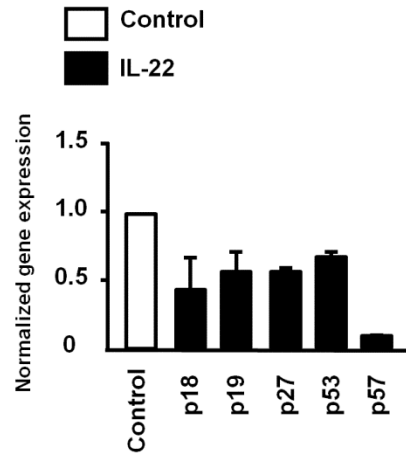


Supplementary Figure 1. Th22-derived IL-22 has no effect on colon cancer cell apoptosis.

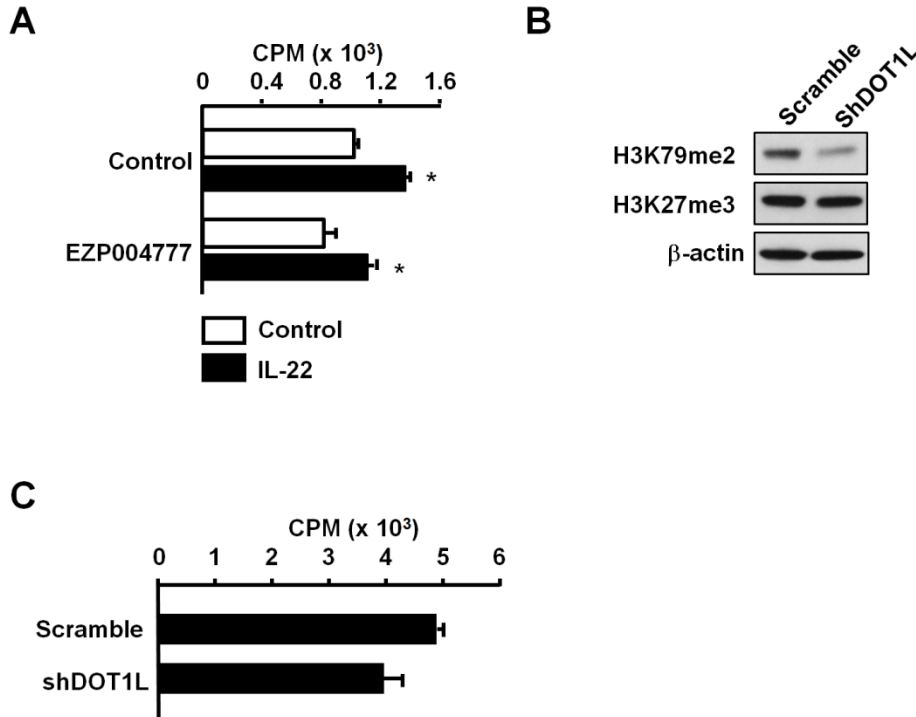
(A) Colon cancer cells were treated with or without IL-22 for 24 hours. Annexin V⁺ antibody was used to detect cell apoptosis by FACS. One of 3 experiments is shown.

(B,C) Colon cancer cells were treated with different concentration of IL-22 and with or without 5-FU for 24 hours. Annexin V⁺ antibody was used to detect cell apoptosis by FACS. Normalized Annexin V percent was shown in B. One of 3 experiments is shown.



Supplementary Figure 2. IL-22 reduced cyclin genes expression.

mRNA expression levels of p18, p19, p27, p53 and p57 were detected by real-time PCR after IL-22 treated for 12 hours. Results are expressed as the relative values (mean \pm SD). One of 3 experiments with triplicates is shown. $P < 0.05$.

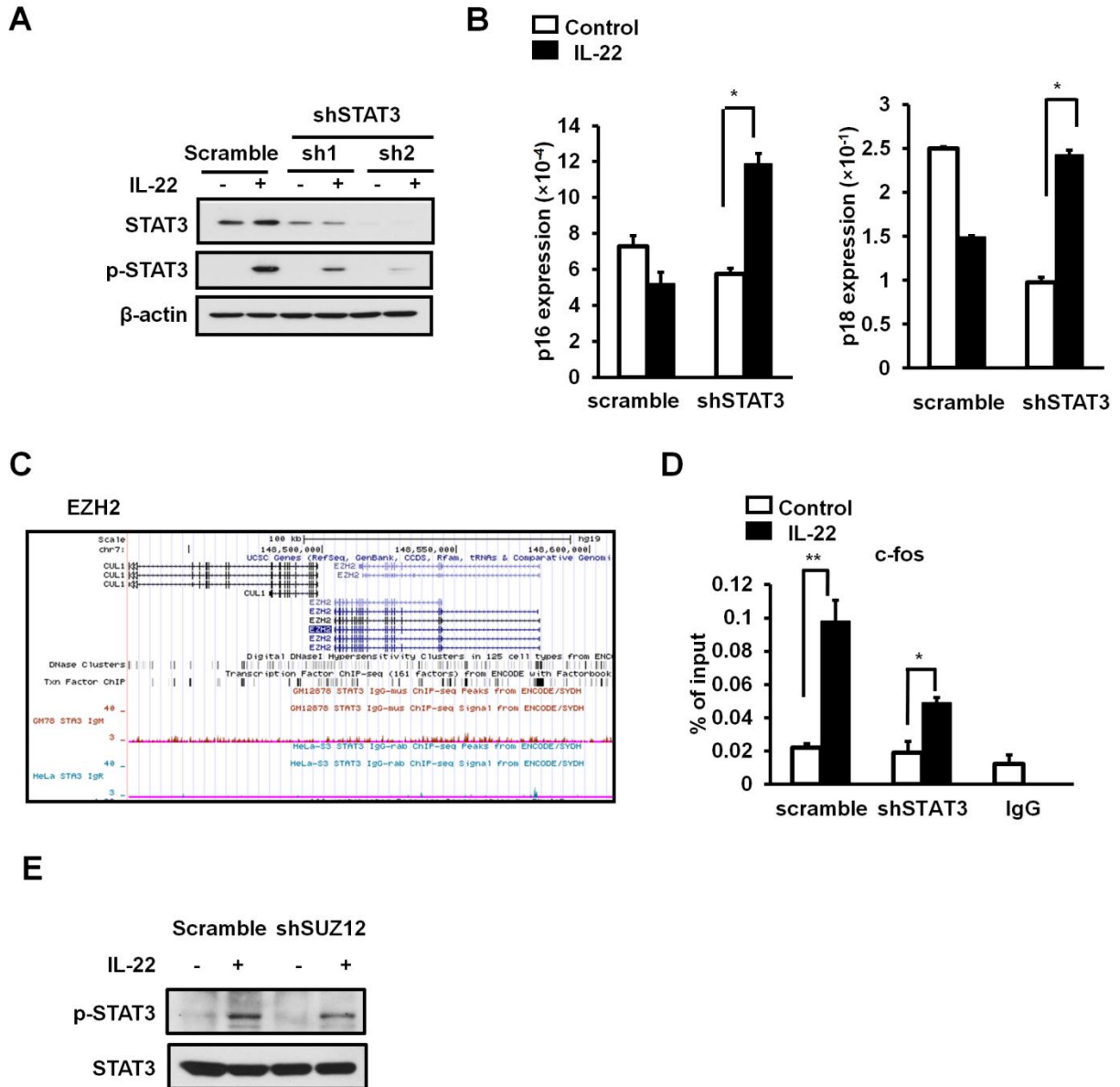


Supplementary Figure 3. IL-22-induced colon cancer proliferation is not DOT1L dependent.

(A) IL-22 stimulated colon cancer cells treated with or without DOT1L inhibitor EPZ004777 for 24 hours. Cell proliferation was detected by H³ Thymidine Incorporation. n=3, * $P < 0.05$.

(B) DLD-1 cells were transfected with control vector (scramble) or shDOT1L. Total levels of H3K79me2 and H3K27me3 were detected by western blotting.

(C) Cells transfected with scramble or shDOT1L were treated with or without IL-22 for 24 hours. Cell proliferation was detected by H³ Thymidine Incorporation. One of 3 experiments is shown.



Supplementary Figure 4: STAT3 manipulation and ChIP positive control.

(A) STAT3 manipulation. DLD-1 cells were transfected with control vector (scramble) or shSTAT3-1 and shSTAT3-2. The amount of phosphorylated STAT3 and STAT3 protein was detected by western blotting.

(B) DLD-1 cells transfected with scramble or shSTAT3 lentiviral vectors were treated with IL-22 for 12 hours. The levels of cyclin-dependent kinase inhibitors were

quantified by real-time PCR. Results are expressed as the relative values (mean \pm SD). One of 3 experiments with triplicates is shown. * $P < 0.05$.

(C) EZH2 showed no binding position with STAT3 based on the ENCODE STAT3-ChIP-Seq data base.

(D) DLD-1 cells transfected with scramble or shSTAT3 were treated with IL-22 for 0.5 hour. STAT3-ChIP was performed to examine STAT3 occupancy at the promoter area of c-fos as a positive control. n=3, ** $P < 0.01$, * $P < 0.05$.

(E) DLD-1 cells were transfected with control vector (scramble) or shSUZ12. Phosphorylated STAT3 was detected by western blotting with or without IL-22 treatment for 0.5 hour.

Supplementary table 1. Real-Time PCR primers

Target gene	Forward primer	Reverse primer
GAPDH	GAAGGTGAAGGTCGGAGT	GAAGATGGTGATGGGATTTT
CCND1	GGCCATGCTGAAGGCGGAGG	GCTCCAGCGACAGGAAGCGG
CCND3	CCTCCAAGCTGCGCGAGACC	GGCAGAGAGAGCCGGTGCAG
CCNE1	AGCCCCATCATGCCGAGGGA	TGGGGATCAGGGAGCAGGGG
CCNE2	TGAGCCGAGCGGTAGCTGGT	GGGATTCCGTCTGGCTGGGC
CCNA1	GTGGAGTTGTGCTGGCTAC	TCAGGGAGTGCTTTCTTT
CDK4	CACTCTGGTACCGAGCTCCCGA	GGCTCCACGGGGCAGGGATA
p16	ATGCCGCGGAAGGTCCCTCA	AAAGCGGGGTGGGTTGTGGC
p18	GGAACGAGTTGGCGTCCGCA	GGAAACCTGCTCTGGCCGCA
p19	GAGCTGGTGCATCCCGACG	GGGCAGGAGAAACAAGAAGAGAAAG
p21	GCCCAGTGGACAGCGAGCAG	GCCGGCGTTTGGAGTGGTAGA
p27	GCGACCTGCAACCGACGATTCT	GAGGCCAGGCTTCTTGGGCG
p53	TTTGAGGTGCGTGTTTGT	GGCGGGAGGTAGACTGA
p57	CTGACCAGCTGCACTCGGGGATTTT	GCCGCCGGTTGCTGCTACATGA
EZH2	TGCAGTTGCTTCAGTACCCATAAT	ATCCCCGTGTACTTTCCCATCATAAT
Suz12	TGGGAGACTATTCTTGATGGGAAG	GGAGCCGTAGATTTATCATTGGTC
EED	GCCTGCGCCAAGAAGCAGA	TCCAGGTGCATTTGGCGTGT
BMI-1	TGCTGATGCTGCCAATGG	TTACTTTCCGATCCAATCTGTTCTG
RIN1A	GAATACGAGGCCCATCAAGA	GCTCACATCTTCTCCATCCC
CBX8	GATGGTCGCAGAAGTACAGCAC	GCTTTGAGGAGGAAGGTTTTGG

Supplementary table 2. ChIP primers

Target gene	Forward primer	Reverse primer
SUZ12 (TSS)	CCCGGAATTCTGCTTTTTCTACCT	CAGTTTCACCTTCAGACAGAAC
EED (TSS)	AGGGAGGCGGAGGAATATGT	CTTTCCTCCGAGTCTCGT
EED (11.6kb)	ACTGTGGAATTTCTTAGGCTGATG	CAGAGGATGGCTCGTATTGCT
c-fos	GCAGCCCGCAGCAGTT	GCCTTGGCGCGTGTCTAATC
p16 (-0.3kb)	GGGCTCTCACAAGTAGGAAAG	GGGTGTTTGGTGTGATAGGG
p16 (-0.6kb)	CCCGTCCGTATTAATAAACC	GACTGCTCTCTCCTTCCC
p21 (1.9kb)	GCCAATCATTCTCCAAGTAAAAA	GTGCGCTGGACACATTTCC