Supplementary Table 1.
Sequences of each cDNA of TALE DNA-binding repeats.

SCR	CTGACCCCAGACCAAGTTGTCGCGATTGCAAGCAACAACGGAGGCAAACAAG
	CCTTAGAAACAGTCCAGAGATTGTTGCCGGTGCTGTGCCAAGACCACGGC
	CTGACCCCAGAACAAGTTGTCGCGATTGCAAGCAACAACGGAGGCAAACAAG
	CCTTAGAAACAGTCCAGAGATTGTTGCCGGTGCTGTGCCAAGCCCACGGC
	CTGACCCCGGACCAGGTGGTTGCAATCGCGTCACACGATGGGGGAAAGCAGG
	CCCTAGAAACCGTTCAGCGACTCCTGCCCGTCCTGTGCCAGGCCCACGGC
	CTGACCCCCGCCCAGGTTGTCGCTATTGCTAGTAACGGCGGAGGCAAACAGG
	CGCTGGAAACAGTTCAGCGCCTCTTGCCGGTCTTGTGTCAGGACCACGGC
	CTGACCCCGGACCAGGTGGTTGCAATCGCGTCACACGATGGGGGAAAGCAGG
	CCCTAGAAACCGTTCAGCGACTCCTGCCCGTCCTGTGCCAGGACCACGGC
	CTGACCCCGGAACAGGTGGTTGCAATCGCGTCACACGATGGGGGAAAGCAGG
	CCCTAGAAACCGTTCAGCGACTCCTGCCCGTCCTGTGCCAGGCCCACGGC
	CTGACCCCGGACCAGGTGGTTGCAATCGCGTCACACGATGGGGGAAAGCAGG
	CCCTAGAAACCGTTCAGCGACTCCTGCCCGTCCTGTGCCAGGCCCACGGC
	CTGACCCCAGCCCAGGTTGTGGCCATCGCCAGCAACATAGGTGGCAAGCAGG
	CCCTCGAAACCGTCCAGAGACTGTTACCGGTTCTCTGCCAGGACCACGGC
	CTGACCCCGGACCAGGTGGTTGCAATCGCGTCACACGATGGGGGAAAGCAGG
	CCCTAGAAACCGTTCAGCGACTCCTGCCCGTCCTGTGCCAGGACCACGGC
	CTGACCCCAGAACAGGTTGTGGCCATCGCCAGCAACATAGGTGGCAAGCAGG
	CCCTCGAAACCGTCCAGAGACTGTTACCGGTTCTCTGCCAGGCCCACGGC
	CTGACCCCGGACCAGGTGGTTGCAATCGCGTCACACGATGGGGGAAAGCAGG
	CCCTAGAAACCGTTCAGCGACTCCTGCCCGTCCTGTGCCAGGCCCACGGC
	CTGACCCCGGCCCAGGTGGTTGCAATCGCGTCACACGATGGGGGAAAGCAGG
	CCCTAGAAACCGTTCAGCGACTCCTGCCCGTCCTGTGCCAGGACCACGGC
	CTGACCCCGGACCAGGTGGTTGCAATCGCGTCACACGATGGGGGAAAGCAGG
	CCCTAGAAACCGTTCAGCGACTCCTGCCCGTCCTGTGCCAGGACCACGGC
	CTGACCCCCGAACAGGTTGTCGCTATTGCTAGTAACGGCGGAGGCAAACAGG
	CGCTGGAAACAGTTCAGCGCCTCTTGCCGGTCTTGTGTCAGGCCCACGGC
	CTGACCCCGGACCAGGTGGTTGCAATCGCGTCACACGATGGGGGAAAGCAGG
	CCCTAGAAACCGTTCAGCGACTCCTGCCCGTCCTGTGCCAGGCCCACGGC
	CTGACCCCCAGCCCAAGTTGTCGCGATTGCAAGCAACAACGGAGGCAAACAAG
	CCTTAGAAACAGTCCAGAGATTGTTGCCGGTGCTGTGCCAAGACCACGGC
D17	CTGACCCCGGACCAGGTGGTTGCAATCGCGTCACACGATGGGGGAAAGCAGG
	CCCTAGAAACCGTTCAGCGACTCCTGCCCGTCCTGTGCCAGGACCACGGC
	CTGACCCCGGAACAGGTGGTTGCAATCGCGTCACACGATGGGGGAAAGCAGG
	CCCTAGAAACCGTTCAGCGACTCCTGCCCGTCCTGTGCCAGGCCCACGGC
	CTGACCCCGGACCAGGTGGTTGCAATCGCGTCACACGATGGGGGAAAGCAGG
	CCCTAGAAACCGTTCAGCGACTCCTGCCCGTCCTGTGCCAGGCCCACGGC
	CTGACCCCCGCCCAGGTTGTCGCTATTGCTAGTAACGGCGGAGGCAAACAGG
	CGCTGGAAACAGTTCAGCGCCTCTTGCCGGTCTTGTGTCAGGACCACGGC
	CTGACCCCCGACCAGGTTGTCGCTATTGCTAGTAACGGCGGAGGCAAACAGG
	CGCTGGAAACAGTTCAGCGCCTCTTGCCGGTCTTGTGTCAGGACCACGGC
	CTGACCCCGGAACAGGTGGTTGCAATCGCGTCACACGATGGGGGAAAGCAGG
	CCCTAGAAACCGTTCAGCGACTCCTGCCCGTCCTGTGCCAGGCCCACGGC
	CTGACCCCAGACCAGGTTGTGGCCATCGCCAGCAACATAGGTGGCAAGCAGG
	CCCTCGAAACCGTCCAGAGACTGTTACCGGTTCTCTGCCAGGCCCACGGC
	CTGACCCCAGCCCAGGTTGTGGCCATCGCCAGCAACATAGGTGGCAAGCAGG
	CCCTCGAAACCGTCCAGAGACTGTTACCGGTTCTCTGCCAGGACCACGGC
	CTGACCCCGGACCAGGTGGTTGCAATCGCGTCACACGATGGGGGAAAGCAGG
	CCCTAGAAACCGTTCAGCGACTCCTGCCCGTCCTGTGCCAGGACCACGGC
	CTGACCCCGGAACAGGTGGTTGCAATCGCGTCACACGATGGGGGAAAGCAGG
	CCCTAGAAACCGTTCAGCGACTCCTGCCCGTCCTGTGCCAGGCCCACGGC
	CTGACCCCCGACCAGGTTGTCGCTATTGCTAGTAACGGCGGAGGCAAACAGG
	CGCTGGAAACAGTTCAGCGCCTCTTGCCGGTCTTGTGTCAGGCCCACGGC
	CTGACCCCAGCCCAAGTTGTCGCGATTGCAAGCAACAACGGAGGCAAACAAG
	CCTTAGAAACAGTCCAGAGATTGTTGCCGGTGCTGTGCCAAGACCACGGC
	CTGACCCCAGACCAGGTTGTGGCCATCGCCAGCAACATAGGTGGCAAGCAGG
	CCCTCGAAACCGTCCAGAGACTGTTACCGGTTCTCTGCCAGGACCACGGC
	CTGACCCCGGAACAGGTGGTTGCAATCGCGTCACACGATGGGGGAAAGCAGG
	CCCTAGAAACCGTTCAGCGACTCCTGCCCGTCCTGTGCCAGGCCCACGGC
	CTGACCCCGGACCAGGTGGTTGCAATCGCGTCACACGATGGGGGAAAGCAGG
	CCCTAGAAACCGTTCAGCGACTCCTGCCCGTCCTGTGCCAGGCCCACGGC
	CTGACCCCCGCCCAGGTTGTCGCTATTGCTAGTAACGGCGGAGGCAAACAGG
	CGCTGGAAACAGTTCAGCGCCTCTTGCCGGTCTTGTGTCAGGACCACGGC

D17 cDNA encoding TALE molecule designed to target the *PD-1* promoter sequence. Scrambled (SCR) TALE which recognized TGGCTCCCACACCCTCG used as a control.

Supplementary Table 2.
Sequences of primers for RT-PCR.

GAPDH	Forward	ACAACTTTGGTATCGTGGAAGG
	Reverse	GCCATCACGCCACAGTTTC
PD-1	Forward	AAGTTTCAGGGAAGGTCAG
	Reverse	CTGGGCATGTGTAAAGGT

Supplementary Table 3.
Sequences of sgRNA.

PD-L1 sgRNA 1	GATCCCCGACCGCTGCATGATCAGCTAGTTTTAGAGCTAGAAATAGCAAGTTAAA AAAGGCTAGTCCGTTATCAACTTGAAAAAGTGGCACCGAGTCGGTGCTTTTTTA
PD-L1 sgRNA 2	GATCCCCGGCTGCATGATCAGCTATGGGTTTTAGAGCTAGAAATAGCAAGTTAAA AAAGGCTAGTCCGTTATCAACTTGAAAAAGTGGCACCGAGTCGGTGCTTTTTTA

1   **SUPPLEMENTARY FIGURES**

2   Supplementary Figure S1

3   (A) Schematic structure of pEU-NTP-GM for expression in a cell-free protein expression

4   system. Each NTP-GM protein was expressed with wheat germ extract and purified by

5   glutathione beads (open arrow in left panel). After treatment with PreScission protease,

6   the cleaved end-product (solid arrow in right panel) was confirmed and used for a DNA

7   methylation assay. CBB protein staining images are shown. (B) *PD-1* mRNA expression

8   in CEM, Jurkat, and MOLT-4 cells. Expression levels were normalized to *GAPDH* mRNA

9   expression. Values represent the mean ± SD. Three independent experiments were

10 performed. (C) Bisulfite sequencing analysis of CR-C and CR-B from non-treated Jurkat,

11 MOLT-4, and CEM cells.

12

13 Supplementary Figure S2

14 (A) Effects of NTP-GM-D17 on *PD-1* mRNA expression on primary PBMCs. Expression

15 levels were normalized to *GAPDH* mRNA expression. Values represent the mean ± SD

16 of data obtained from three independent experiments. (B) NTP-GM-D17 represses PD-1

17   expression in primary PBMCs. Representative results of FACS analysis of the expression

18   of PD-1 and CD3 are shown. (C) Expansion of PBMCs increases the number of PD-1$^+$

19   cells. PBMCs were cultured for 14 days in the presence of anti-CD3, anti-CD16 and IL-

20   2, and subjected to FACS analysis. (D) Effects of NTP-GM-D17^{E752A} on *PD-1* mRNA

21   expression. Expression levels were normalized to *GAPDH* mRNA expression. Values

22   represent the mean ± SD of three independent experiments. (E) No toxic effects of 1, 10,

23   and 20 nM NTP-GM protein on PBMCs. Cytotoxicity assay was done by measuring LDH

24   in the culture supernatant of PBMCs treated for 5 days with NTP-GM or NTP-SCR

25   proteins. (F) NTP-GM-D17 reduces *PD-1* mRNA expression in PBMCs. PBMCs were

26   treated for 5 days with NTP-GM-D17, and expression levels were evaluated at day 6, 9

27   and 12 and normalized to the level of *GAPDH* mRNA. Data are shown as the mean ± SD

28   (n = 3). N, non-treated; S, NTP-GM-SCR; D, NTP-GM-D17.

29

30   Supplementary Figure S3

31   (A) Tumor size monitored on day 7 after tumor inoculation. Luminescence signals of total

32   7 mice, which were used in experiments shown in Figure 5C and Supplementary Figure

33 S3B, were integrated for analysis. No significant difference was observed in two groups

34 of mice injected with control NK cells or treated NK cells. (B) IVIS imaging of mice

35 injected the treated NK cells. (C) Integrated data of luminescence signals. Data of

36 chronological monitoring by the IVIS imaging system on these three mice were analyzed.

37 Tumor-bearing mice were injected with the treated NK cells. ROI, region of interest.

38

39 Supplementary Figure S4

40 (A) No apparent tumor formation by NTP-GM-D17. Ventrotomy images of mice injected

41 with treated NK cells (protocol shown in Figure 5A) after 15 weeks from last injection

42 are shown. NT, non-treated mouse. (B) No remarkable increase of white blood cell count

43 in mice injected with treated NK cells. Numbers of white blood cells were counted.

Supplementary Figure S1

A

pEU-NTP-GMs plasmid

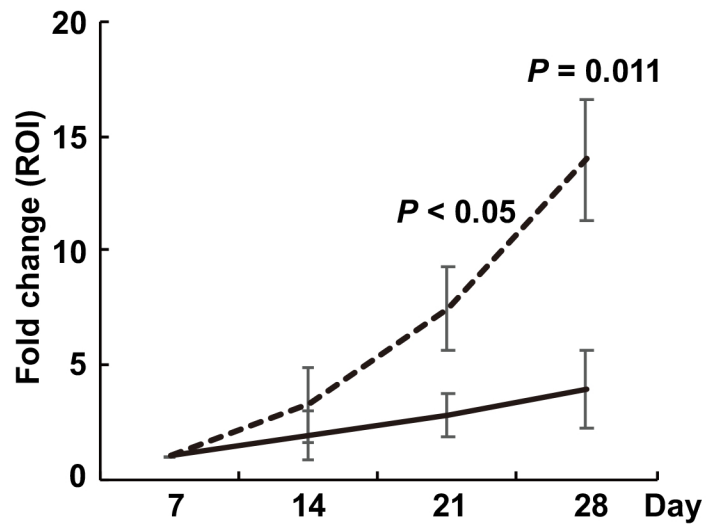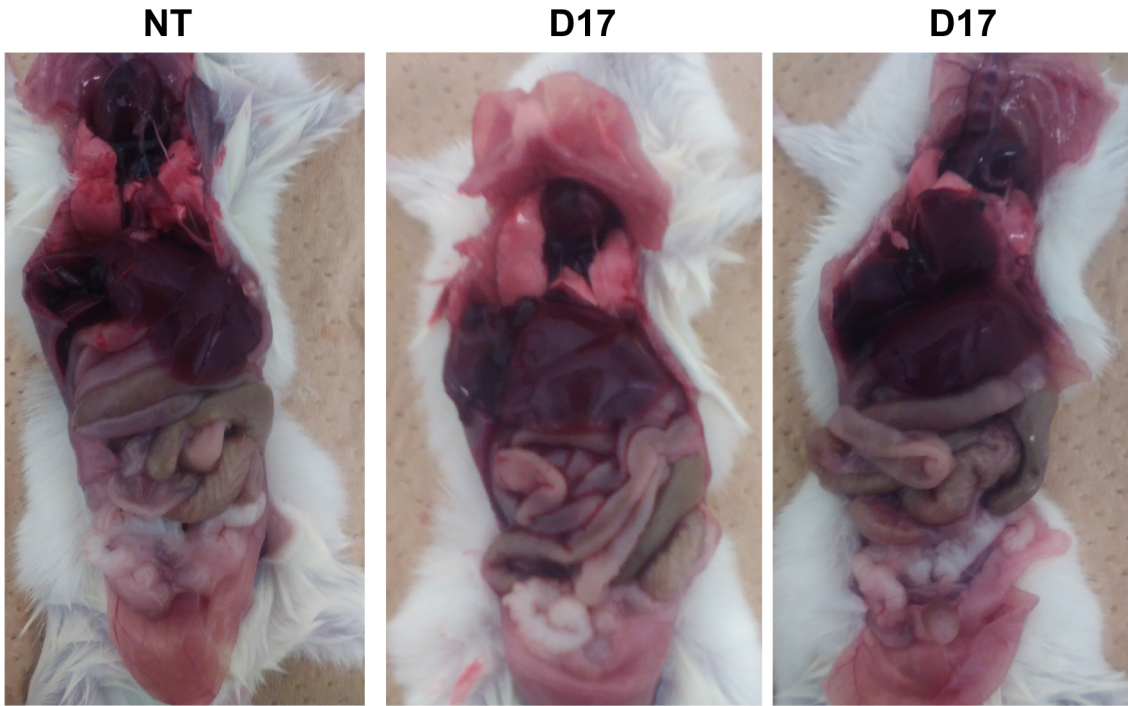| GST/PS | NTP | TALE | DNMT3A/3L |

B

C
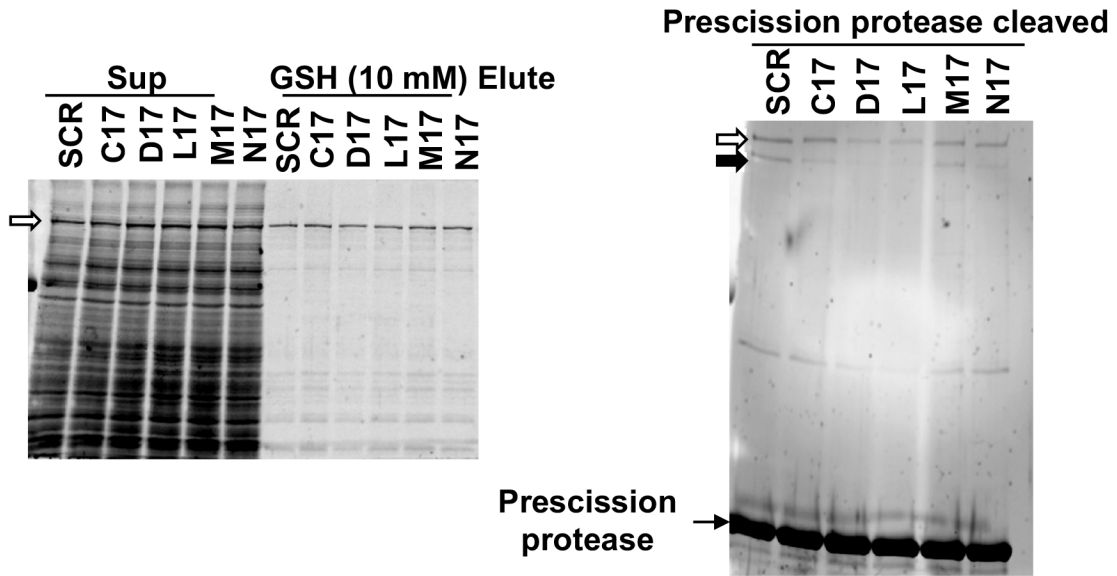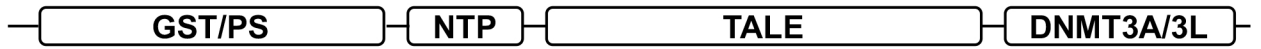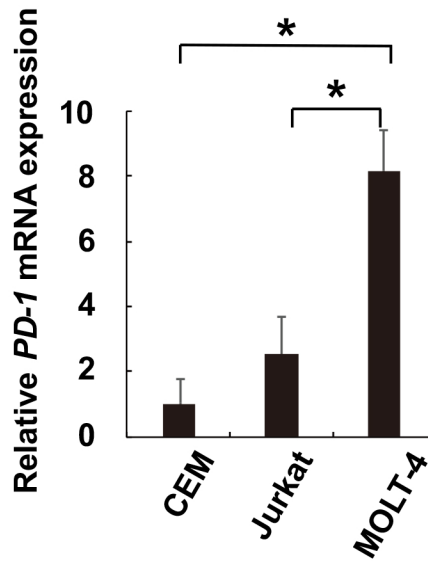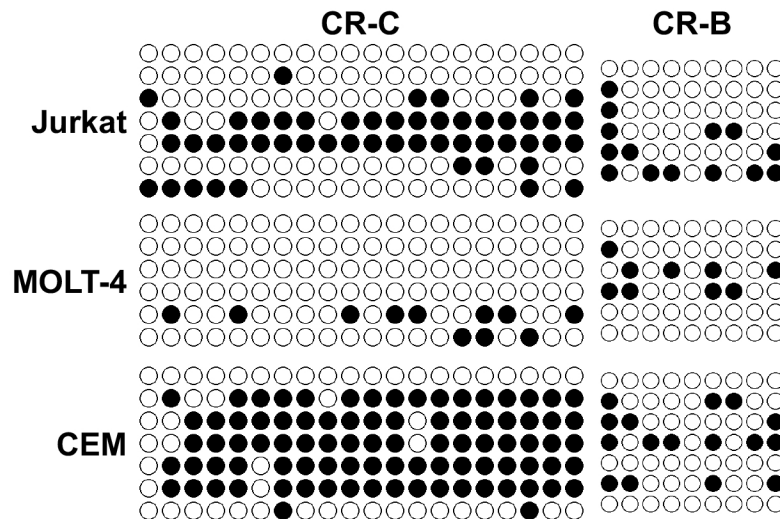
Supplementary Figure S2
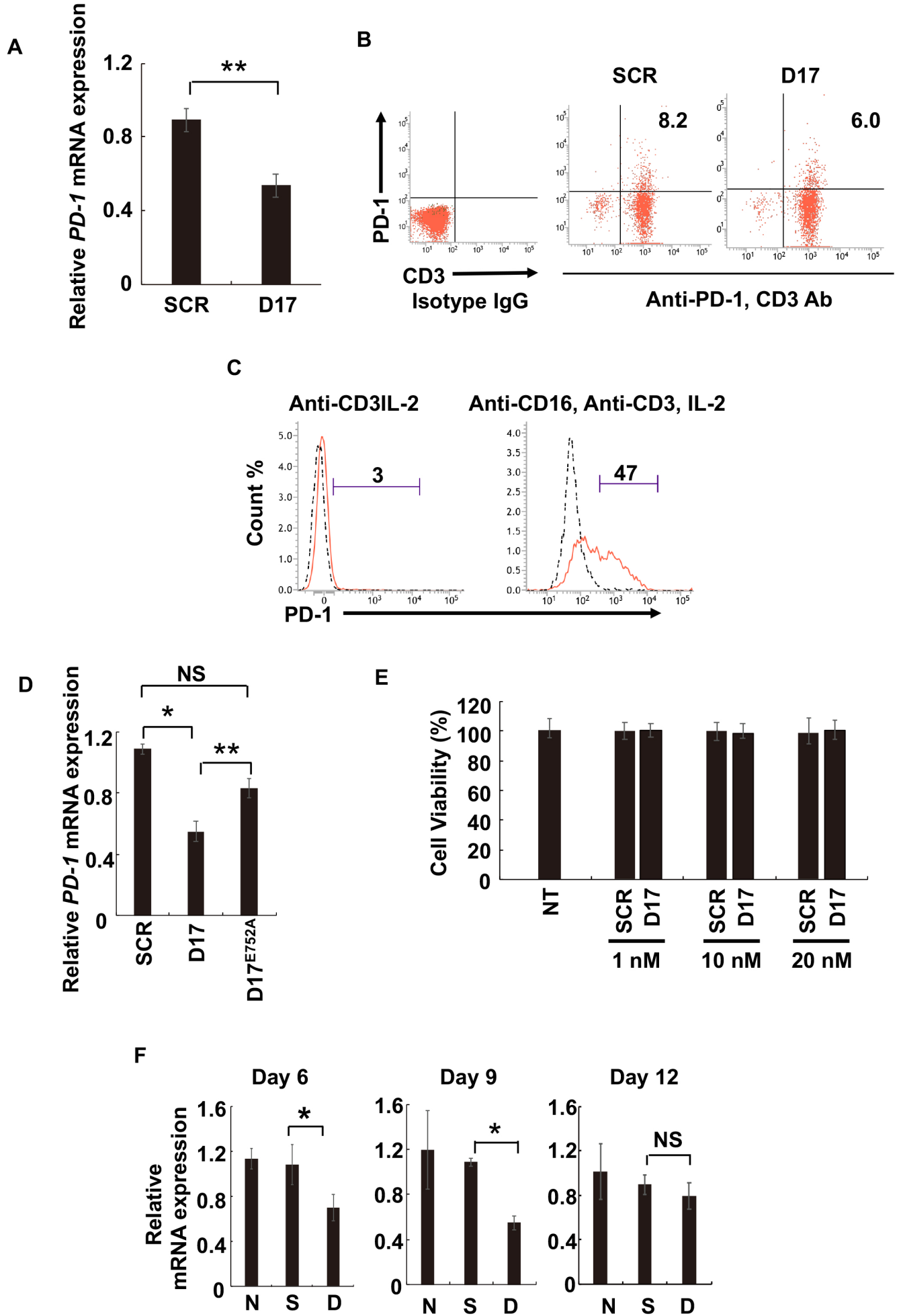
Supplementary Figure S3

A

B

C

Supplementary Figure S4

A

NT | D17 | D17

B