Supplemental figure 1. Biophysical characterization of full nanobody panel. (a) Gating for yeast surface display selections. **(b)** Tabulated averaged melting temperatures for all nanobody candidates are represented in a table ± SD.

Supplemental figure 2. Quantified colony formation screen. (a) Bar graph of full colony formation screen for all 11 nanobodies, analyzed using a one-way ANOVA (N=8, error bars ± SD). (* $p < 0.0332$, ** $p < 0.0021$, *** $p < 0.0002$, **** $p < 0.0001$).

Supplemental figure 3. Apoptosis screen for full panel of nanobodies. (a) Apoptosis screen for all 11 nanobodies in **(a)** CaSki and **(b)** C33A was analyzed using a one-way ANOVA (N=3, error bars ± SD). **(b)** Significant nanobodies from the CaSki screen were further screened in C33A HPV(-) cervical cancer cells (N=3, error bars ± SD) and analyzed with a one-way ANOVA. **(c)** Flow cytometry gating schema for the apoptosis screen. **(d)** Representative dot plots for CaSki and C33A cell lines in apoptosis screen with Empty control and A2 nanobody. (* $p < 0.0332$, ** $p < 0.0021$, *** $p < 0.0002$, **** $p < 0.0001$).

Supplemental figure 4. ISG56 screen and dose-dependent relationship of nanobody C11. HEK293T cells were transfected with expression plasmids encoding N-RIG-I, TRIM25, USP15, pISG56-luc, and HPV16 E6 without and with **(a)** the full range of nanobodies or **(b)** increasing concentrations of the C11 E6-targeting nanobodies as indicated. Luciferase activities were normalized by co-transfection with phRL-TK. Cell lysates were collected after 24 h and luciferase activities were determined by Dual Luciferase Assay (Promega). Shown are the means ± SD of triplicate samples for one of three representative experiments (N=3).

Supplemental figure 5. PROTAC^{E6} induction of IFNB mRNA levels. The induction of IFNB mRNA was measured using RT-qPCR (N=3). A one-way ANOVA was performed, and error bars represent ± SD. (* $p < 0.0332$, ** $p < 0.0021$, *** $p < 0.0002$, **** $p < 0.0001$).

Supplemental figure 6. Mouse body weight. Mouse body weight was recorded throughout treatment and plotted (N=5).

Supplemental Material:

Reagent	**Company**	**Catalogue number**
Yeast surface display library	Andy Kruse	Requested
Propidium iodide	BD Bioscience	556463
Annexin-V-APC	BioLegend	640920
α-CD4 (GK1.5)	Bio Cell	BE0003
α-CD8 (2.43)	Bio Cell	BE0061
In vivo JetPEI	PolyPlus Transfections	201-50G
CaSki	ATCC	CRM-CRL-1550
C33A	ATCC	HTB-31
HEK293T	Eric Lau (GeneHunter)	Requested
pcDNA-Xpress-His-USP15	Addgene	23216
pFlagCMV2-EFP	Addgene	12449
P1322 HPV16-E6	Addgene	8642

Table of primers:

Target	**Forward 5'-3'**	**Reverse 5'-3'**
ISG15	GAGAGGCAGCGAACTCATCT	CTTCAGCTCTGACACCGACA
IFNB	CTTGGATTCCTACAAAGAAGCAGC	TCCTCCTTCTGGAACTGCTGCA
GAPDH	GTCTCCTCTGACTTCAACAGCG	ACCACCCTGTTGCTGTAGCCAA
Yeast pYAL F	CCTCTATACTTTAACGTCAAGGAG	-