCHYQRLPPHILWATGLKSGSETPGTSES  
ATPESDKKYSIGLAIGTNSVGWAVITDEYKVPKSKFKVLGNTDRHSIKKNLIGALLFDSGETAEATRLKRTA  
RRRYTRRKNRICYLQEIFSNEMAKVDDSFHRLSEESFLVEEDKKHERHPIFGNIVDEVAYHEKYPTIYHLR  
KKLV DSTDKADLR LIYLALAHMIKFRGHFLIEGDLNPDNSDVKLFIQLVQTYNQLFEENPINASGVDKAIL  
SARLSKSRLENLIAQLPGEKKNLFGNLIASLGLTPNFKSNFDLAEDAQLQSKDYYDDDLNLLAQIGD  
QYADFLAAKNLSDAILSDILRVNTEITKAPLSASMIKRYDEHHQDLTLLKALVRQQLPEKYKEIFFDQSKN  
GYAGYIDGGASQEEFYKFIKPILEKMDGTEELLVKNREDLLRKQRTFDNGSIPHQIHLGELHAILRRQEDF  
YPFLKDNREKIEKILTFRIPYYVGLARGNSRFAMWTRKSEETITPWNFEVVDKGASAQSFIERMTNFDK  
NLPNEKVLPKHSLLYEYFTVYNELTKVKYVTEGMKPAFLSGEQKKAIVDILLFKTNRKVTVKQLKEDYFKK  
IECFDSVEISGVEDRFNASLGTYHDLLKIKDKDFLDNEENEDILEDIVLTLTLFEDREMIEERLKYAHLFDD  
KVMKQLKRRRYTGWGRLSRKLINGIRDKQSGKTILDFLKSDFANRNFMLIHDDSLTFKEDIQKAQVSG  
QGDSLHEHIANLAGSPAIKKILQTVKVVDELVKVMGRHKPENIVIEMARENQTTQKGQKNSRERMKRIEE  
GIKELGSQILKEHPVENTQLQNEKLYLYLQNGRDMYVDQELDINRLSDYDVDHIVPQSFLKDDSIDNKVL  
TRSDKNRGKSDNVPSEEVVKKMKNYWRQLLNAKLITQRKFDNLTKAERGGSELKAGFIKRQLVETRQI  
TKHVAQILDSRMNTKYDENDKLIREVKVITLKSCLVSDFRKDFQFYKVRINNYHHAHDAYLNAVVG TALIK  
KYPKLESEFVYGDYKVYDVRKMIKSEQEIGKATAKYFFYSNIMNFFKTEITLANGEIRKRPLIETNGETGEI  
VWDKGRDFATVRKVL SMPQVNIVKKT EVQTGGFSKESILPKRNSDKLIARKKDWDPK KYGGFDSPTVAY  
SVLVVAKVEKGSKKLKSVKELLGITIMERSSEFEKNPIDFLEAKGYKEVKKDLIILPKYSLFELENGRKRML  
ASAGELQKGNELALPSKYVNFYLASHYEKLGSPEDNEQKQLFVEQHKHYLDEIIEQISEFSKRVLADAN  
LDKVL SAYNKH RDKPIREQAENIHLFTLNLGAPAAFKYFDTTIDRKRYTSTKEVLDATLIHQ SITGLYETRI  
DLSQLGGDSGGSTNLSDIIEKETGKQLVIQESILMLPEEVEEVIGNKPESDILVHTAYDESTDENVMLLTS  
APEYK PWALVIQDSNGENKIKMLSGGSPKKRKY

**SaBE3-Gam:**

MAKPAKRIKSAAAAYVPQNRDAVITDIKRIGDLQREASRLETEMNDIAEITEKFAARIAPIKTDIETLSKGVQ  
GWCEANRDELTTNGGKVKTANLVTGDVSWRVRPPSVSIRGMDAVMETLERLGLQRFIRTKQEINKEAILLE  
PKAVAGVAGITVKSIEDFSIIPFEQEAGISGSETPGTSESATPESSESSTGPVAVDPTLRRRIEPHEFEVFF  
DPRELKRETCCLLYEINWGGRRHSIWRHTSQNTNKHVEVNFIEKFTTERRYFCPNTRCSITWFLSWSPCGECS  
RAITEFLSRYPHVTLFIYIARLYHHADPRNRQGLRDLISSGVTIQIMTEQESGYCWRNFVNYSNEAHP  
RYPHLWVRLYVLELYCIILGLPPCLNLRKQPQLTFFTIALQSCHYQRLPPHILWATGLKSGSETPGTSES  
ATPESGKRNILGLAIGITSVGYGIIDYETRDVIDAGVRLFKEANVENNEGRRSKRGARRLKRHRHRIQR  
VKLLFDYNLLTDHSELSGINPYEARVKLSQKLEEEFSAALLHLAKRRGVHNVNEEEDTGNELSTKE  
QISRNSKALEEKYVAELQLERLKKDGEVRGSINRFKTSYVKEAKQLLVQKAYHQLDQSFIDTYIDLETR  
RTYYEGPGEPSFGWKDIKEWYEMLMGHCTYFPEELRSVKYAYNADLYNALNDLNNLVITRDENEKLEY  
YEKFQIENVFQKQKPTLQIAKEILVNEEDIKGYRVTSTGKPEFTNLKVYHDIKDITARKEIENAELLDQIA  
KILTIIYQSSEDIQEELTNLNSLTQEEIEQISNLKGYTGTHNLSLKAINLILDELWHTNDNQIAIFNRLKLVPKK  
VDLSQQKEIPTTLVDDFILSPVVKRSFIQSIVINAIKKYGLPNDIIIELAREKNSKDAQKMINEMQKRNRT  
NERIEEII RTTGKENAKYLIEKIKLHDMQEGKCLYSLEAIPLEDLLNPNFYEV DHIIPRSVSFDNSFNKVLV  
KQEENSKGNRTPFQYLSSSDSKISYETFKKHILNLA KGGRISKTKKEYLLEERDINRFSVQKDFINRNLV  
DTRYATRGLMNLRSYFRVNNLDVKVKSINGGFTSFLRRKWKFKKERNKGYKHAEDALI ANADFIFKE  
WKKLDKAKKVMENQMFEKQAESMPEIETE QEYKEIFITPHQIKHIKDFKDYKYSHRVDKKNRELINDTL  
YSTRKDDKGNTLIVNNLNGLYDKDNDKLLKLINKSPEKLLMYHHPQTYQKLKLIMEQY GDEKNPLYKYY  
EETGNLYLTKYSKKNPVIKKIKYYGNKLNALHDITDDYPNSRNKVVKLSLKP YRFDVYLDNGVYK FVTVK  
NLDVIKKENYEVNSKCYEEAKLKKISNQAEFIASFYNNDLIKINGEL YRVIGVNNDLLNRIEVN MIDITYRE  
YLENMNDKRPPRIIKTIASKTQSIKKYSTDILGNLYEVKSKKHPQIIKGGSPKKRKYSSDYKDHDG DYKD  
HDIDYKDDDDKSGGSTNLSDIIEKETGKQLVIQESILMLPEEVEEVIGNKPESDILVHTAYDESTDENVMLLTS  
SDAPEYK PWALVIQDSNGENKIKMLSGGSPKKRKY

**BE4:**

MSSETGPVAVDPTLRRRIEPHEFEVFFDPRELKRETCCLLYEINWGGRRHSIWRHTSQNTNKHVEVNFIEK  
TTERYFCPNTRCSITWFLSWSPCGECSRAITEFLSRYPHVTLFIYIARLYHHADPRNRQGLRDLISSGVTIQ  
IMTEQESGYCWRNFVNYSNEAHPRYPHLWVRLYVLELYCIILGLPPCLNLRKQPQLTFFTIALQSC

HYQRLPPHILWATGLKSGSSGGSSGGSETPGTSESATPESSGGSSGGSDKKYSIGLAIGTNSVGWAVIT  
DEYKVPSSKFKVLGNTDRHSIKKNLIGALLFDSGETAEATRLKRTARRRYTRRKNRICYLQEIFSNEMAKV  
DSSFHRLLEESFLVEEDKKHERHPIFGNIVDEVAYHEKYPTIYHLRKKLVDSTDKADLRILIYALAHMIKFR  
GHFLIEGDLNPDNSDVKLFIQLVQTYNQLFEENPINASGVDAKAILSARLSKSRLENLIAQLPGEKKNGL  
FGNLIALSLGLTPNFKSNFDLAEDAKLQLSKDYDDDLNLLAQIGDQYADLFLAAKNLSDAILLSDILRVNT  
EITKAPLSASMIKRYDEHHQDLTLLKALVRQQLPEKYKEIFFDQSKNGYAGYIDGGASQEEFYKFIKPILEK  
MDGTEELLVKNLREDLLRKQRTFDNGSIPHQIHLGELHAILRRQEDFYFPLKDNREKIEKILTFRIPYYVGPL  
ARGNSRFAMTRKSEETITPWNFEEVVDKGASAQSFIERMTNFDKNLPNEKVLPHKSHLLYEYFTVYNELT  
KVKYVTEGMRKPAFLSGEQKKAIVDLLFKTNRKVTVKQLKEDYFKKIECFDSVEISGVEDRFNASLGTYHD  
LLKIIKDKDFLDNEENEDILEDIVLTLTFEDREMIEERLKYAHLFDDKVMKQLKRRRYTGWGRLSRKLING  
IRDKQSGKTILDFLKSDGFANRNFQMQLIHDDSLTFKEDIQKAQVSGQGDSLHEHIANLAGSPAIAKKGILQTV  
KVVDLVKVMGRHHPENIVEMARENQTTQKGQKNSRERMKRIEIEGKELGSQILKEHPVENTQLQNEKLY  
LYYLQNGRDMYVDQELDINRLSDYDVIDHVPQSFLKDDSIDNKVLRSDKNRGKSDNVPSEEVVKKMK  
NYWRQLLNAKLITQRKFDNLTKAERGGLSELDKAGFIKRLVETRQITKHVAQILD SRMNTKYDENDKLIR  
EVKIVITLKSCLVSDFRKDFQFYKREINNYHHAHDAYLNAVVG TALIKKYPKLESEFVYGDYKVDVRKMI  
AKSEQEIGKATAKYFFYSNIMNFFKTEITLANGEIRKRPLIETNGETGEIVWDKGRDFATVRKVL SMPQVNI  
VKKTEVQTGGFSKESILPKRNSDKLIARKKDWDPKKGFFSPTVAYSVLVAKVEKGKSKKLSVKELL  
GITIMERSSEFEKNPIDFLEAKGYKEVKKDLIILPKYSLFELENGRKRMLASAGELQKGNELALPSKYVNFL  
YLASHYEKLGSPEDNEQKQLFVEQHKHYLDEIIEQISEFSKRVLADANLDKVL SAYNKHRDKPIREQAEN  
IIHLFTLNLGAPAAFYFDTTIDRKRYTSTKEVL DATLIHQ SITGLYETRIDLSQLGGDSGGSGGGSTNL  
SDIIEKETGKQLVIQESILMLPEEVEEVIGNKPESDILVHTAYDESTDENVMLLTSDAPEYKPWALVIQDSNG  
ENKIKMLSGGSGGGSTNLSDIIEKETGKQLVIQESILMLPEEVEEVIGNKPESDILVHTAYDESTDENVM  
LLTSDAPEYKPWALVIQDSNGENKIKMLSGGSPKKKRK

**BE4-Gam:**

MAKPAKRIKSAAAAYVPQNRDAVITDIKRIGDLQREASRLETEMNDAIAEITEKFAARIAPIKTDIETLSKGVQ  
GWCEANRDEL TNGGKVKTANLVTGDVSWVRPPSVSIRGMDAVMETLERLGLQRFIRTKQEINKEAILLE  
PKAVAGVAGITVKSIEDFSIIPFEQEAGISGSETPGTSESATPESSSETGPVAVDPTLRRRIEPHEFEVFF  
DPRELKRETCCLLYEINWGGRRHSIWRHTSQNTNKHVEVNFIEKFTTERRYFCPNTRCSITWFLSWSPCGECS  
RAITEFLSRYPHVTLFIYIARLYHHADPRNRQGLRDLISSGVTIQIMTEQESGYCWRNFVNYSNEAHP  
RYPHLWVRLYVLELYCIILGLPPCLNLRKQPQLTFFTIALQSCHYQRLPPHILWATGLKSGGSSGGSSGS  
ETPGTSESATPESSGGSSGGSDKKYSIGLAIGTNSVGWAVITDEYKVPSSKFKVLGNTDRHSIKKNLIGAL  
LFDSETAEATRLKRTARRRYTRRKNRICYLQEIFSNEMAKVDDSSFHRLLEESFLVEEDKKHERHPIFGNI  
VDEVAYHEKYPTIYHLRKKLVDSTDKADLRILIYALAHMIKFRGHFLIEGDLNPDNSDVKLFIQLVQTYNQ  
LFEENPINASGVDAKAILSARLSKSRLENLIAQLPGEKKNGLFGNLIALSLGLTPNFKSNFDLAEDAKLQLS  
KDYDDDLNLLAQIGDQYADLFLAAKNLSDAILLSDILRVNTEITKAPLSASMIKRYDEHHQDLTLLKALVR  
QQLPEKYKEIFFDQSKNGYAGYIDGGASQEEFYKFIKPILEKMDGTEELLVKNLREDLLRKQRTFDNGSIP  
HQIHLGELHAILRRQEDFYFPLKDNREKIEKILTFRIPYYVGPLARGNSRFAMTRKSEETITPWNFEEVVD  
KGASAQSFIERMTNFDKNLPNEKVLPHKSHLLYEYFTVYNELTKVKYVTEGMRKPAFLSGEQKKAIVDLLFK  
TNRKVTVKQLKEDYFKKIECFDSVEISGVEDRFNASLGTYHDLLKIIKDKDFLDNEENEDILEDIVLTLTFED  
REMIEERLKYAHLFDDKVMKQLKRRRYTGWGRLSRKLINGIRDKQSGKTILDFLKSDGFANRNFQMQLIH  
DDSLTFKEDIQKAQVSGQGDSLHEHIANLAGSPAIAKKGILQTVKVVDLVKVMGRHHPENIVEMARENQ  
TQKGQKNSRERMKRIEIEGKELGSQILKEHPVENTQLQNEKLYLYYLQNGRDMYVDQELDINRLSDYD  
VIDHVPQSFLKDDSIDNKVLRSDKNRGKSDNVPSEEVVKKMKNYWRQLLNAKLITQRKFDNLTKAERGGLS  
ELDKAGFIKRLVETRQITKHVAQILD SRMNTKYDENDKLIREVKIVITLKSCLVSDFRKDFQFYKREINNY  
HHAHDAYLNAVVG TALIKKYPKLESEFVYGDYKVDVRKMIAKSEQEIGKATAKYFFYSNIMNFFKTEITLA  
NGEIRKRPLIETNGETGEIVWDKGRDFATVRKVL SMPQVNI VKKTEVQTGGFSKESILPKRNSDKLIARKK  
DWDPKKGFFSPTVAYSVLVAKVEKGKSKKLSVKELLGITIMERSSEFEKNPIDFLEAKGYKEVKKDLI  
ILPKYSLFELENGRKRMLASAGELQKGNELALPSKYVNFLYLASHYEKLGSPEDNEQKQLFVEQHKHYL  
DEIIEQISEFSKRVLADANLDKVL SAYNKHRDKPIREQAENIIHLFTLNLGAPAAFYFDTTIDRKRYTSTK  
EVL DATLIHQ SITGLYETRIDLSQLGGDSGGSGGGSTNLSDIIEKETGKQLVIQESILMLPEEVEEVIGNK  
PESDILVHTAYDESTDENVMLLTSDAPEYKPWALVIQDSNGENKIKMLSGGSGGGSTNLSDIIEKETGK  
QLVIQESILMLPEEVEEVIGNKPESDILVHTAYDESTDENVMLLTSDAPEYKPWALVIQDSNGENKIKMLSG  
GSPKKKRK

**SaBE4:**

MSSETGPVAVDPTLRRRIEPHEFEVFFDPRELKRETCCLLYEINWGGRRHSIWRHTSQNTNKHVEVNFIEK  
FTTERRYFCPNTRCSITWFLSWSPCGECSRAITEFLSRYPHVTLFIYIARLYHHADPRNRQGLRDLISSGVTIQ

IMTEQESGYCWRNFVNYSPSNEAHWP RYPHLWVRLYVLELYCIILGLPCLNILRRKQPQLTFFTIALQSC  
HYQRLPPHILWATGLKSGGSSGGSSGSETPGTSESATPESSGGSSGGSGKRNILGLAIGITSVGYGIIDY  
ETRDVIDAGVRLFKEANVENNEGRRSKRGARRLKRRRRHRIQRVKLLFDYNLLTDHSELGINPYEARV  
KGLSQKLSEEEFSAALLHLAKRRGVHNVNEVEEDTGNELSTKEQISRNSKALEEKYVAELQLERLKKDGE  
VRGSINRFKTSDYVKEAKQLLKVQKAYHQLDQSFIDTYIDLETRRYYEGPGEKSPFGWKDIKEWYEML  
MGHCTYFPEELRSVKYAYNADLYNALNDLNLVITRDENEKLEYEKFQIIEVFKQKKKPTLKQIAKEILV  
NEEDIKGYRVTSTGKPEFTNLKVYHDIKDITARKEIIEAELLDQIAKILTIYQSSEDIQEELTNLNSLTQEEI  
EQISNLKGYTGTHNLSLKAINLILDELWHTNDNQIAIFNRLKLVPKKVDLSQQKEIPTTLVDDFILSPVVKRSF  
IQSIKVINAIKKYGLPNDIIIELAREKNSKDAQKMINEMQKRNRTNERIEEIIIRTTGKENAKYLIEKIKLHDMQ  
EGKCLYSLEAIPLEDLLNPFNYEVDHIIPRSVDFNSFNKVLVKQEENSKKGNRTPFQYLSSSDSKISYE  
TFKKHILNLAQKGRISKTKKEYLLEERDINRFSVQKDFINRNLVDTRYATRGLMNLRSYFRVNNLDVKVK  
SINGGFTSFLRRKWKFKKERNKGYKHAEDALIINANADFIKKEWKKLDKAKKVMENQMFEEKQAESMPEI  
ETEQEYKEIFITPHQIKHIKDFKDYKYSHRVDKKNRELINDTLYSTRKDDKGNTLIVNNLNGLYDKDNDKL  
KKLINKSPEKLLMYHHPQTYQKLKLIMEQYGDENPLYKYEEETGNYLTKYSKKNPVIKKIKYYGNKL  
NAHLDITDDYPNSRNKVVKLSLKPYPYRFDVYLDNGVYKFTVKNLDVIKKENYYEVNSKCYEEAKLKKISN  
QAEFIASFYNNDLIKINGELRYVIGVNNDLNRIEVMIDITYREYLENMNDKRPRIIKTIASKTQSIKKYSTD  
ILGNLYEVKSKKHPQIIKGGSPKKRKYSSDYKDHDGDYKDHDIDYKDDDDKSGGSGGSGGSTNLSDI  
EKETGKQLVIQESILMLPEEVEEVIGNKPESDILVHTAYDESTDENVMMLTSDAPEYKPWALVIQDSNGEN  
KIKMLSGGSGGSGGSTNLSDIIEKETGKQLVIQESILMLPEEVEEVIGNKPESDILVHTAYDESTDENVMML  
TSDAPEYKPWALVIQDSNGENKIKMLSGGSPKKRKY

**SaBE4-Gam:**

MAKPAKRIKSAAYVPQNRDAVITDIKRIGDLQREASRLETEMNDIAEITEKFAARIAPIKTDIETLSKGVQ  
GWCEANRDELNTGGKVKTANLVTGDVSWRVRPPSVSIRGMDAVMETLERLGLQRFIRTKQEINKEAILL  
PKAVAGVAGITVKSIEDFSIIPFEQEAGISGSETPGTSESATPESSSETGPVAVDPTLRRRIEPHEFEVFF  
DPRELKTCCLLYEINWGGRRHSIWRHTSQNTNKHVEVNFIEKFTTERRYFCPNTRCSITWFLSWSPCGECS  
RAITEFLSRYPHVTLFIYARLYHHADPRNRQGLRDLISSGVTIQIMTEQESGYCWRNFVNYSPSNEAHWP  
RYPHLWVRLYVLELYCIILGLPCLNILRRKQPQLTFFTIALQSCHYQRLPPHILWATGLKSGGSSGGSSGS  
ETPGTSESATPESSGGSSGGSGKRNILGLAIGITSVGYGIIDYETRDVIDAGVRLFKEANVENNEGRRSK  
RGARRLKRRRRHRIQRVKLLFDYNLLTDHSELGINPYEARVKGLSQKLSEEEFSAALLHLAKRRGVHN  
VNEVEEDTGNELSTKEQISRNSKALEEKYVAELQLERLKKDGEVRGSINRFKTSDYVKEAKQLLKVQKAY  
HQLDQSFIDTYIDLETRRYYEGPGEKSPFGWKDIKEWYEMLMGHCTYFPEELRSVKYAYNADLYNALN  
DLNNDLITRDENEKLEYEKFQIIEVFKQKKKPTLKQIAKEILVNEEDIKGYRVTSTGKPEFTNLKVYHDIK  
DITARKEIIEAELLDQIAKILTIYQSSEDIQEELTNLNSLTQEEIEQISNLKGYTGTHNLSLKAINLILDELW  
TNDNQIAIFNRLKLVPKKVDLSQQKEIPTTLVDDFILSPVVKRSFIQSIKVINAIKKYGLPNDIIIELAREKNSK  
DAQKMINEMQKRNRTNERIEEIIIRTTGKENAKYLIEKIKLHDMQEGKCLYSLEAIPLEDLLNPFNYEVDHI  
IPRSVDFNSFNKVLVKQEENSKKGNRTPFQYLSSSDSKISYETFKKHILNLAQKGRISKTKKEYLLEER  
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