

Supplementary Information

Improved prime editors enable pathogenic allele correction and cancer modelling in adult mice

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Supplementary Table 1. Sequences of pegRNAs and sgRNAs used in this study. All sequences are shown in 5' to 3' orientation.

Supplementary Table 2. Sequences of primers used for pegRNA cloning

Supplementary Table 3. Sequences of primers used for genomic DNA amplification and high throughput sequencing.

Supplementary Table 4. Potential genetic engineered liver cancer models using prime editors.

Supplementary Table 5. In vivo on target analysis at SERPINA1 site by UdiTaS.

Supplementary Sequences 1. Sequences of reporter cell line used in this study

Supplementary Sequences 2. Sequence of backbone plasmid used for pegRNA and nicking sgRNA cloning

Supplementary Sequences 3. Sequences of prime editors

Supplementary Note 1. FACS gating examples for GFP-positive or Cherry-positive cells.

Figure S1

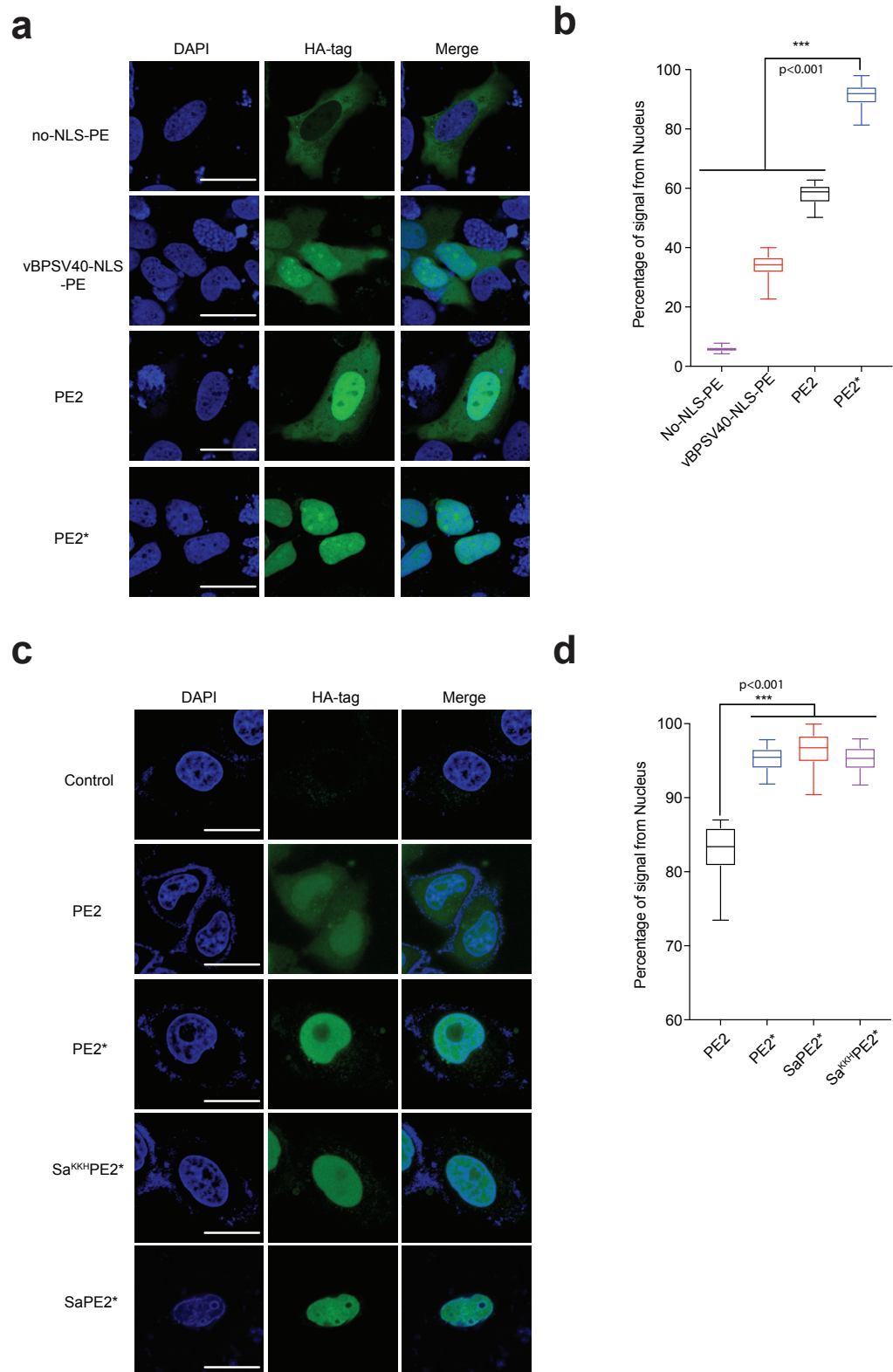
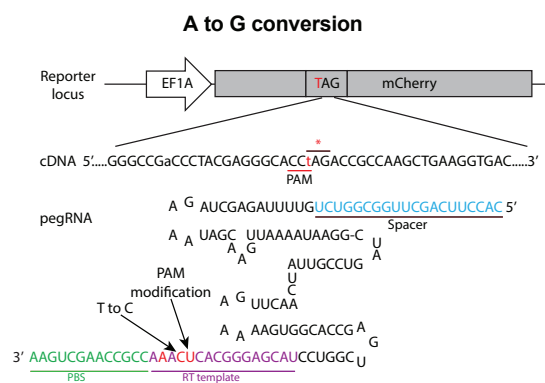
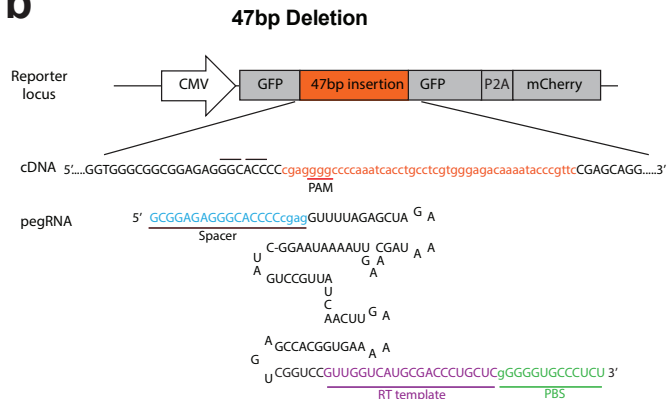


Figure S2

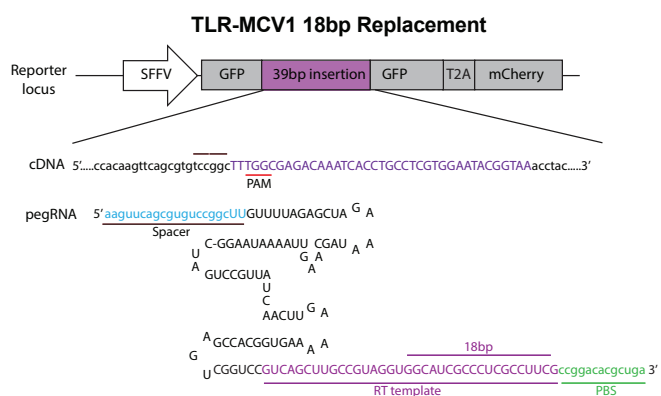
a



b



c



d

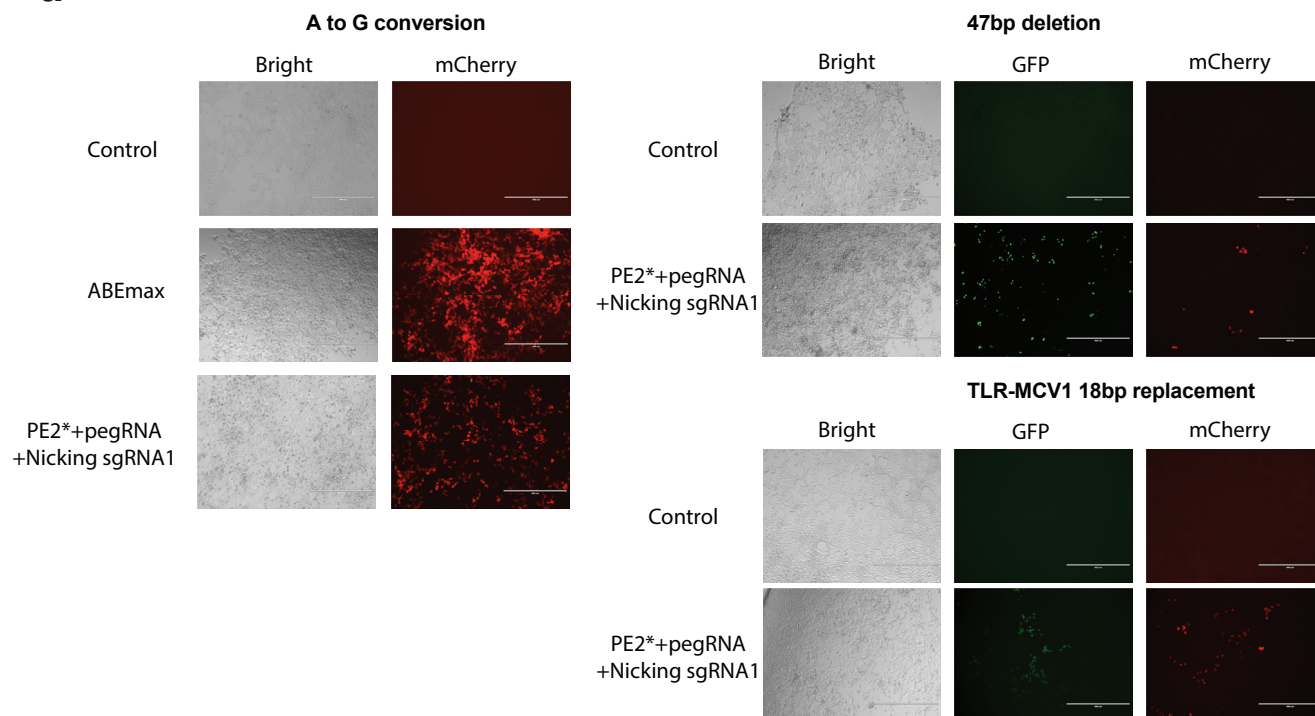


Figure S3

a

CCR5 Delta32 Deletion

PE2

CAAAAAGAAGGTCTTCATTACACCTGCAGCTCTCATTTTCCATACAGTCAGTATCAATTCTGGAAGAATTTCCAGACATTAAGATAGTCATCTTGGGGCTGGTCC	WT	94.82%
CAAAAAGAAGGTCTTCATTACACCTGCAGCTCTCATTTTCCCTATA-----TTAAAGATAGTCATCTTGGGGCTGGTCC	Precise	3.86%
CAAAAAGAAGGTCTTCATTACACCTGCAGCTCTCATTTTCCA-----GACATTAAGATAGTCATCTTGGGGCTGGTCC	-32	0.17%
CAAAAAGAAGGTCTTCATTACACCTGCAGCTCTCATTTTCCCTATAG-----TAAAGATAGTCATCTTGGGGCTGGTCC	-32	0.08%
CAAAAAGAAGGTCTTCATTACACCTGCAGCTCTCATTTTCCCTATA-----TAAAGATAGTCATCTTGGGGCTGGTCC	-33	0.06%
CAAAAAGAAGGTCTTCATTACACCTGCAGCTCTC-----ATCAATTCTGGAAGAATTTCCAGACATTAAGATAGTCATCTTGGGGCTGGTCC	-18	0.04%
CAAAAAGAAGGTCTTCATTACACCTGCAGCTCTCATTTTCCATACAGTCAGTATCAATTCTGGAAGAATTTCCAGAC--AAAGATAGTCATCTTGGGGCTGGTCC	-3	0.03%
CAAAAAGAAGGTCTTCATTACACCTGCAGCTCTCATTTTCCATACAGTCAGTATCAATTCTGGAAGAATTTCCAGACATTAAAGATAGTCATCTTGGGGCTGGTCC	+1	0.01%

PE2*

CAAAAAGAAGGTCTTCATTACACCTGCAGCTCTCATTTTCCATACAGTCAGTATCAATTCTGGAAGAATTTCCAGACATTAAGATAGTCATCTTGGGGCTGGTCC	WT	91.25%
CAAAAAGAAGGTCTTCATTACACCTGCAGCTCTCATTTTCCCTATA-----TTAAAGATAGTCATCTTGGGGCTGGTCC	Precise	6.08%
CAAAAAGAAGGTCTTCATTACACCTGCAGCTCTCATTTTCCA-----GACATTAAGATAGTCATCTTGGGGCTGGTCC	-32	0.25%
CAAAAAGAAGGTCTTCATTACACCTGCAGCTCTCATTTTCCCTATAG-----TAAAGATAGTCATCTTGGGGCTGGTCC	-32	0.14%
CAAAAAGAAGGTCTTCATTACACCTGCAGCTCTCATTTT-----GACATTAAGATAGTCATCTTGGGGCTGGTCC	-33	0.08%
CAAAAAGAAGGTCTTCATTACACCTGCAGCTCTCATTTTCCCTATA-----TAAAGATAGTCATCTTGGGGCTGGTCC	-33	0.06%
CAAAAAGAAGGTCTTCATTACACCTGCAGCTCTC-----ATCAATTCTGGAAGAATTTCCAGACATTAAGATAGTCATCTTGGGGCTGGTCC	-18	0.06%
CAAAAAGAAGGTCTTCATTACACCTGCAGCTCTCATTTTCCATACAGTCAGTATCAATTCTGGAAGAATTTCCAGAC--AAAGATAGTCATCTTGGGGCTGGTCC	-3	0.04%
CAAAAAGAAGGTCTTCATTACACCTGCAGCTCTCATTT-----GTCAGTATCAATTCTGGAAGAATTTCCAGACATTAAGATAGTCATCTTGGGGCTGGTCC	-8	0.03%
CAAAAAGAAGGTCTTCATTACACCTGCAGCTCTCATTTTCCATACAGTCAGTATCAATTCTGGAAGAATTTCCAGACATTAAAGATAGTCATCTTGGGGCTGGTCC	+1	0.03%

Sa^{KKH}PE2*

CAAAAAGAAGGTCTTCATTACACCTGCAGCTCTCATTTTCCATACAGTCAGTATCAATTCTGGAAGAATTTCCAGACATTAAGATAGTCATCTTGGGGCTGGTCC	WT	96.36%
CAAAAAGAAGGTCTTCATTACACCTGCAGCTCTCATTTTCCATACA-----TTAAAGATAGTCATCTTGGGGCTGGTCC	Precise	2.85%
CAAAAAGAAGGTCTTCATTACACCTGCAGCTCTCATTTTCCA-----GACATTAAGATAGTCATCTTGGGGCTGGTCC	-32	0.06%
CAAAAAGAAGGTCTTCATTACACCTGCAGCTCTCATTTT-----GACATTAAGATAGTCATCTTGGGGCTGGTCC	-33	0.04%
CAAAAAGAAGGTCTTCATTACACCTGCAGCTCTCATTTTCCATACAGTCAGTATCAATTCTGGAAGAATTTCCAGAC--AAAGATAGTCATCTTGGGGCTGGTCC	-3	0.02%
CAAAAAGAAGGTCTTCATTACACCTGCAGCTCTCATTTTCCATACAGTCAGTATCAATTCTGGAAGAATTTCCAGAC-----TCATCTTGGGGCTGGTCC	-11	0.02%
CAAAAAGAAGGTCTTCATTACACCTGCAGCTCTCATTTTCCATACAGTCAGTATCAATTCTGGAAGAA-----TAGTCATCTTGGGGCTGGTCC	-17	0.01%

Figure S4

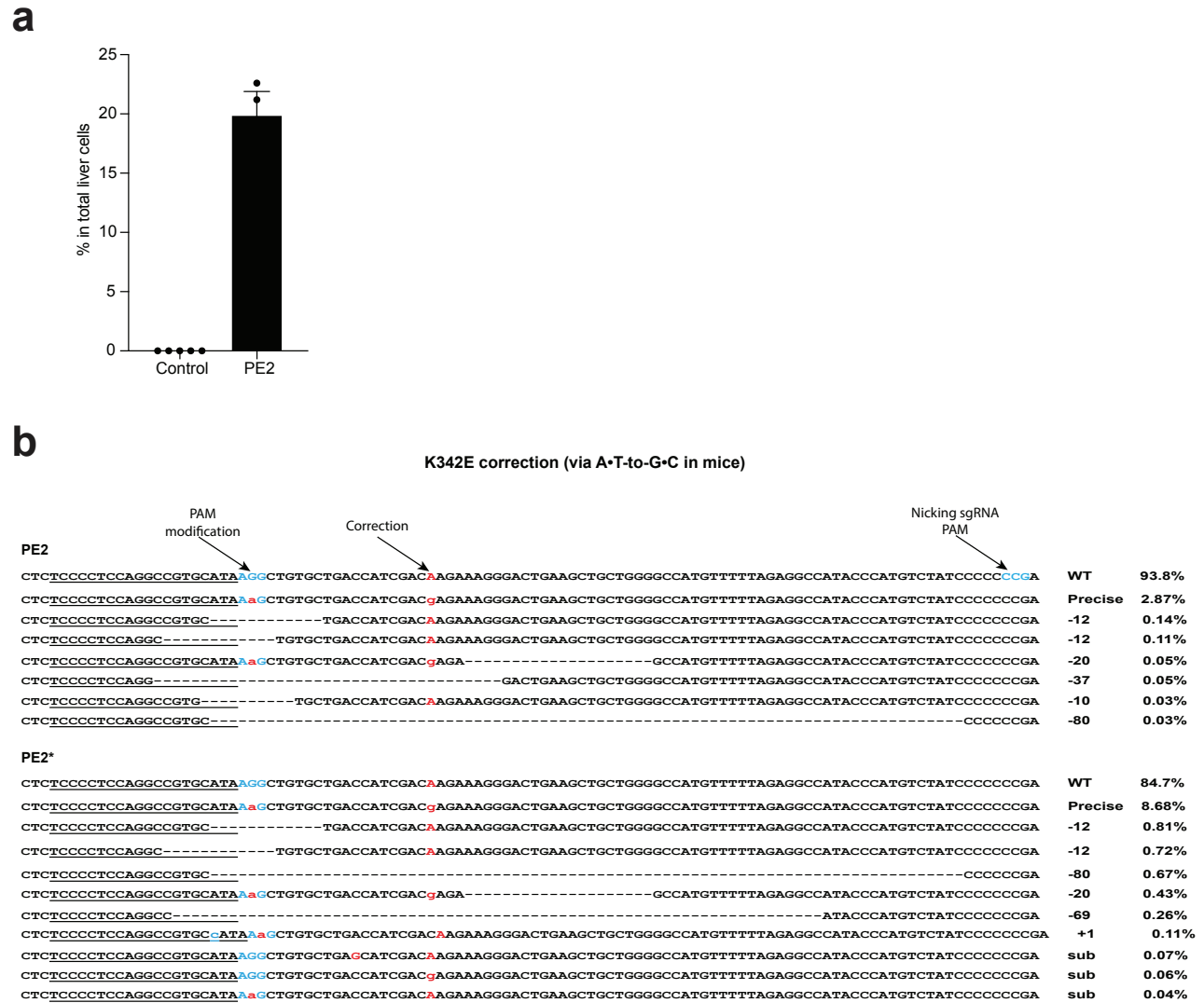


Figure S5

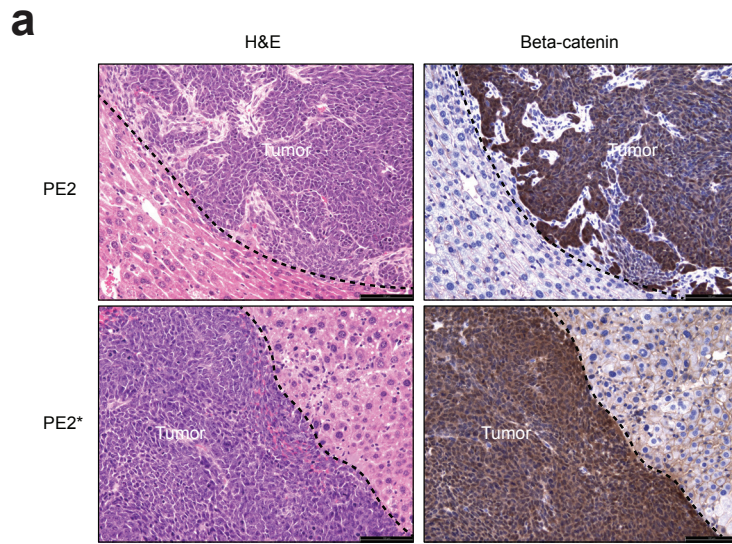
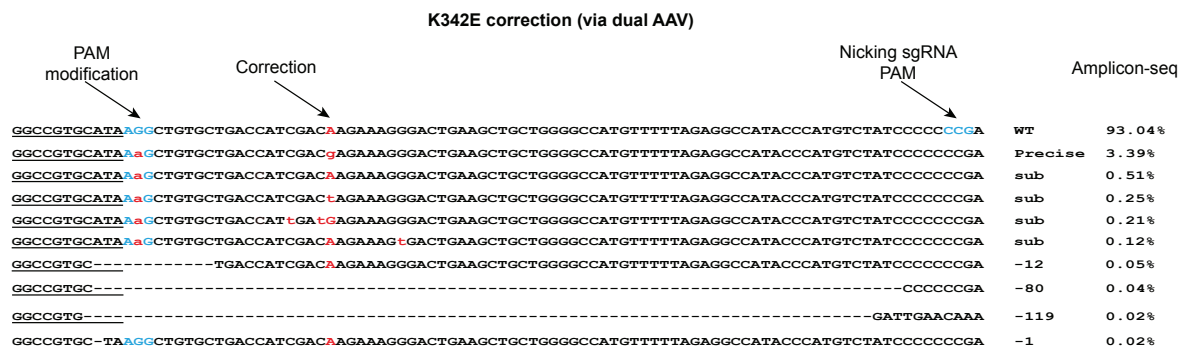
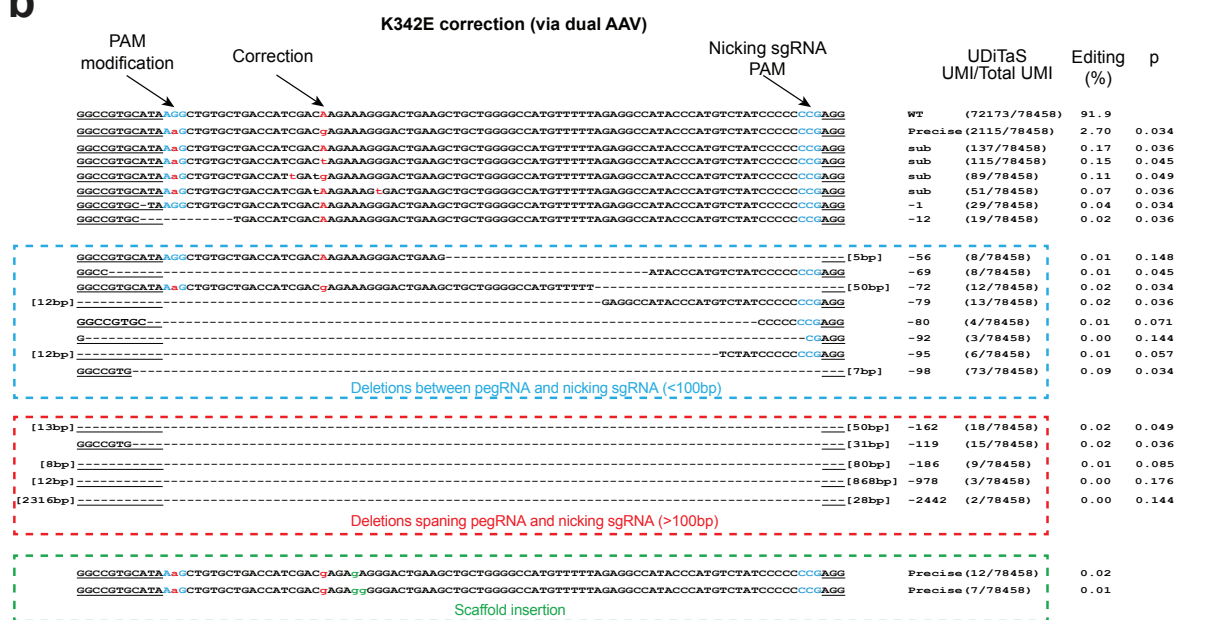
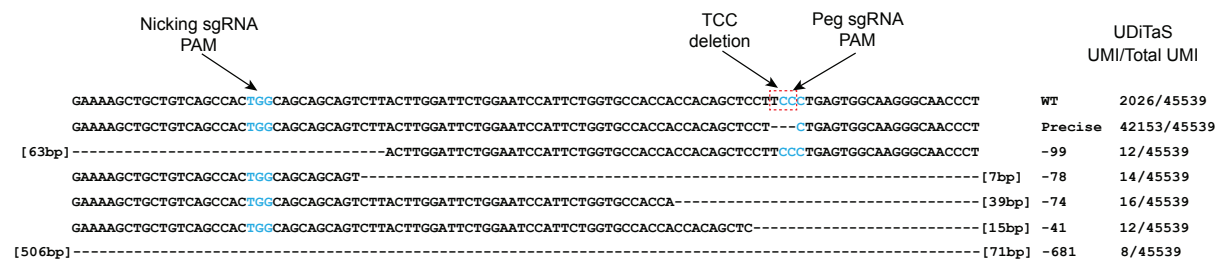


Figure S6

a

**b**

S45 deletion (via TCC deletion)



Supplementary Fig. 1 Optimized prime editor increases the degree of nuclear import. (a) Representative immunofluorescence images of prime editors transfected into U2OS cells immunostained with a HA tag antibody to visualize subcellular localization. PE2 contains two Bipartite SV40 NLSs, whereas the PE2* variant include an extra N-terminal c-Myc NLS and a C-terminal variant bipartite SV40 NLS (vBPSV40) and SV40. DNA was stained with DAPI. (b) Average percentages of HA-tag signal from nucleus for different prime editors. (c-d) Representative immunofluorescence images and quantification in HeLa cells. For (b) and (d), >90 cells were analyzed for each group from 3 independent experiments. *** $P < 0.001$ by one-way ANOVA with Tukey's multiple comparisons test. In the boxes, the top, middle and bottom lines represent the 25, 50 and 75 percentiles, respectively. Whiskers indicated the min and max percentiles and outliers are not shown. Scale bars, 10 μ m.

Supplementary Fig. 2 Prime editing in reporter cells by PE2 and PE2*. (a) Sequence of reporter locus and pegRNA used for repair of mCherry reporter in HEK293T cells. Bar above the cDNA indicates the stop codon with the target "t" for conversion indicated in red. Two additional silent mutations are included to discourage recutting of the repaired DNA sequence. (b) Sequence of reporter and pegRNA used for generation of a 47bp deletion to restore function of the GFP reporter in HEK293T cells. The bars above the cDNA indicates three nucleotide blocks that correspond to codons in the GFP reporter. (c) Sequence of reporter and pegRNA used for replacement of a 18bp element to restore function of the GFP reporter. The bars above the cDNA indicates three nucleotide blocks that correspond to codons in the GFP reporter. (d) Representative images of HEK293T reporter cells (n=3) transfected with control, ABEmax or PE2*. Scale bar, 400 μ m.

Supplementary Fig.3 Sequencing analysis of the CCR5 prime editing by PE2, PE2*, or Sa^{KKH}PE2*.

The percentage of most common sequences in PE2, PE2* and Sa^{KKH}PE2* transfected cells is shown on the right (representative of n=3, determined by Illumina sequencing). The PE target site is underlined. The PAM sequences are indicated in light blue for SpCas9 and green for SaCas9^{KKH}. The box denotes the 32bp sequence deleted in CCR5delta32. Two "t" mutations in red were included in the PE2 and PE2* RT template (Fig. 2d) to demonstrate that sequence collapse was not a function of nuclease-induced microhomology mediated deletion and to reduce re-cutting of deletion allele. Deleted bases are indicated by dashes and inserted bases are in blue.

Supplementary Fig.4 Sequencing analysis of SERPINA1 editing in the liver of PiZ mouse.

(a) Evaluating prime editor expression in mouse liver. FVB mice were injected with 30 μ g of control vector or PE2 plasmid with an incorporated 3xHA-tag. Livers were harvested at day 2 and IHC staining were performed with an HA-tag antibody. Quantification of HA⁺ cells. Numbers are mean $\pm$ sem (n=5 images from 4 mice for each group).

(b) The percentage of most common sequences in the liver of PE2 and PE2*-treated mice is shown on the right (representative liver of n=3, determined by Illumina sequencing). The PE target site is underlined. The PAM sequences are in light blue. Nucleotide substitutions are labeled in red. Deleted bases are indicated by dashes. Inserted bases are shown in blue/lower case.

Supplementary Fig.5 Liver tumors are positive for nuclear beta-Catenin. (a) Representative H&E and beta-catenin IHC staining (n=3) in PE2 or PE2*-induced S45F tumors in Fig. 4. Scale bars: 100 μ m (20X lens).

Supplementary Fig. 6 Sequencing analysis of the *Ctnnb1* and *SERPINA1* prime editing by PE2 or PE2*.

(a) The percentage of most common sequences in the liver of dual AAV-treated PiZ mice determined by amplicon sequencing is shown on the right (representative liver of n=3). A portion of the PE target site is underlined. The PAM sequences are in light blue. Nucleotide substitutions are labeled in red. Deleted bases are indicated by dashes. (b) Length distribution of precise editing and other indels at *SERPINA1* (*K342E correction*) and *Ctnnb1* target sites by UDiTaS. Also included are sequence modifications that may be associated with pegRNA scaffold insertions⁷. Data for a representative liver per group is shown (n=3 mice).

Supplementary Table 1. Sequences of pegRNAs and sgRNAs used in this study. All sequences are shown in 5' to 3' orientation.

sgRNA scaffold

GTTTTAGAGCTAGAAATAGCAAGTTAAATAAGGCTAGTCCGTTATCAACTTGAAAAAGTGGGACCGAGTCGGTCC

pegRNA	spacer sequence (5'-3')	3' extension	PBS (nt)	RT (nt)	Figure	PE
mCherry A to G	CACCTTCAGCTTG CGGTCT	TACGAGGGCACTCAAACCGCCAAGCT GAAG	14	16	Figure 1B	PE2 or PE2*
mCherry A to G	GGTCACCTTCAGC TTGGCGGT	TACGAGGGCACCCAGACTGCCAAGCT GAAGGTGA	16	17	Figure 1B	Sa ^{KKH} PE2*
GFP-insertion	AAGTTCAGCGTGT CCGGCTT	GTCAGCTTGCCGTAGGTGGCATCGCC CTCGCCTTCG	13	36	Figure 1C	PE2 or PE2*
GFP-insertion	TGAACTTCAGGGT CAGCTTGCC	ACAAGTTCAGCGTGTCGGCGAGGGC GAGGGCGATGCCACGTACGGCAAGCT GACCCTGAAGTTC	18	47	Figure 1C	Sa ^{KKH} PE2*
GFP-deletion	GCGGAGAGGGCAC CCCCGA	GTTGGTCATGCGACCCTGCTCGGGGG TGCCCTCTCC	14	22	Figure 1D	PE2 or PE2*
GFP-deletion	GGTCATGCGACCC TGCTCGGA	CGGAGAGGGCACCCCCGAGCAGGGTC GCATG	15	16	Figure 1D	Sa ^{KKH} PE2*
EMX1 +5 G to T	GAGTCCGAGCAGA AGAAGAA	ATGGGAGCACTTCTTCTTCTGCTC	14	10	Figure 2A	PE2 or PE2*
EMX1 +3 +8 G to T	CAGAAGCTGGAGG AGGAAGGGC	TGCTCGGAATCAGACCCTTCTCTCTC CAGCT	15	16	Figure 2A	SaCas9 PE2* or Sa ^{KKH} PE2*
EMX1 +4 3bp deletion	GAGTCCGAGCAGA AGAAGAA	ATGTGATGGGAGTTCTTCTTCTGCTC	14	12	Figure 2B	PE2 or PE2*
EMX1 +1 3bp deletion	CAGAAGCTGGAGG AGGAAGGGC	TTCTGCTCGGACTCAGCTTCTCTCTC CAGCT	15	16	Figure 2B	SaCas9 PE2* or Sa ^{KKH} PE2*
EMX1 +4 6bp Insertion	GAGTCCGAGCAGA AGAAGAA	GAGCAGAAGAAGAAAAGCTTGGGCTC CCATCACAT	14	21	Figure 2C	PE2 or PE2*
EMX1 +1 6bp Insertion	CAGAAGCTGGAGG AGGAAGGGC	TGCTCGGACTCAGGCCAAGCTTCTTC CTCTCCAGCT	15	22	Figure 2C	SaCas9 PE2* or Sa ^{KKH} PE2*
CCR5-delta32- deletion	AGATGACTATCTT TAATGTC	ATTACACCTGCAGCTCTCATTTTCTT TATATTAAGATAGTCATC	16	29	Figure 2D	PE2 or PE2*
CCR5-delta32- deletion	AAGATGACTATCT TTAATGTCT	AGCTCTCATTTTCCATACATTAAAGA TAGTCATC	17	17	Figure 2D	Sa ^{KKH} PE2*
Serpina1 G to A	TCCCTCCAGGCC GTGCATA	TCTTGTCGATGGTCAGCACAGCTTTA TGCACGGCTGGAG	13	27	Figure 3A	PE2 or PE2*
Serpina1 G to A	CAGCTTCAGTCCC TTTCTCGT	ATCGACAAGAAAGGACTGAAGCT	15	9	Figure 3A	Sa ^{KKH} PE2*
Serpina1 A to G	TCCCTCCAGGCC GTGCATA	TCTCGTCGATGGTCAGCACAGCTTTA TGCACGGCTGGAG	13	27	Figure 3B	PE2 or PE2*
Ctnnb1 C to T	AGGGTTGCCCTTG CCACTCA	GCTCCTTTCTGAGTGGCAAGGGCAA	13	13	Figure 4A	PE2 or PE2*
Ctnnb1 C to T	AGGGTTGCCCTTG CCACTCA	ACAGCTCCTTTGAGTGGCAAGGGCAA	13	13	Figure 4D	PE2*

Nicking sgRNA	spacer sequence (5'-3')	Figure	PE
mCherry A to G	GCGCTTCAAGGTGCACATGGA	Figure 1B	PE2 or PE2*
mCherry A to G	GCTGTCCCTCAGTTCATGTA	Figure 1B	PE2 or PE2*
mCherry A to G	GATGGAGGGCTCCGTGAACGGCC	Figure 1B	Sa ^{KKH} PE2*
mCherry A to G	GTTTCGCTGGGACATCCTGTCCC	Figure 1B	Sa ^{KKH} PE2*
GFP-insertion-sp-NK1	GTAGGTCAGGGTGGTCACGA	Figure 1C	PE2 or PE2*
GFP-insertion-sp-NK2	GCTCTCGCCCTTGCTCACCA	Figure 1C	PE2 or PE2*
GFP-insertion-saKKH-NK1	GCAAGGGCGAGGAGCTGTTAC	Figure 1C	Sa ^{KKH} PE2*

GFP-insertion-saKKH-NK2	GTGACCACCCTGACCTACGGCG	Figure 1C	Sa ^{KKH} PE2*
GFP-deletion-sp-NK1	GAGAAGCCGTAGCCCATCACG	Figure 1D	PE2 or PE2*
GFP-deletion-sp-NK2	GATCTTCATGGCGGGCATGG	Figure 1D	PE2 or PE2*
GFP-deletion-saKKH-NK1	GATCACCGGCACCCTGAACGGCG	Figure 1D	Sa ^{KKH} PE2*
GFP-deletion-saKKH-NK2	GCAGCCCCTACCTGCTGAGCCA	Figure 1D	Sa ^{KKH} PE2*
EMX1 +5 G to T-sp-NK1	GTTGCCCCACCTAGTCATTGG	Figure 2A	PE2 or PE2*
EMX1 +5 G to T-sp-NK2	GGCCGTTTGTACTTTGTCCTC	Figure 2A	PE2 or PE2*
EMX1 +3 +8 G to T-sa-NK1	GCCTGGGCCAGGGAGGGAGGGGC	Figure 2A	SaCas9 PE2* or Sa ^{KKH} PE2*
EMX1 +3 +8 G to T-sa-NK2	GTGGTTGCCCCACCCTAGTCATT	Figure 2A	SaCas9 PE2* or Sa ^{KKH} PE2*
EMX1 +4 3bp deletion-sp-NK1	GTTGCCCCACCTAGTCATTGG	Figure 2B	PE2 or PE2*
EMX1 +4 3bp deletion-sp-NK2	GGCCGTTTGTACTTTGTCCTC	Figure 2B	PE2 or PE2*
EMX1 +1 3bp deletion-sa-NK1	GCCTGGGCCAGGGAGGGAGGGGC	Figure 2B	SaCas9 PE2* or Sa ^{KKH} PE2*
EMX1 +1 3bp deletion-sa-NK2	GTGGTTGCCCCACCCTAGTCATT	Figure 2B	SaCas9 PE2* or Sa ^{KKH} PE2*
EMX1 +4 6bp Insertion-sp-NK1	GTTGCCCCACCTAGTCATTGG	Figure 2C	PE2 or PE2*
EMX1 +4 6bp Insertion-sp-NK2	GGCCGTTTGTACTTTGTCCTC	Figure 2C	PE2 or PE2*
EMX1 +1 6bp Insertion-sa-NK1	GCCTGGGCCAGGGAGGGAGGGGC	Figure 2C	SaCas9 PE2* or Sa ^{KKH} PE2*
EMX1 +1 6bp Insertion-sa-NK2	GTGGTTGCCCCACCCTAGTCATT	Figure 2C	SaCas9 PE2* or Sa ^{KKH} PE2*
CCR5-deletion-sp-NK1	GCTGTGTTTGCCTCTCTCCC	Figure 2E	PE2 or PE2*
CCR5-deletion-sp-NK2	GACAAGTGTGATCACTTGGG	Figure 2E	PE2 or PE2*
CCR5-deletion-sp-NK3	GCAGGACGGTCACCTTTGGGG	Figure 2E	PE2 or PE2*
CCR5-deletion-saKKH-NK1	GCATCTTTACCAGATCTCAAAAA	Figure 2E	Sa ^{KKH} PE2*
CCR5-deletion-saKKH-NK2	GTGGCTGTGTTTGCCTCTCTCCC	Figure 2E	Sa ^{KKH} PE2*
Serpina1 G to A-sp-NK1	GGGGGGGATAGACATGGGTA	Figure 3A	PE2 or PE2*
Serpina1 G to A-sp-NK2	GACCTCGGGGGGATAGACA	Figure 3A	PE2 or PE2*
Serpina1 G to A-sp-NK3	GGGTTTGTGTAACCTTGACCT	Figure 3A	PE2 or PE2*
Serpina1 G to A-sp-NK4	GTTCAATCATTAAGAAGACAA	Figure 3A	PE2 or PE2*
Serpina1 G to A	GCACGTGAGCCTTGCTCGAGGCC	Figure 3A	Sa ^{KKH} PE2*
Serpina1 G to A	GCCCATGTCTATCCCCCGGAGG	Figure 3A	Sa ^{KKH} PE2*
Serpina1 A to G (mouse_injection)	GGGTTTGTGTAACCTTGACCT	Figure 3B	PE2 or PE2*
Ctnnb1 C to T	GAAAAGCTGCTGTACGCCAC	Figure 4A	PE2 or PE2*

Supplementary Table 2. Sequences of primers used for pegRNA cloning

pegRNA	Sequence (5'-3')	Figure	PE
mCherry A to G_F	TATCTTGTGGAAGGACGAAACACCGCACCTTCAGCTTGGCGGTCTGTTTAA GAGCTAGAAATAG	Figure 1B	PE2 or PE2*
mCherry A to G_R	CGGTATCGATAAGCTTGATATCGAATTCAAAAAATTCAGCTTGGCGGTTCG AGTGCCCTCGTAGGACCGACTCGGTCCCACTTTTTC	Figure 1B	PE2 or PE2*
mCherry A to G_F	TATCTTGTGGAAGGACGAAACACCGGTACCTTCAGCTTGGCGGTGTTTAA TACTCTGGAACAG	Figure 1B	Sa ^{KKH} PE2*
mCherry A to G_R	CGACGGTATCGATAAGCTTGATATCGAATTCAAAAAATTCACCTTCAGCTTG GCAGTCTGGGTGCCCTCGTATCTCGCCAACAAGTTGACGAGAT	Figure 1B	Sa ^{KKH} PE2*
GFP-insertion_F	TGGAAAGGACGAAACACCGAAGTTCAGCGTGTCCGGCTGTTTATAGAGCTAG AAATAG	Figure 1C	PE2 or PE2*
GFP-insertion_R	GTATCGATAAGCTTGATATCAAAAAATCAGCGTGTCCGGCGAAGGCGAGGGC GATGCCACCTACGGCAAGCTGACGGACCGACTCGGTCCCACTTTTTC	Figure 1C	PE2 or PE2*
GFP-insertion_F	GTGGAAGGACGAAACACCGTGAACCTCAGGGTCAGCTTGCCGTTTATGACT CTGGAACAGA	Figure 1C	Sa ^{KKH} PE2*

GFP-insertion_R	ATCTCGTCAACTTGTGGCGAGAACAAGTTCAGCGTGTCCGGCGAGGGCGAG GGCGATGCCACGTACGGCAAGCTGACCCGTAAGTTCTTTTTTTGAATTCGAT ATCAAGCTTATCGATACCGTCG	Figure 1C	Sa ^{KKH} PE2*
GFP-deletion_F	TGGAAAGGACGAAACACCGCGGAGAGGGCACCCCCGAGTTTTAGAGCTAGA AATAG	Figure 1D	PE2 or PE2*
GFP-deletion_R	GTATCGATAAGCTTGATATCAAAAAAGGAGAGGGCACCCCCGAGCAGGGTCG CATGACCAACGGACCGACTCGGTCCCACTTTTTCAAG	Figure 1D	PE2 or PE2*
GFP-deletion_F	GTGGAAGGACGAAACACCGGGTCATGCGACCCCTGCTCGGAGTTTTAGTACTC TGGAAACAG	Figure 1D	Sa ^{KKH} PE2*
GFP-deletion_R	CGACGGTATCGATAAGCTTGATATCGAATTCAAAAAACATGCGACCCCTGCT CGGGGGTGCCCTCTCCGTCTCGCCAACAAGTTGACGAGAT	Figure 1D	Sa ^{KKH} PE2*
EMX1 +5 G to T- sp_F	TGGAAAGGACGAAACACCGGAGTCCGAGCAGAAGAAGAAGTTTTAGAGCTAG AATAG	Figure 2A	PE2 or PE2*
EMX1 +5 G to T- sp_R	GTATCGATAAGCTTGATATCAAAAAAGAGCAGAAGAAGAAGTGTCCCATGG ACCGACTCGGTCCCACTTTTTC	Figure 2A	PE2 or PE2*
EMX1 +3 +8 G to T-sa_F	GTGGAAGGACGAAACACCGCAGAAGCTGGAGGAGGAAGGGCGTTTTAGTACT CTGGAACAG	Figure 2A	SaCas9 PE2* or Sa ^{KKH} PE2*
EMX1 +3 +8 G to T-sa_R	CGACGGTATCGATAAGCTTGATATCGAATTCAAAAAAGCTGGAGGAGGAA GGGTCTGATTCGAGCATCTCGCCAACAAGTTGACGAGAT	Figure 2A	SaCas9 PE2* or Sa ^{KKH} PE2*
EMX1 +4 3bp deletion-sp_F	TGGAAAGGACGAAACACCGGAGTCCGAGCAGAAGAAGAAGTTTTAGAGCTAG AATAG	Figure 2B	PE2 or PE2*
EMX1 +4 3bp deletion-sp_R	GTATCGATAAGCTTGATATCAAAAAAGAGCAGAAGAAGAACTCCCATCACAT GGACCGACTCGGTCCCACTTTTTC	Figure 2B	PE2 or PE2*
EMX1 +1 3bp deletion-sa_F	GTGGAAGGACGAAACACCGCAGAAGCTGGAGGAGGAAGGGCGTTTTAGTACT CTGGAACAG	Figure 2B	SaCas9 PE2* or Sa ^{KKH} PE2*
EMX1 +1 3bp deletion-sa_R	CGACGGTATCGATAAGCTTGATATCGAATTCAAAAAAGCTGGAGGAGGAA GCTGAGTCCGAGCAGAATCTCGCCAACAAGTTGACGAGAT	Figure 2B	SaCas9 PE2* or Sa ^{KKH} PE2*
EMX1 +4 6bp Insertion-sp_F	TGGAAAGGACGAAACACCGGAGTCCGAGCAGAAGAAGAAGTTTTAGAGCTAG AATAG	Figure 2C	PE2 or PE2*
EMX1 +4 6bp Insertion-sp_R	GTATCGATAAGCTTGATATCAAAAAAGAGCAGAAGAAGAAAGCTTGGGCTC CCATCACATGGACCGACTCGGTCCCACTTTTTC	Figure 2C	PE2 or PE2*
EMX1 +1 6bp Insertion-sa_F	GTGGAAGGACGAAACACCGCAGAAGCTGGAGGAGGAAGGGCGTTTTAGTACT CTGGAACAG	Figure 2C	SaCas9 PE2* or Sa ^{KKH} PE2*
EMX1 +1 6bp Insertion-sa_R	CGACGGTATCGATAAGCTTGATATCGAATTCAAAAAAGCTGGAGGAGGAA GAAGCTTGGCCTGAGTCCGAGCATCTCGCCAACAAGTTGACGAGAT	Figure 2C	SaCas9 PE2* or Sa ^{KKH} PE2*
CCR5-deletion- sp_F	TGGAAAGGACGAAACACCGAGATGACTATCTTTAATGTCTTTTAGAGCTAG AATAG	Figure 2E	PE2 or PE2*
CCR5-deletion- sp_R	GTATCGATAAGCTTGATATCAAAAAAGATGACTATCTTTAATATAAGGAAAA TGAGAGCTGCAGGTGGACCGACTCGGTCCCACTTTTTC	Figure 2E	PE2 or PE2*
CCR5-deletion- saKKH_F	GTGGAAGGACGAAACACCGAAGATGACTATCTTTAATGTCTGTTTTAGTACT CTGGAACAG	Figure 2E	Sa ^{KKH} PE2*
CCR5-deletion- saKKH_R	GTATCGATAAGCTTGATATCAAAAAAGATGACTATCTTTAATATAAGGAAAA TGAGAGCTGCAGGTGTAATGGACCGACTCGGTCCCACTTTTTC	Figure 2E	Sa ^{KKH} PE2*
Serpina1 G to A gblocks	TATATATCTTGTGGAAGGACGAAACACCGtTATATATCTTGTGGAAGGAC GAAACACCGTccccctccaggccgtgcatagtttttagagctagaaatagcaag ttaaataaaggctagtcggttatcaacttg	Figure 3A	PE2 or PE2*
Serpina1 G to A gblocks	TATATATCTTGTGGAAGGACGAAACACCGcaTATATATCTTGTGGAAGGA CGAAACACCGTccccctccaggccgtgcatagtttttagagctagaaatagcaa gttaaataaaggctagtcggttatcaacttg	Figure 3A	Sa ^{KKH} PE2*
Serpina1 A to G gblocks	TATATATCTTGTGGAAGGACGAAACACCGTATATATCTTGTGGAAGGACG AAACACCGTccccctccaggccgtgcatagtttttagagctagaaatagcaagt taaataaaggctagtcggttatcaacttg	Figure 3B	PE2 or PE2*
Ctnnb1 C to T gblocks	ATCTTGTGGAAGGACGAAACACCGAGGGTTGCCCTTGCCACTCAgtttttag agctagaaatagcaagttaaataaaggctagtcggttatcaacttgaaaaag tgggaccgagtcggtccGCTCTTCTCTGAGTGCAAGGGCAATTTTTTTGA ATTCGATATCAAGCTTATCGATACCGT	Figure 4A	PE2 or PE2*

Supplementary Table 3. Sequences of primers used for genomic DNA amplification and high throughput sequencing.

Figure	Description	PE		Sequence
Figure 2A~2C	EMX1_locus	PE2/PE2* or SaCas9	5p-DS1_EMX1	ctacacgacgctcttccgatctCCTCCTGAGT TTCTCATCTGTGCC
Figure 2A~2C			3p-DS1_EMX1	agacgtgtgctcttccgatctTCTGCCCTCGT GGGTTTGTG

Figure 2A~2C		PE2*/SaKKH PE2*	5p-DS2_EMX1	ctacacgacgctcttccgatctGGACAAAGTA CAAACGGCAGAAGC
Figure 2A~2C			3p-DS2_EMX1	agacgtgtgctcttccgatctCAGCCAGCCCA TTGCTTGTC
Figure 2D~2E	CCR5-deletion	PE2/PE2* or SaKKHPE2*	DS-5P-CR5_UMI-deletion	CTACACGACGCTCTTCCGATCTNNWNNVHBGT CTCTCCCAGGAATCATCTTTACCAG
Figure 2D~2E			3p_DS_constant	AGACGTGTGCTCTTCCGAT
Figure 2D~2E			5p-DS_CCR5	ctacacgacgctcttccgatctGTCTCTCCCA GGAATCATCTTTACCAG
Figure 2D~2E			3p-DS_CCR5	agacgtgtgctcttccgatctCGACACCGAAG CAGAGTTTTTAGGAT
Figure 3A~3D	Serpina1 G to A or Serpina1 A to G	PE2/PE2* or SaKKHPE2*	5p-AAT-DS	ctacacgacgctcttccgatctATAAGGCTGT GCTGACCATCG
Figure 3A~3D				
Figure 3A~3D			3p-AAT-DS	agacgtgtgctcttccgatctGGGAGACTTG GTATTTTGTTCA
Figure 3A~3D				
Figure 3A~3D				
Figure 3A~3D				
Figure 4	Ctnnb1 TCC deletion	PE2/PE2*	ctnnb1-Uditas-FWD	GTGACTGGAGTTTCAGACGTGTGCTCTTCCGAT CTGCTTCTTCAGGTAGCATTTTCAGTTTAC
Figure 4			ctnnb1-Uditas-REV	GTGACTGGAGTTTCAGACGTGTGCTCTTCCGAT CTGCTTCCAAACACAAATGCTTTACCAG
Figure 5	Serpina1 A to G	AAV	SerpinA1-Uditas-FWD	GTGACTGGAGTTTCAGACGTGTGCTCTTCCGAT CTagccttacaacgtgtctctgcttc
Figure 5			SerpinA1-Uditas-REV	GTGACTGGAGTTTCAGACGTGTGCTCTTCCGAT CTgcagttatTTTTgggtgggatca

Supplementary Table 4. Potential genetic engineered liver cancer models using prime editors.

Strain	Target gene	Accompanying gene/mutation
FVB/B6	p53 R270H	c-Myc
FVB/B6	HrasG12V	c-Myc
FVB/B6	NrasG12V	c-Myc
FVB/B6	KrasG12V	p53 R270H
FVB/B6	Ctnnb1 S45F	YapS127A
FVB/B6	NrasG12V	Akt
FVB/B6	Ctnnb1 S45F	Akt
FVB/B6	Ctnnb1 S45F	c-Met

Supplementary Table 5. In vivo on target analysis at SERPINA1 site by UdiTaS.

Figure	Sample	total_reads		precise_editing		small_indels(<2 0bp)_or_substit utions		Deletions between pegRNA and nicking sgRNA (<100bp)		Deletion (large_deletio ns > 100bp)		AAV_insertion	
		total_ #	Uniqu e_UM l#	total_ #	Uniqu e_UM l#	total_ #	Unique _UMl#	total_ #	Uniqu e_UM l#	total_ #	Uniqu e_UMl #	total_ #	Uniqu e_UM l#
Figure 5D and 5E	Neg-R1	13207 68	46632	96	14	377	29	54	7	9	1	0	0
Figure 5D and 5E	Neg-R2	13447 84	71231	112	18	385	52	44	5	14	2	0	0

Figure 5D and 5E	Neg-R3	11274 85	51684	56	5	512	38	19	3	3	1	0	0
Figure 5D and 5E	6wks-R1	18170 81	77854	19854	924	4352	211	1322	71	79	13	22	3
Figure 5D and 5E	6wks-R2	19454 21	81256	17526	865	2464	238	1165	62	85	11	19	3
Figure 5D and 5E	6wks-R3	15214 78	65424	11548	614	3716	189	1327	55	82	10	5	1
Figure 5D and 5E	10wks-R1	13254 75	63367	25513	1256	7785	419	1985	112	124	17	61	7
Figure 5D and 5E	10wks-R2	18547 88	74541	27452	1274	5562	298	1428	86	75	21	32	6
Figure 5D and 5E	10wks-R3	16548 76	78458	36525	2115	1223 5	712	2565	177	228	54	216	18

Supplementary Sequences 1. Sequences of reporter cell line used in this study

mCherry Reporter sequence for A-to-G transition :

PAM-sgRNA **stop_codon**

ATGGTGAGCAAGGGCGAGGAGGACAACATGGCCATCATCAAGGAGTTCATGCGCTTCAAGGTGCACATGG
AGGGCTCCGTGAACGGCCACGAGTTCGAGATCGAGGGtGAGGGtGAGGGCCGaCCCTACGAGGGCACCCtA
GACCGCAAGCTGAAGGTGACCAAGGGCGGaCCCTGCCCTTCGCCTGGGACATCCTGTCCCCTCAGTTC
ATGTACGGCTCCAAGGCCTACGTGAAGCACCCCGCGACATCCCCGACTACTTGAAGCTGTCTTCCCCG
AGGGCTTCAAGTGGGAGCGCGTGATGAACTTCGAGGACGGCGGCGTGGTGACCGTGACCCAGGACTCCTC
CCTGCAGGACGGCGAGTTCATCTACAAGGTGAAGCTGCGCGGCACCAACTTCCCCCTCCGACGGCCCCGTA
ATGCAGAAGAAGACCATGGGCTGGGAGGCCTCCTCCGAGCGGATGTACCCCGAGGACGGCGCCCTGAAGG
GCGAGATCAAGCAGAGGCTGAAGCTGAAGGACGGCGGCCACTACGACGCCGAGGTCAAGACCACCTACAA
GGCCAAGAAGCCCGTGAGCTGCCCGGCGCCTACAACGTCAACATCAAGCTGGACATCACCTCCCACAAC
GAGGACTACACCATCGTGGAACAGTACGAGCGCGCCGAGGGCCGCCACTCCACCGGCGGCATGGACGAGC
TGTACAAGTAA

Traffic Light Reporter sequence for 47bp deletion:

GFP-47bp_Insertion-P2A-mCherry

ATGCCCCGCATGAAGATCGAGTGCCGCATCACCGGCACCCTGAACGGCGTGAGTTCGAGCTGGTGGGCG
GCGGAGAGGGCACCCCcgaggggccccaaatcacctgcctcgaggagacaaaatacccgttcCGAGCAG
GGtCGCATGACCAACAAGATGAAGAGCACCAAGGCGCCCTGACCTTCAGCCCCCTACCTGCTGAGCCACG
TGATGGGCTACGGCTTCTACCACTTCGGCACCTACCCAGCGGCTACGAGAACCCTTCTGCACGCCAT
CAACAACGGCGGCTACACCAACACCCGCATCGAGAAGTACGAGGACGGCGGCGTGCTGCACGTGAGCTTC
AGCTACCGCTACGAGGCCGCGCGGTGATCGGCGACTTCAAGGTGGTGGGCACCGGCTTCCCCGAGGACA
GCGTGATCTTACCGACAAGATCATCCGCAGCAACGCCACCGTGGAGCACCTGCACCCCATGGGCGAcAA
CGTGCTGGTGGGCAGCTTCGCCCCGACCTTCAGCCTGCGCGACGGCGGCTACTACAGCTTCGTGGTGGAC
AGCCACATGCACTTCAAGAGCGCCATCCACCCAGCATCCTGCAGAACGGGGGCCCCATGTTTCGCCTTCC

GCCGCGTGGAGGAGCTGCACAGCAACACCGAGCTGGGCATCGTGGAGTACCAGCACGCCTTCAAGACCCC
 CATCGCCTTCGCCAGATCTCGAGCTCGA^{gg}gccacgaattttctcgctactcaagcaggcggcgatgtcg
 aggaaaaccctggtcctGTGAGCAAGGGCGAGGAGGACAACATGGCCATCATCAAGGAGTTCATGCGCTT
 CAAGGTGCACATGGAGGGCTCCGTGAACGGCCACGAGTTCGAGATCGAGGGCGAGGGCGAGGGCCGCCCC
 TACGAGGGCACCCAGACCGCCAAGCTGAAGGTGACCAAGGGCGGCCCCCTGCCCTTCGCCTGGGACATCC
 TGTCCCCTCAGTTCATGTACGGCTCCAAGGCCTACGTGAAGCACCCCGCCGACATCCCCGACTACTTGAA
 GCTGTCCTTCCCCGAGGGCTTCAAGTGGGAGCGCGTGATGAACTTCGAGGACGGCGGCGTGGTGACCGTG
 ACCCAGGACTCCTCCCTGCAGGACGGCGAGTTCATCTACAAGGTGAAGCTGCGCGGCACCAACTTCCCCT
 CCGACGGCCCCGTAATGCAGAAGAAGACCATGGGCTGGGAGGCCTCCTCCGAGCGGATGTACCCCGAGGA
 CGGCGCCCTGAAGGGCGAGATCAAGCAGAGGCTGAAGCTGAAGGACGGCGGCCACTACGACGCCGAGGTC
 AAGACCACCTACAAGGCCAAGAAGCCCGTGCAGCTGCCCGCGCCTACAACGTCAACATCAAGCTGGACA
 TCACCTCCCACAACGAGGACTACACCATCGTGGAACAGTACGAGCGCGCCGAGGGCCGCCACTCCACCGG
 CGGCATGGACGAGCTGTACAAGTAATAG

Traffic Light Reporter sequence for 39bp deletion + 18bp insertion:

GFP-39bp_Insertion-T2A-mCherry

atggtgagcaagggcgaggagctgttcaccggggtggtgccatcctggtcgagctggacggcgacgtaa
 acggccacaagtccagcgtgtccggcTTTGGCGAGACAAATCACCTGCCTCGTGGAATACGGTAAaccta
 cggcaagctgacctgaagttcatctgcaccaccggcaagctgcccgtgccctggcccacctcgtgacc
 acctgacctacggcgtgcagtgttcagccgtaccccgaccacatgaagcagcagacttcttcaagt
 cgcctatgccgaaggctacgtccaggagcgcaccatcttcttcaaggacgacggcaactacaagaccg
 cgccgaggtgaagttcgagggcgacacctggtgaaccgcacgcagctgaagggcatcgacttcaaggag
 gacggcaacatcctggggcacaagctggagtacaactacaacagccacaacgtctatatcatggccgaca
 agcagaagaacggcatcaaggtgaacttcaagatccgccacaacatcgaggacggcagcgtgcagctcgc
 cgaccactaccagcagaacacccccatcgggcgacggccccgtgctgctgcccgcacaaccactacctgagc
 acccagtcgcctgagcaaagaccccaacgagaagcgcgatcacatggtcctgctggagttcgtgaccg
 ccgcccgggatacactctcgcatggacgagctgtacaagtaactggatccggtgagggcagaggaagtctt
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 ccttcgcctgggacatcctgtccctcagttcatgtacggctccaaggcctacgtgaagcaccocgccc
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 cgcggcaccaacttcccctccgacggccccgtaatgcagaagaagaccatgggctgggagggcctcctccg
 agcggatgtaccccgaggacggcgccctgaagggcgagatcaagcagaggctgaagctgaaggacggcgg
 ccactacgacgctgaggtcaagaccactacaaggccaagaagcccgtgcagctgcccggcgccctacaac
 gtcaacatcaagttggacatcacctcccacaacgaggactacaccatcgtggaacagtacgaacgcgccc
 agggccgccactccaccggcgcatggacgagctgtacaagtga

Supplementary Sequences 2. Sequence of backbone plasmid used for pegRNA and nicking sgRNA cloning

Backbone of pegRNA used for PE2 or PE2*: U6 promoter + spCas9-sgRNA scaffold

GTGGCACTTTTCGGGGAAATGTGCGCGGAACCCCTATTTGTTTATTTTTCTAAATACATTCAAA
TATGTATCCGCTCATGAGACAATAACCCTGATAAATGCTTCAATAATATTGAAAAAGGAAGAGT
ATGAGTATTCAACATTTCCGTGTCGCCCTTATTCCTTTTTTTCGGGCATTTTGCCTTCCTGTTT
TTGCTCACCCAGAAACGCTGGTGAAAGTAAAAGATGCTGAAGATCAGTTGGGTGCACGAGTGGG
TTACATCGAACTGGATCTCAACAGCGGTAAGATCCTTGAGAGTTTTCGCCCCGAAGAACGTTTT
CCAATGATGAGCACTTTTAAAGTTCTGCTATGTGGCGCGGTATTATCCCGTATTGACGCCGGGC
AAGAGCAACTCGGTGCGCGCATACACTATTCTCAGAATGACTTGGTTGAGTACTCACCAGTCAC
AGAAAAGCATCTTACGGATGGCATGACAGTAAGAGAATTATGCAGTGCTGCCATAACCATGAGT
GATAACACTGCGGCCAACTTACTTCTGACAACGATCGGAGGACCGAAGGAGCTAACCGCTTTTT
TGCACAACATGGGGGATCATGTAACCTCGCCTTGATCGTTGGGAACCGGAGCTGAATGAAGCCAT
ACCAAACGACGAGCGTGACACCACGATGCCTGTAGCAATGGCAACAACGTTGCGCAAACTATTA
ACTGGCGAACTACTTACTCTAGCTTCCCGGCAACAATTAATAGACTGGATGGAGGCGGATAAAG
TTGCAGGACCACTTCTGCGCTCGGCCCTTCCGGCTGGCTGGTTTATTGCTGATAAATCTGGAGC
CGGTGAGCGTGGGTCTCGCGGTATCATTGCAGCACTGGGGCCAGATGGTAAGCCCTCCCGTATC
GTAGTTATCTACACGACGGGGAGTCAGGCAACTATGGATGAACGAAATAGACAGATCGCTGAGA
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TGATTTAAACTTCATTTTTTAATTTAAAGGATCTAGGTGAAGATCCTTTTTTGATAATCTCATG
ACCAAAATCCCTTAACGTGAGTTTTTCGTTCCACTGAGCGTCAGACCCCGTAGAAAAGATCAAAG
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ACCAGCGGTGGTTTGTTCGCGGATCAAGAGCTACCAACTCTTTTTCCGAAGGTAACGGCTTC
AGCAGAGCGCAGATACCAAATACTGTCTTCTAGTGTAGCCGTAGTTAGGCCACCACTTCAAGA
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CGATAAGTCGTGTCTTACCGGGTTGGACTCAAGACGATAGTTACCGGATAAGGCGCAGCGGTG
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AAGCGGAAGAGCGCCCAATACGCAAACCGCCTCTCCCCGCGCGTTGGCCGATTCATTAATGCAG
CTGGCACGACAGGTTTCCCGACTGGAAAGCGGGCAGTGAGCGCAACGCAATTAATGTGAGTTAG
CTCACTCATTAGGCACCCCAGGCTTTACACTTTATGCTTCCGGCTCGTATGTTGTGTGGAATTG
TGAGCGGATAACAATTTACACAGGAAACAGCTATGACCATGATTACGCCAAGCGCGCAATTAA
CCCTCACTAAAGGGAACAAAAGCTGGAGCTCCACCGCGGTGGCGGCCGCCCTTACACGAGGG
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AAAGTATTTGATTTCTTGGCTTTATATATCTTGTGGAAAGGACGAAACACCGGTGTGCAGGTG
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TCGTCAAGAAGGCGATAGAAGGCGATGCGCTGCGAATCGGGAGCGGCGATACCGTAAAGCACGA
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CTGATAGCGGTCCGCCACACCCAGCCGGCCACAGTCGATGAATCCAGAAAAGCGGCCATTTTCC
ACCATGATATTTCGGCAAGCAGGCATCGCCATGGGTACGACGAGATCCTCGCCGTGCGGCATGC

GCGCCTTGAGCCTGGCGAACAGTTCGGCTGGCGCGAGCCCCTGATGCTCTTCGTCCAGATCATC
CTGATCGACAAGACCGGCTTCCATCCGAGTACGTGCTCGCTCGATGCGATGTTTCGCTTGGTGG
TCGAATGGGCAGGTAGCCGGATCAAGCGTATGCAGCCGCCGATTGCATCAGCCATGATGGATA
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CCAGTCCCTTCCCGCTTCAGTGACAACGTCGAGCACAGCTGCGCAAGGAACGCCCGTCGTGGCC
AGCCACGATAGCCGCGCTGCCTCGTCTCTGCAGTTCATTTCAGGGCACCCGGACAGGTTCGGTCTTGA
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CCATCTTGTTCAATCATGCGAAACGATCCTCATCCTGTCTCTTGATCAGATCTTGATCCCCTGC
GCCATCAGATCCTTGGCGGCAAGAAAGCCATCCAGTTTACTTTGCAGGGCTTCCCAACCTTACC
AGAGGGCGCCCCAGCTGGCAATTCCGACGGATCAAGAACCTGCTGACGTTTTAGAGCTAGAAATAG
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TGAGTCGTATTACGCGCGCTCACTGGCCGTCGTTTTACAACGTCGTGACTGGGAAAACCCCTGGC
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CCCGCACCGATCGCCCTTCCCAACAGTTGCGCAGCCTGAATGGCGAATGGGACGCGCCCTGTAG
CGGCGCATTAAGCGCGGGCGGGTGTGGTGGTTACGCGCAGCGTGACCGCTACACTTGCCAGCGCC
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AAGCTCTAAATCGGGGGCTCCCTTTAGGGTTCCGATTTAGTGCTTTACGGCACCTCGACCCCCAA
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TTGACGTTGGAGTCCACGTTCTTTAATAGTGGACTCTTGTTCCAAACTGGAACAACACTCAACC
CTATCTCGGTCTATTCTTTTGATTTATAAGGGATTTTGCCGATTTTCGGCCTATTGGTTAAAAAA
TGAGCTGATTTAACAAAAATTTAACGCGAATTTTAACAAAATATTAACGCTTACAATTTAG

Backbone of Nicking sgRNA used for PE2 or PE2*: U6 promoter + spCas9-sgRNA scaffold

GTGGCACTTTTCGGGGAAATGTGCGCGGAACCCCTATTTGTTTATTTTTCTAAATACATTCAAATATGTA
TCCGCTCATGAGACAATAACCCTGATAAATGCTTCAATAATATTGAAAAAGGAAGAGTATGAGTATTCAA
CATTTCCGTGTGCGCCCTTATTCCCTTTTTTTCGGGCATTTTGCCTTCCTGTTTTTGCTCACCCAGAAACGC
TGGTGAAGTAAAAGATGCTGAAGATCAGTTGGGTGCACGAGTGGGTACATCGAACTGGATCTCAACAG
CGGTAAGATCCTTGAGAGTTTTTCGCCCCGAAGAACGTTTTTCCAATGATGAGCACTTTTAAAGTTCTGCTA
TGTGGCGCGGTATTATCCCGTATTGACGCCGGGCAAGAGCAACTCGGTGCGCGCATACTACTATTCTCAGA
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GAGCTAACCGCTTTTTTGCACAACATGGGGGATCATGTAACCTCGCCTTGATCGTTGGGAACCGGAGCTGA
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ATTAACGGCGAACTACTTACTCTAGCTTCCCGGCAACAATTAATAGACTGGATGGAGGCGGATAAAGTT
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AGGGTCGGAACAGGAGAGCGCACGAGGGAGCTTCCAGGGGGAAACGCCTGGTATCTTTATAGTCCTGTGC
GGTTTCGCCACCTCTGACTTGAGCGTCGATTTTTGTGATGCTCGTCAGGGGGGCGGAGCCTATGAAAAA
CGCCAGCAACGCGGCCTTTTTACGGTTCCCTGGCCTTTTGCTGGCCTTTTGCTCACATGTTCTTTCTGCG
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GCAATTAATGTGAGTTAGCTCACTCATTAGGCACCCAGGCTTTACACTTTATGCTTCCGGCTCGTATGT
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CAGTTTTAAATATGTTTTAAATGGACTATCATATGCTTACCGTAACTTGAAAGTATTTTCGATTTCTT
GGCTTTATATATCTTGTGGAAAGGACGAAACACCGGTGTGCAGGTGAGTGATCCAAACGCCCGGCGGCAA
CCGAGCGTTCTGAACAAATCCAGATGGAGTTCTGAGGTCATTACTGGATCTATCAACAGGAGTCCAAGCG
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CACGGGTAGCCAACGCTATGTCCTGATAGCGGTCCGCCACACCCAGCCGCCACAGTCGATGAATCCAGA
AAAGCGGCCATTTTCCACCATGATATTCGGCAAGCAGGCATCGCCATGGGTCACGACGAGATCCTCGCCG
TCGGGCATGCGCGCCTTGAGCCTGGCGAACAGTTTCGGCTGGCGCGAGCCCTGATGCTCTTCGTCCAGAT
CATCCTGATCGACAAGACCGGCTTCCATCCGAGTACGTGCTCGCTCGATGCGATGTTTCGCTTGGTGGTC
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GCAGGAGCAAGGTGAGATGACAGGAGATCCTGCCCCGGCACTTCGCCCAATAGCAGCCAGTCCCTTCCCCG
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CTCTTGATCAGATCTTGATCCCCTGCGCCATCAGATCCTTGGCGGCAAGAAAGCCATCCAGTTTACTTTG
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GGCGTTACCCAACCTAATCGCCTTGACGACATCCCCCTTTGCGCAGCTGGCGTAATAGCGAAGAGGCC
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CTCTTGTTCCAACTGGAACAACACTCAACCCTATCTCGGTCTATTCTTTTGATTTATAAGGGATTTTGC
CGATTTCGGCCTATTGGTTAAAAAATGAGCTGATTTAACAAAAATTTAACGCGAATTTTAAACAAAATATT
AACGCTTACAATTTAG

Backbone of pegRNA or Nicking sgRNA used for for SaPE2* and SaPE2*: U6 promoter +
SaCas9 sgRNA scaffold

GTGGCACTTTTCGGGGAAATGTGCGCGGAACCCCTATTTGTTTATTTTTCTAAATACATTCAAATATGTA
TCCGCTCATGAGACAATAACCCTGATAAATGCTTCAATAATATTGAAAAAGGAAGAGTATGAGTATTCAA
CATTTCCGTGTCGCCCTTATTCCCTTTTTTTCGGGCATTTTGCCTTCCTGTTTTTGCTCACCCAGAAACGC
TGGTGAAGTAAAGATGCTGAAGATCAGTTGGGTGCACGAGTGGGTACATCGAACTGGATCTCAACAG
CGGTAAGATCCTTGAGAGTTTTTCGCCCCGAAGAACGTTTTTCCAATGATGAGCACTTTTAAAGTTCTGCTA
TGTGGCGCGGTATTATCCCGTATTGACGCCGGGCAAGAGCAACTCGGTCGCCGCATACACTATTCTCAGA
ATGACTTGGTTGAGTACTCACCAGTCACAGAAAAGCATCTTACGGATGGCATGACAGTAAGAGAATTATG
CAGTGCTGCCATAACCATGAGTGATAACACTGCGGCCAACTTACTTCTGACAACGATCGGAGGACCGAAG
GAGCTAACCGCTTTTTTGCACAACATGGGGGATCATGTAACCTCGCCTTGATCGTTGGGAACCGGAGCTGA
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GCAGGACCACTTCTGCGCTCGGCCCTTCCGGCTGGCTGGTTTTATTGCTGATAAATCTGGAGCCGGTGAGC
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GACGGGGAGTCAGGCAACTATGGATGAACGAAATAGACAGATCGCTGAGATAGGTGCCTCACTGATTAAAG
CATTGGTAAC TGTGACACCAAGTTTACTCATATATACTTTAGATTGATTTAAACCTTCATTTTTAATTTA
AAAGGATCTAGGTGAAGATCCTTTTTTGATAATCTCATGACCAAAATCCCTTAACGTGAGTTTTCGTTCCA
CTGAGCGTCAGACCCCGTAGAAAAGATCAAAGGATCTTCTTGAGATCCTTTTTTTCTGCGCGTAATCTGC
TGCTTGCAAACAAAAAAACCACCGCTACCAGCGGTGGTTTTGTTTGCCGGATCAAGAGCTACCAACTCTTT
TTCCGAAGGTAAC TGGCTTCAGCAGAGCGCAGATACCAATACTGTCCTTCTAGTGTAGCCGTAGTTAGG
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GCCAGTGGCGATAAGTCGTGTCTTACCGGGTTGGACTCAAGACGATAGTTACC GGATAAGGCGCAGCGGT
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GGTTTCGCCACCTCTGACTTGAGCGTCGATTTTTTGATGCTCGTCAGGGGGGCGGAGCCTATGGAAAAA
CGCCAGCAACGCGGCCTTTTTTACGGTTCCCTGGCCTTTTTGCTGGCCTTTTTGCTCACATGTTCTTTCTGCG
TTATCCCCTGATTCTGTGGATAACCGTATTACCGCCTTTGAGTGAGCTGATACCGCTCGCCGCAGCCGAA
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GCAATTAATGTGAGTTAGCTCACTCATTAGGCACCCCAGGCTTTACACTTTATGCTTCCGGCTCGTATGT
TGTGTGGAATTGTGAGCGGATAACAATTTACACAGGAAACAGCTATGACCATGATTACGCCAAGCGCGC
AATTAACCCTCACTAAAGGGAACAAAAGCTGGAGCTCCACCGCGGTGGCGGCCGCCCTTACC **GAGGG**
CCTATTTCCCATGATTCCTTCATATTTGCATATACGATACAAGGCTGTTAGAGAGATAATTGGAATTAAT
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CACGGGTAGCCAACGCTATGTCCTGATAGCGGTCCGCCACACCCAGCCGGCCACAGTCGATGAATCCAGA
AAAGCGGCCATTTTCCACCATGATATTCGGCAAGCAGGCATCGCCATGGGTACGACGAGATCCTCGCCG
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CATCCTGATCGACAAGACCGGCTTCCATCCGAGTACGTGCTCGCTCGATGCGATGTTTCGCTTGGTGGTC
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CTCGTCCTGCAGTTCATTCAGGGCACCGGACAGGTCGGTCTTGACAAAAAGAACCGGGCGCCCCCTGCGCT
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TTTTGCCGATTTTCGGCCTATTGGTTAAAAAATGAGCTGATTTAACAAAAATTTAACGCGAATTTTAACAA
AATATTAACGCTTACAATTTAG

PegRNA used for for SaPE2* : U6 promoter-sgRNA-Scaffold-RT template-PBS (CCR5
pegRNA as an example)

GTGGCACTTTTCGGGGAAATGTGCGCGGAACCCCTATTTGTTTATTTTTCTAAATACATTCAAATATGTA
TCCGCTCATGAGACAATAACCCTGATAAATGCTTCAATAATATTGAAAAAGGAAGAGTATGAGTATTCAA
CATTTCCGTGTGCGCCCTTATTCCCTTTTTTTCGGGCATTTTGCCTTCCTGTTTTTGTCTACCCAGAAACGC
TGGTGAAAGTAAAAGATGCTGAAGATCAGTTGGGTGCACGAGTGGGTACATCGAACTGGATCTCAACAG
CGGTAAGATCCTTGAGAGTTTTTCGCCCCGAAGAACGTTTTTCCAATGATGAGCACTTTTAAAGTTCTGCTA
TGTGGCGCGGTATTATCCCGTATTGACGCCGGGCAAGAGCAACTCGGTGCGCGCATACTACTATTCTCAGA
ATGACTTGGTTGAGTACTCACCAGTCACAGAAAAGCATCTTACGGATGGCATGACAGTAAGAGAATTATG
CAGTGCTGCCATAACCATGAGTGATAACACTGCGGCCAACTTACTTCTGACAACGATCGGAGGACCGAAG
GAGCTAACCGCTTTTTTGCACAACATGGGGGATCATGTAACCTCGCCTTGATCGTTGGGAACCGGAGCTGA
ATGAAGCCATACCAAACGACGAGCGTGACACCACGATGCCTGTAGCAATGGCAACAACGTTGCGCAAACCT
ATTAAC TGGCGAACTACTTACTCTAGCTTCCCGGCAACAATTAATAGACTGGATGGAGGCGGATAAAGTT
GCAGGACCACTTCTGCGCTCGGCCCTTCCGGCTGGCTGGTTTTATTGCTGATAAATCTGGAGCCGGTGAGC
GTGGGTCTCGCGGTATCATTGCAGCACTGGGGCCAGATGGTAAGCCCTCCCGTATCGTAGTTATCTACAC
GACGGGGAGTCAGGCAACTATGGATGAACGAAATAGACAGATCGCTGAGATAGGTGCCTCACTGATTAAG
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TGCTTGCAACAAAAAAACCACCGCTACCAGCGGTGGTTTTGTTTGCCGGATCAAGAGCTACCAACTCTTT
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GCCAGTGGCGATAAGTCGTGTCTTACCGGGTTGGACTCAAGACGATAGTTACCGGATAAGGCGCAGCGGT
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AGGGTCGGAACAGGAGAGCGCACGAGGGAGCTTCCAGGGGGAAACGCCTGGTATCTTTATAGTCCTGTGCG
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CGCCAGCAACGCGGCCTTTTTACGGTTCCTGGCCTTTTGCTGGCCTTTTGCTCACATGTTCTTTCTCCTGCG
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TGTGTGGAATTGTGAGCGGATAACAATTTACACAGGAAACAGCTATGACCATGATTACGCCAAGCGCGC
AATTAACCCTCACTAAAGGGAACAAAAGCTGGAGCTCCACCGCGGTGGCGGCCGCCCTTCACC**GAGGG**
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TAATAGTGGACTCTTGTTCCAAACTGGAACAACACTCAACCCTATCTCGGTCTATTCTTTTGATTTATAA
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ACAAAATATTAACGCTTACAATTTAG

Supplementary Sequences 3. Protein Sequences of prime editors

PE2: BPSV40_NLS-SpCas9H840A-linker-M-MLV_reverse transcriptase-BPSV40

KRTADGSEFESPKKKRKVDKKYSIGLDIGTNSVGWAVITDEYKVPSKKFKVLGNTDRHSIKKNLIGALLF
DSGETAEATRLKRTARRRYTRRKNRICYLQEIFSNEMAKVDDSFHRLEESFLVEEDKKHERHPIFGNIV
DEVAYHEKYPTIYHLRKKLVDSTDKADRLRIYLALAHMIKFRGHFLIEGDLNPDNSDVKLFQVLQVTYN
QLFEENPINASGVDAKILSARLSKSRLENLIAQLPGEKKNGLFGNLIALSLGLTPNFKSNFDLAEDAK
LQLSKDITYDDDLNLLAQIGDQYADLFLAAKNLSDAILLSDILRVNTEITKAPLSASMIKRYDEHHQDLT
LLKALVRQQLPEKYKEIFFDQSKNGYAGYIDGGASQEEFYKFIKPILEKMDGTEELLVKLNREDLLRKQR
TFDNGSIPHQIHLGELHAILRRQEDFYFPLKDNREKIEKILTFRIPIYYVGPLARGNSRFAWMTRKSEETI
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DILEDIVLTLTLFEDREMIEERLKTYAHLFDDKVMKQLKRRRYTGWGRLSRKLINGIRDKQSGKTILDFL
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HKPENIVIEMARENQTTQKGQKNSRERMKRIEEG IKELGSQILKEHPVENTQLQNEKLYLYYLQNGRDMY
VDQELDINRLSDYDVAIVPQSFLKDDSIDNKVLTRSDKNRGKSDNVPSEEVVKMKMKNYWRQLLNAKLIT
QRKFDNLTKAERGGLSELDKAGFIKRQLVETRQITKHVAQILDSRMNTKYDENDKLIREVKVITLKSCLV
SDFRKDFQFYKVREINNYHHAHDAYLNAVVGTA L IKKYPKLESEFVYGDKVYDVRKMIKSEQEI GKAT
AKYFFYSNIMNFFKTEITLANGEIRKRPLIETNGETGEIVWDKGRDFATVRKVL SMPQVNIVKKTEVQTG
GFSKESILPKRNSDKLIARKKDWDPKKYGGFDSPTVAYSVLVAKVEKGKSKKLKSVKELLGITIMERS
FEKNPIDFLEAKGYKEVKKDLI IKLPKYSLFELENGRKRMLASAGELQKGNELALPSKYVNFYLYLASHYE

KLKGSPEDNEQKQLFVEQHKHYLDEIIEQISEFSKRVLADANLDKVL SAYNKH RDKPIREQAENIIHLF
TLTNL GAPA AAFKYFDTTIDRKRYTSTKEVLDATLIHQSI TGLYETRIDLSQLGGI SGGSSGGSSGSETPG
TSESATPESSGGSSGGSS TLNIEDEYRLHETSKEPDVSLGSTWLSDFPQAWAETGGMGLAVRQAPLI IPL
KATSTPVS IKQYPMSQEARLG I KPHIQRLLDQGILVPCQSPWNTPLLPVKKPGTNDYRPVQDLREVNKR
VEDIHPTVPNPYNLLSGLPPSHQWYTVL DLKDAFFCLRLHPTSQPLFAFEWRDP EMGISGQLTWTRL PQGF
KNSPTL FNEALHRDLAD FRIQH PDLILLQYVDDLLAATSELDCQQGTRALLQTLGNLGYRASAKKAQIC
QKQVKYLG YLLKEGQRWL TEARKETVMGQPTPKTPRQLREFLGKAGFCRLFIPGFAEMAAPLYPLTKPGT
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ETEVIWAKALPAGTSAQRAELIALTQALKMAEGKKLVYTD SRYAFATAHIHGEIYRRRGWLTSEGKEIK
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RTADGSEFEPKKKRKV

PE2*: Cmyc NLS-BPSV40_NLS-SpCas9H840A-linker-M-MLV reverse transcriptase-
vBPSV40_NLS-SV40

PAAKRVKLDGGKRTADGSEFESPKKKRKVDKKYSIGLDIGTNSVGWAVITDEYKVPSKKFKVLGNTDRHS
IKKNLIGALLFDSGETAEATRLKRTARRRYTRRKNRICYLQEIFSNEMAKVDDSFHRLEESFLVEEDKK
HERHPIFGNIVDEVAYHEKYPTIYHLRKKLV DSTDKADLR LIYLA LAHMIKFRGHFLIEGDLNPDNSDVD
KLFIQLVQTYNQLFEENPINASGVDAKAILSARLSKSRLENLIAQLPGEKKNGLFGNLIALSLGLTPNF
KSNFDLAEDAKLQLSKD TYDDDLDNLLAQIGDQYADLFLAAKNLSDAILLS DILRVNTEITKAPLSASMI
KRYDEHHQDLTLLKALVRQQLPEKYKEIFFDQSKNGYAGYIDGGASQEEFYKFIKPILEKMDGTEELLVK
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GMRKPAFLSGEQKKAIVDLLFKTNRKVTVKQLKEDYFKKIECFDSVEISGVEDRFNASLGTYHDLKIIK
DKDFLDNEENEDILEDIVLTLT LFEDREMIEERLKTYAHLFDDKVMKQLKRRRYTGWGRLSRKLINGIRD
KQSGKTILDFLKSDGFANRNF MQLIHDDSLTFKEDIQKAQVSGQGDSLHEHIANLAGSPA I KKGILQTVK
VVDELVKVMGRHKPENIVIEMARENQTQKGQKNSRERMKRIE EG IKELGSQILKEHPVENTQLQNEKLY
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LLGITIMERS SFEKNPIDFLEAKGYKEVKDLIIKLPKYSLFELENGKRMLASAGELQKGNELALPSKY
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REQAENIIHLFTLTNLGAPA AAFKYFDTTIDRKRYTSTKEVLDATLIHQSI TGLYETRIDLSQLGGI SGGSS
SGGSSGSETPGTSESATPESSGGSSGGSS TLNIEDEYRLHETSKEPDVSLGSTWLSDFPQAWAETGGMGL
AVRQAPLI IPLKATSTPVS IKQYPMSQEARLG I KPHIQRLLDQGILVPCQSPWNTPLLPVKKPGTNDYRP
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VAYLSKKLDPVAAGWPPCLRMVAAIAVLTKDAGKLTMGQPLVILAPHAVEALVKQPPDRWLSNARMTHYQ
ALLLDTDRVQFGPVVALNPATLLPLPEEGLQHNCLDILAEAHGTRPDLTDQPLPDADHTWYTDGSSLLQE
GQRKAGAAVTTETEVIWAKALPAGTSAQRAELIALTQALKMAEGKKLVYTD SRYAFATAHIHGEIYRRR

GWLTSEGKEIKNKDEILALLKALFLPKRLSIIHCPGHQKGHSAEARGNRMADQAARKAAITETPDTSTLL
IENSSPSGGSKRTADGSEKRTADSQHSTPPKTKRKVEFEPKKKRKV

SaPE2*: Cmyc_NLS-BPSV40_NLS-SaCas9N580A-linker-M-MLV_reverse_transcriptase-
vBPSV40_NLS-SV40

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FSAALLHLAKRRGVHNVNEVEEDTGNELSTKEQISRNSKALEEKYVAELQLERLKKDGEVRGSINRFKTS
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RSVKYAYNADLYNALNDLNNLVITRDENEKLEYEYEFQIIENVFKQKKKPTLKQIAKEILVNEEDIKGYR
VTSTGKPEFTNLKVYHDIKDITARKEIIEAELLDDQIAKILTIYQSSEDIQEELTNLNSELTQEEIEQIS
NLKGYTGTHNLSLKAINLILDELWHTNDNQIAIFNRLKLVPKKVDLSQQKEIPTTLVDDFILSPVVKRSF
IQSIKVINAIKKYGLPNDIIIEAREKNSKDAQKMINEMQKRNRQTNERIEEIIRTTGKENAKYLIEKI
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LNGLYDKDNDKLLKLINKSPEKLLMYHHDPTQYQKLKLIMEQYGDEKNPLYKYYEETGNYLTKYSKKDNG
PVIKKIKYYGNKLNALDITDDYPNSRNKVVKLSLKPYRFDVYLDNGVYKFVTVKNLDVIKKENYEVNS
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SSTLNIEDEYRLHETSKEPDVSLGSTWLSDFPQAWAETGGMGLAVRQAPLIIFLKATSTPVSIKQYPM SQ
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Sa^{KKH}PE*: Cmyc_NLS-BPSV40_NLS-SaCas9^{KKH}N580A-linker-M-MLV_reverse_transcriptase-
vBPSV40_NLS-SV40

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SDSKISYETFKKHILNLAKGGRISKTKKEYLLEERDINRFSVQKDFINRNLVDTRYATRGLMNLRSYF
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pU6-Ctnb1_pegRNA_S45F: U6 promoter + Spacer + sgRNA scaffold + RT +PBS

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aaaaacgccagcaacgcggcctTTTTACGGTTCCTGGCCTTTTGCTGGCCTTTTGCTCACATGT

Supplementary Note 1. FACS gating examples for GFP-positive or Cherry-positive cells.

