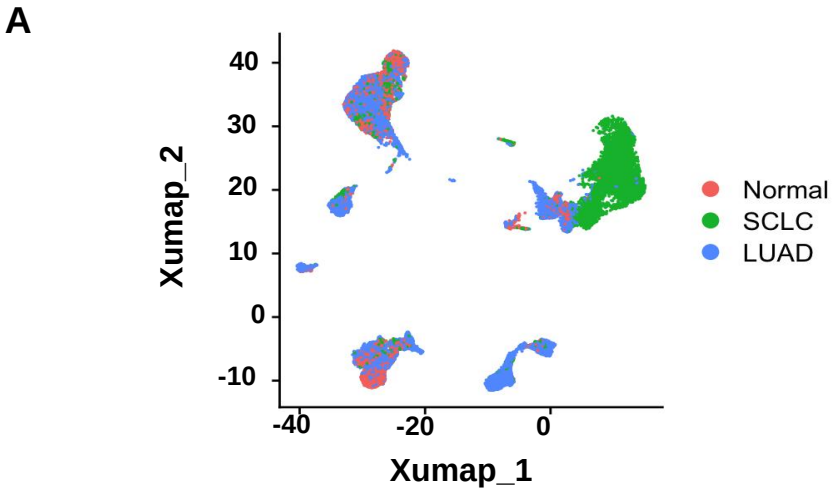
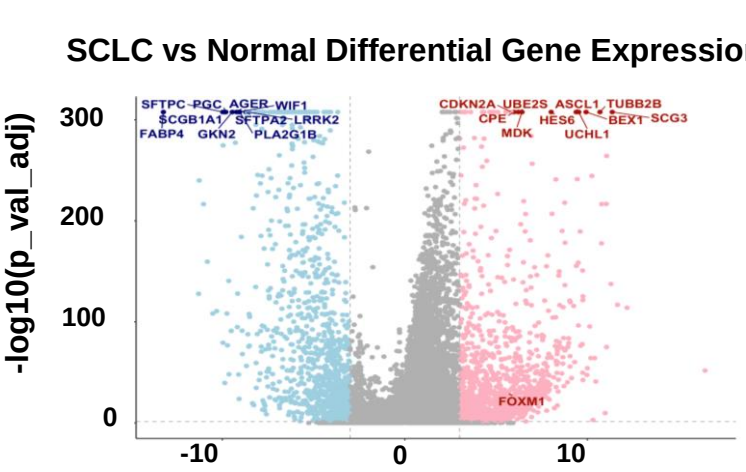
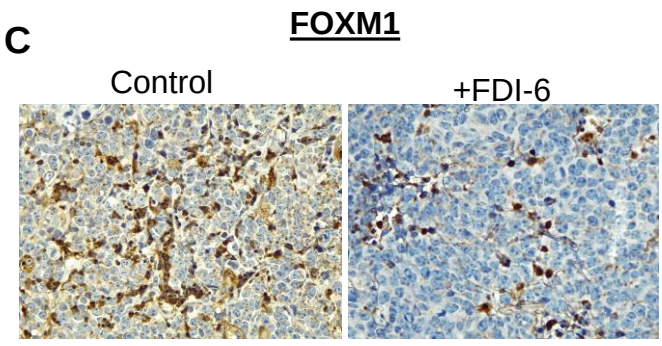
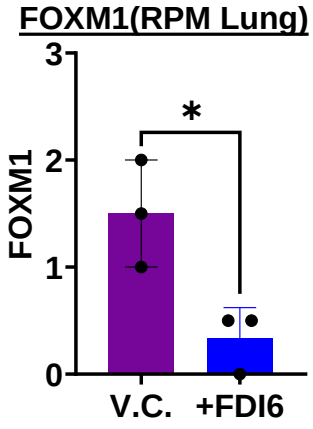
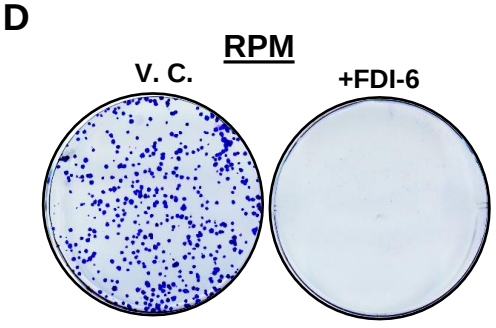
Supplementary Figure S1

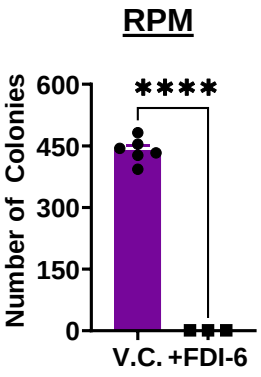






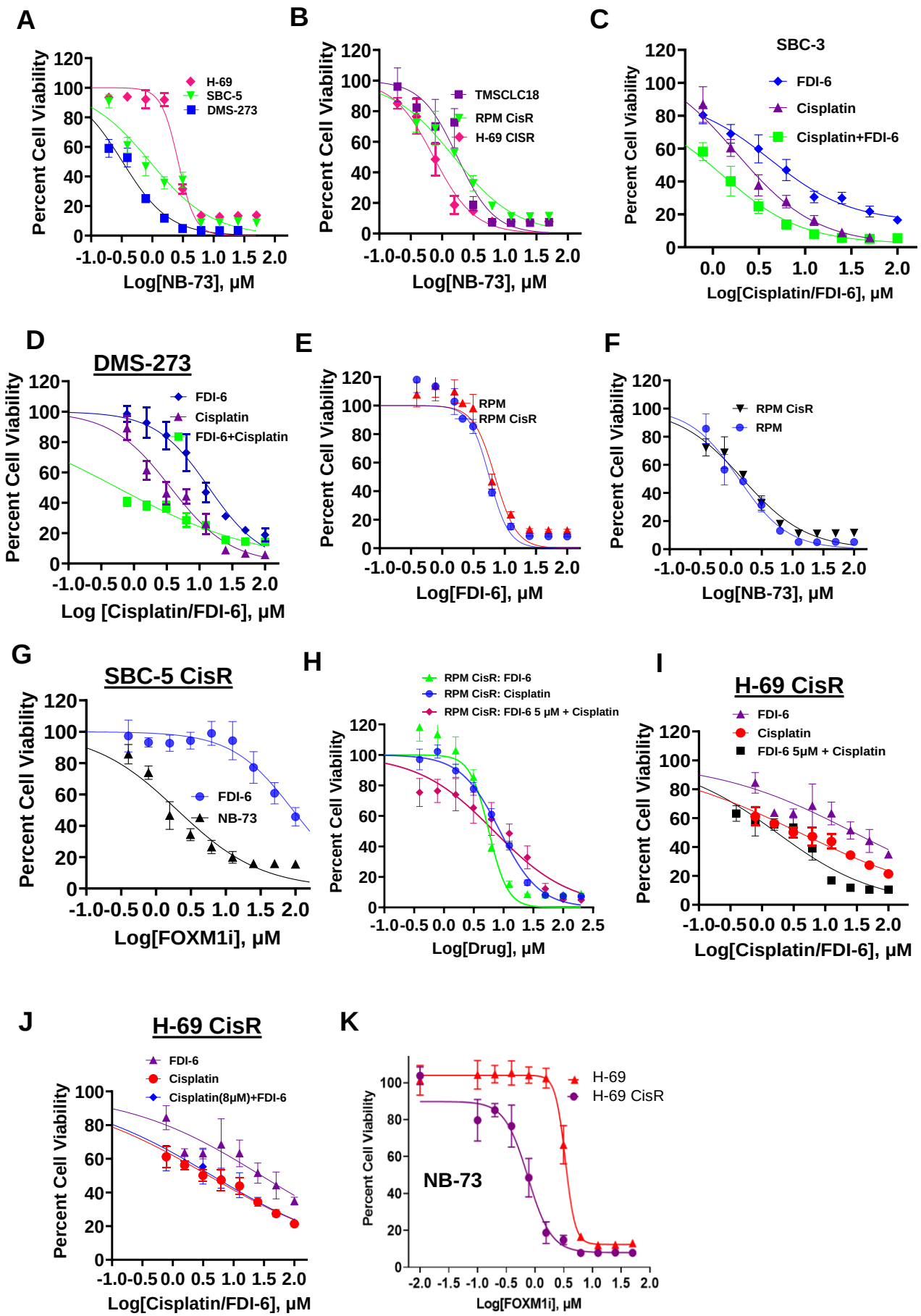






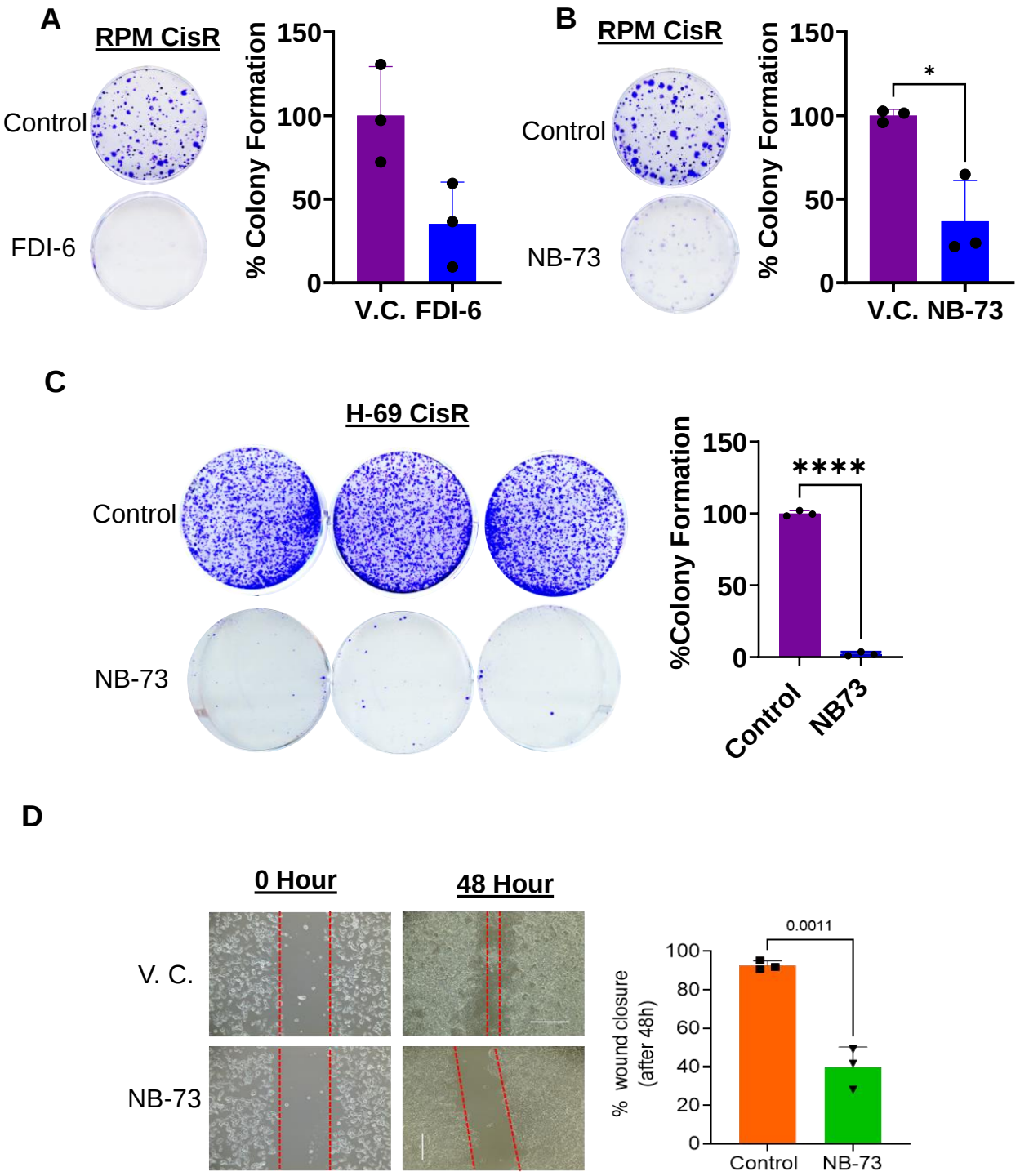
Supplementary Figure S1: Human and murine SCLC cells express a robust amount of FOXM1 and FOXM1 inhibition adversely affects cell viability and colony formation. **A)** Single cell RNA-sequencing data analysis revealed distinct populations of cell clusters between normal, SCLC and Lung adenocarcinoma. **B)** Differential gene expression analysis performed on the single cell data showed FOXM1 overexpression in SCLC cells. **C)** RPM tissue IHC showing robust expression of FOXM1 which is downregulated in FDI-6/FOXM1 inhibitor treatment. **D**) FOXM1 inhibition impairs colony formation of RPM SCLC cells. **E)** Measuring colony numbers from figure **D** showed significant downregulation in colony formation capabilities (n=3/6, student's t test performed for significance analysis, *, $p<0.05$, **, $p < 0.01$, ***, $p < 0.001$, ns, non-significant).

Supplementary Figure S2



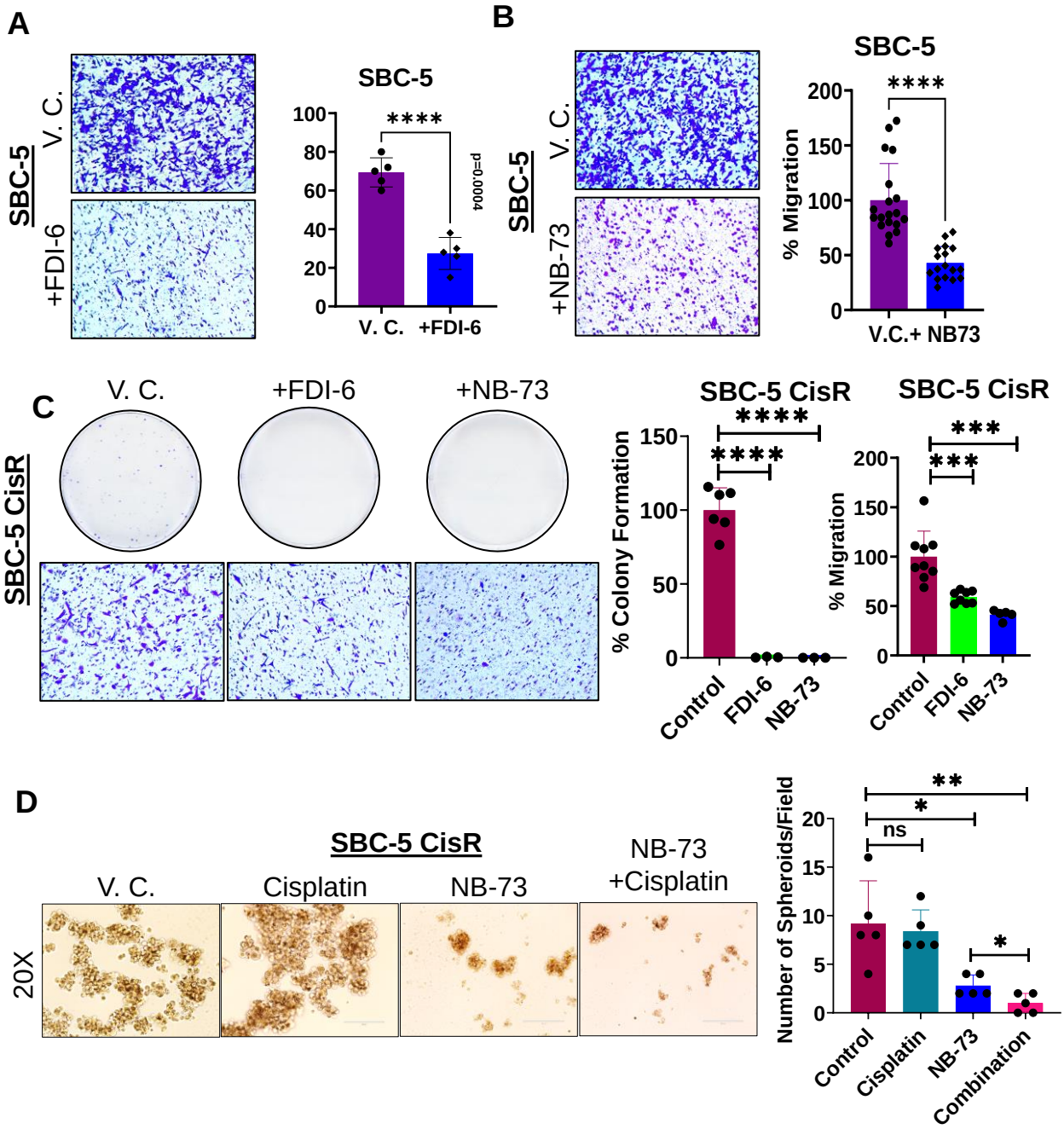
Supplementary Figure S2: FOXM1 inhibition reduces naïve and chemo-resistant SCLC cell viability and shows synergistic anticancer response with cisplatin. **A-B)** FOXM1 inhibitor NB-73 potently decreases viability of SCLC naïve and chemo-resistant SCLC cells. **C-D)** FOXM1 inhibition shows synergistic anticancer response with cisplatin. **E-F)** FOXM1 inhibitors effectively reduce the viability of naïve and chemo-resistant murine cell line models. **G)** SBC-5 CisR cells show reduction in cell viability after FOXM1 inhibition. **H)** RPM CisR cells show synergistic anticancer effects with cisplatin at low concentrations of cisplatin. **I)** FOXM1 inhibition sensitizes H-69 CisR cells towards cisplatin. **J)** High dose cisplatin treatment does not show sensitize chemo-resistant cells to FOXM1 inhibitor FDI-6. **K)** H-69 CisR cells showed higher susceptibility towards FOXM1 inhibition compared to its naïve counterpart H-69.

Supplementary Figure S3



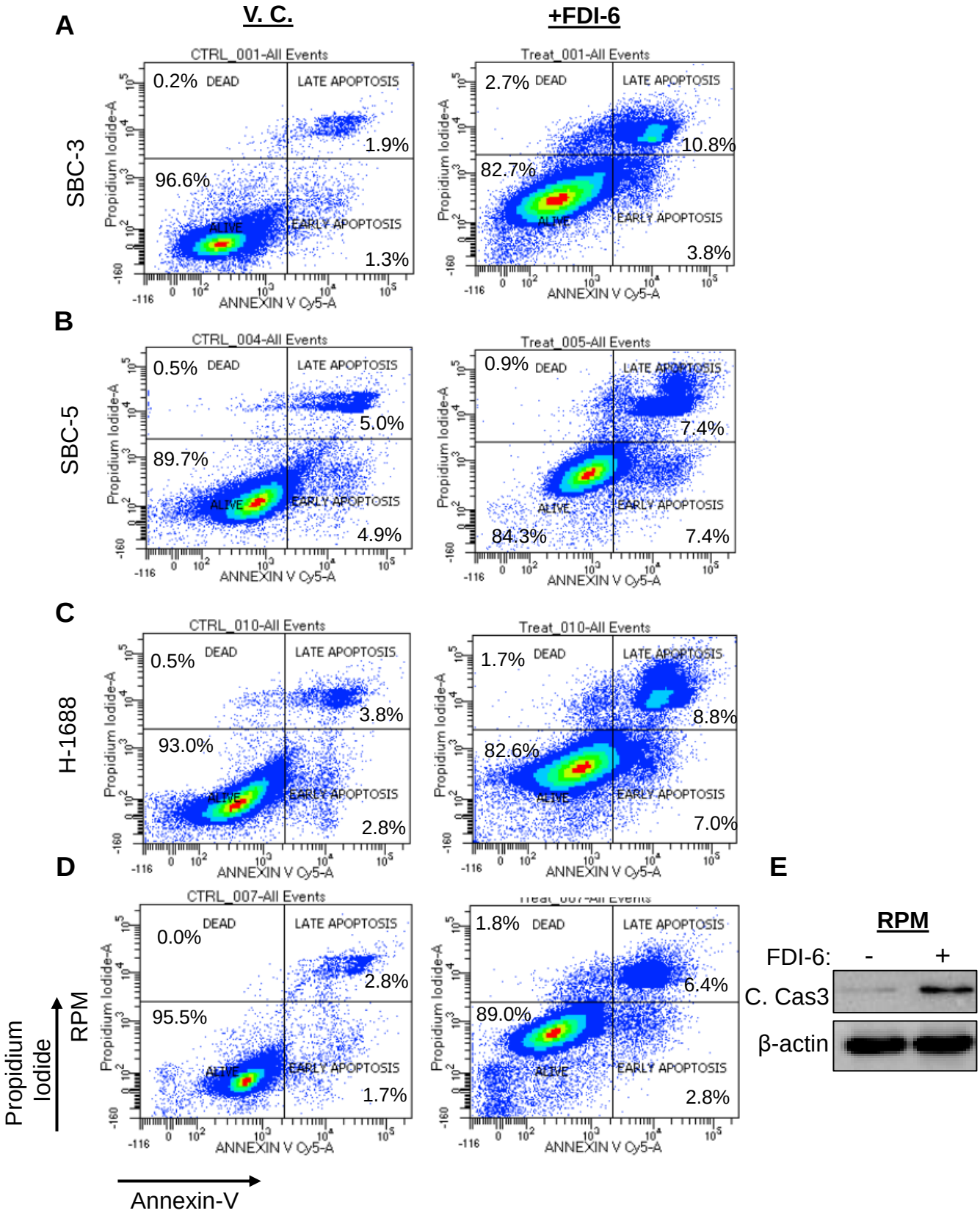
Supplementary Figure S3: FOXM1 inhibition reduces colony formation and wound healing of naïve and chemo-resistant cancer cells. **A-B)** FOXM1 inhibitors decrease colony formation of chemo-resistant RPM cells. **C)** FOXM1 inhibition significantly reduces colony formation of H-69 CisR cells. **D)** FOXM1 inhibitor delays wound healing in scratch assay.

Supplementary S4



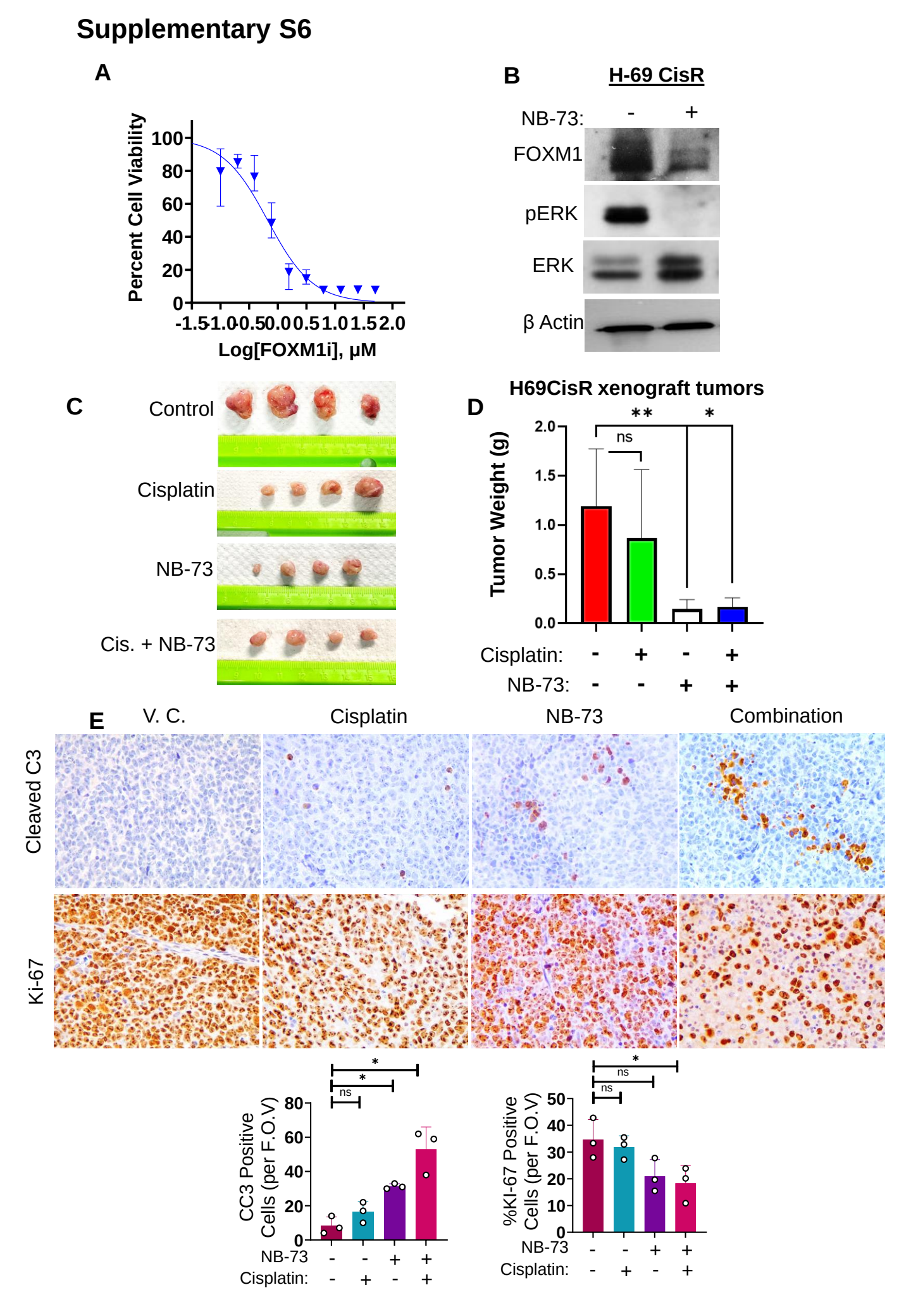
Supplementary Figure S4: FOXM1 inhibition reduces colony formation and migration of naïve and chemo-resistant cancer cells. **A-B)** FOXM1 inhibitors significantly diminish migration of naïve SBC-5 cells. **C)** FOXM1 inhibition significantly reduce colony formation and migration of SBC-5 CisR cells. **D)** FOXM1 inhibitor treatment adversely affects 3D sphere formation.

Supplementary S5



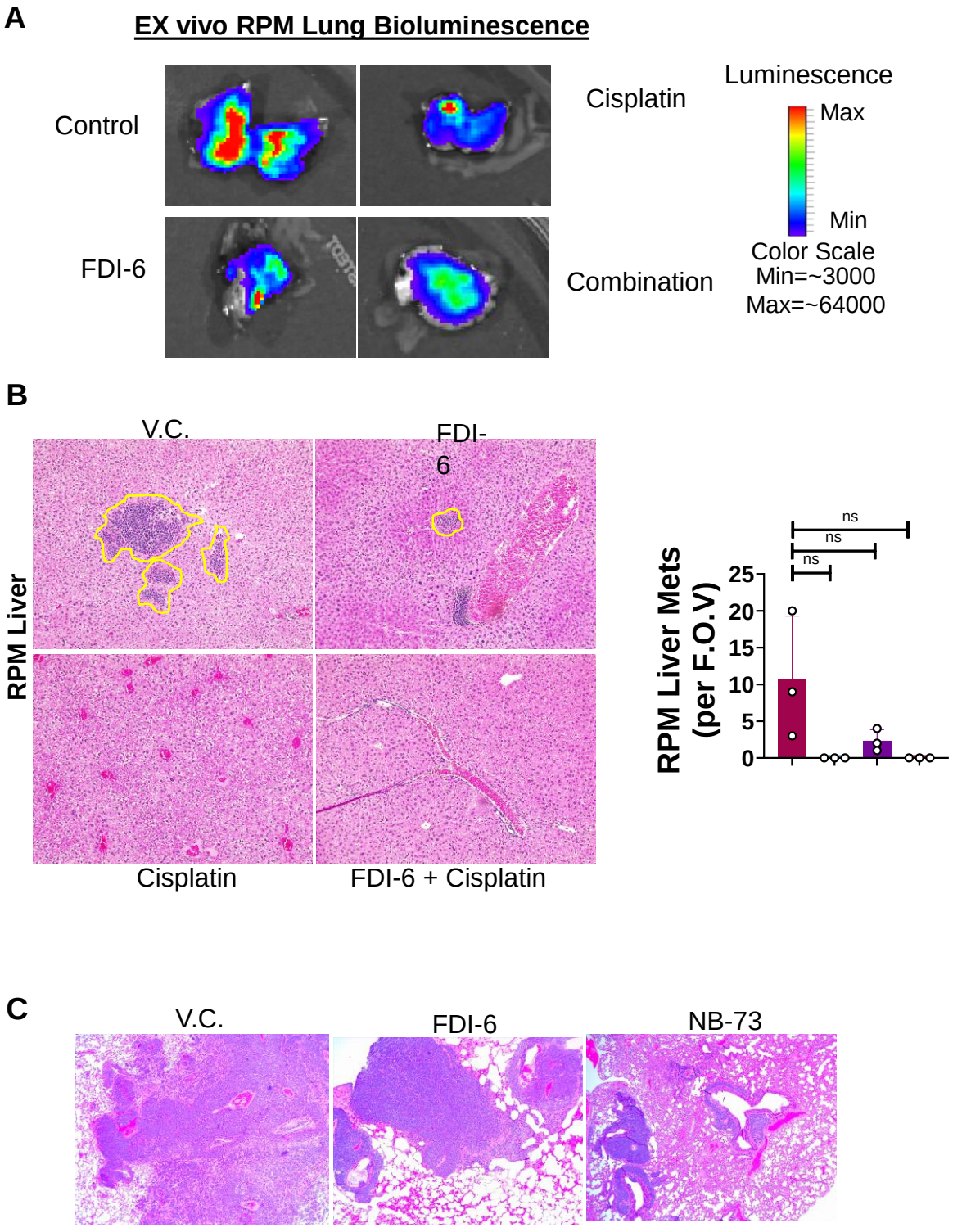
Supplementary Figure S5: FOXM1 inhibition using FDI-6 induced apoptosis in multiple human and murine (RPM) SCLC cell lines. **A-D)** FDI-6 Treatment resulted in the increase of apoptotic cell numbers compared to control cells in SBC-3, SBC-5, H-1688 and RPM cells. **E)** FDI-6 treatment induced the expression of apoptotic markers- cleaved caspase 3 (CC3) in RPM murine cell line model.

Supplementary S6



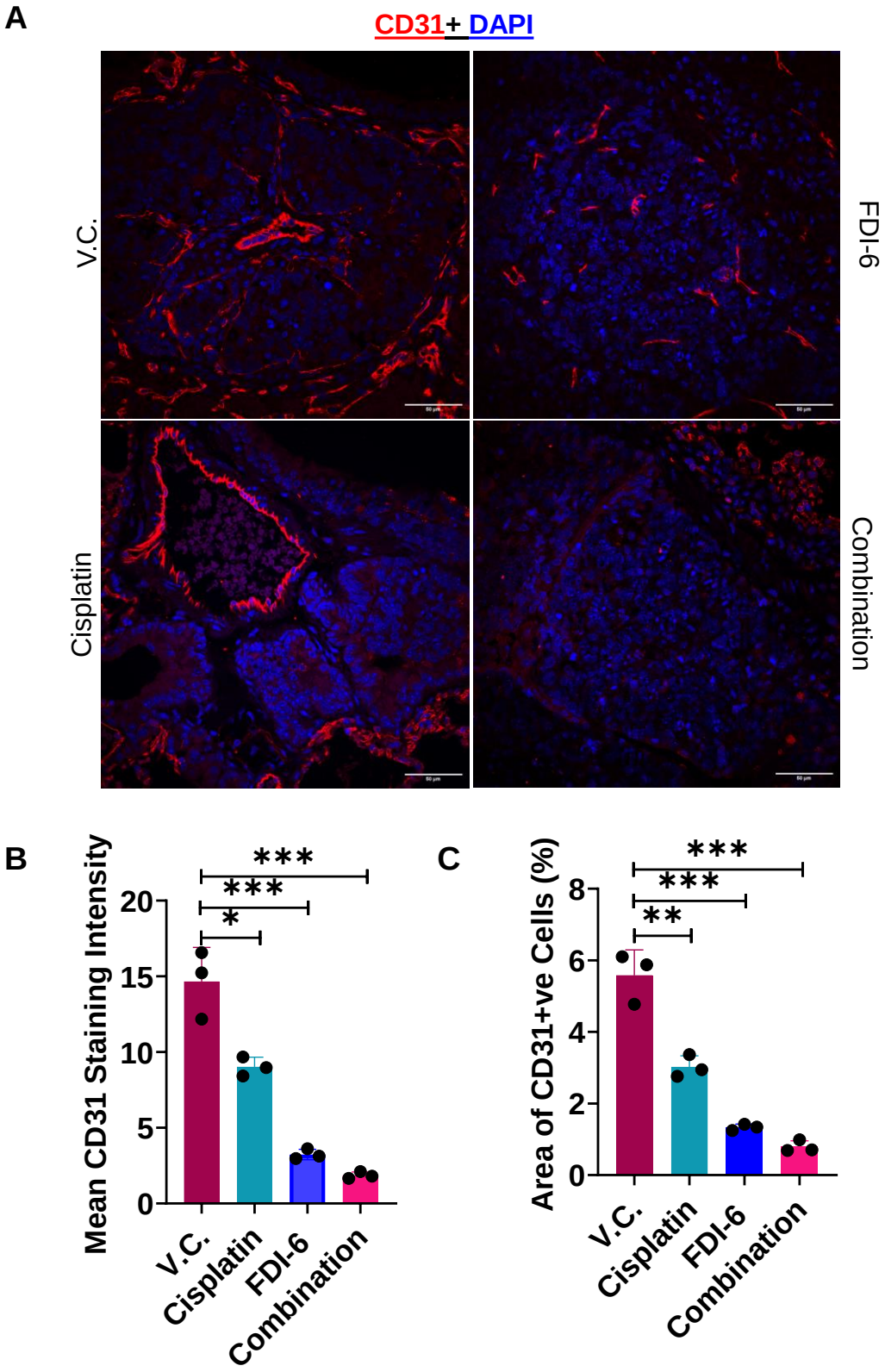
Supplementary Figure S6: FOXM1 inhibition treatment alone or inhibition with cisplatin resulted in the reduction of chemo-resistant SCLC cell viability and tumor progression in cisplatin resistant xenograft mouse model of SCLC. **A)** FOXM1 inhibitor NB-73 reduces viability of chemo-resistant H69 CisR SCLC cell line model. **B)** FOXM1i NB-73 treatment reduced FOXM1 protein and activated ERK (pERK) levels in H-69 CisR cells. **C)** Cisplatin, NB-73 or a combination treatment led to a reduction in SCLC tumor growth in H-69 CisR subcutaneous xenograft mouse model study. **D)** Quantification of xenograft tumor weight which were isolated from different treatment groups (n=4, student's t test performed for significance analysis, *, $p<0.05$, **, $p < 0.01$, ***, $p < 0.001$, ns, non-significant). **E)** IHC staining performed on subcutaneous xenograft tumor tissue sections.

Supplementary S7



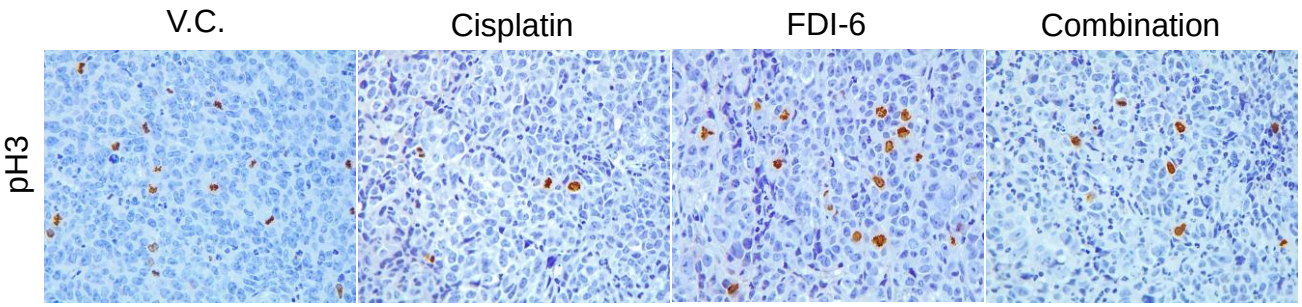
Supplementary Figure S7: Cisplatin and/or FDI-6 treatment resulted in the reduction of lung tumor bioluminescence and hepatic metastasis in RPM mouse model. **A**) Ex vivo bioluminescence imaging of RPM lung showed a reduction in bioluminescence intensity in RPM Mice lung in different treatment groups. **B**) RPM mouse model showed substantial reduction in the number of micro-metastatic nodules as well as the size of these nodules after cisplatin and/or FDI-6 treatment. C) In a pilot study carried out on RPM mouse model showed effectiveness of NB-73 on spontaneous SCLC tumors.

Supplementary S8

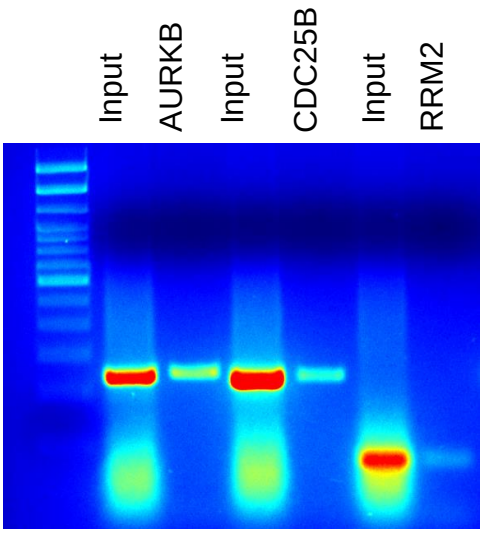


Supplementary Figure S8: Cisplatin and/or FDI-6 treatment resulted in the reduction of angiogenesis in RPM Lung tumors. **A**) Cisplatin, FDI-6 or a combination treatment reduces staining for CD31 (marker of angiogenesis) in RPM lung tumors. **B-C)** Quantification of CD31 staining intensity and area (n=3, student's t test performed for significance analysis, *, $p<0.05$, **, $p < 0.01$, ***, $p < 0.001$, ns, non-significant).

Supplementary S9-S10

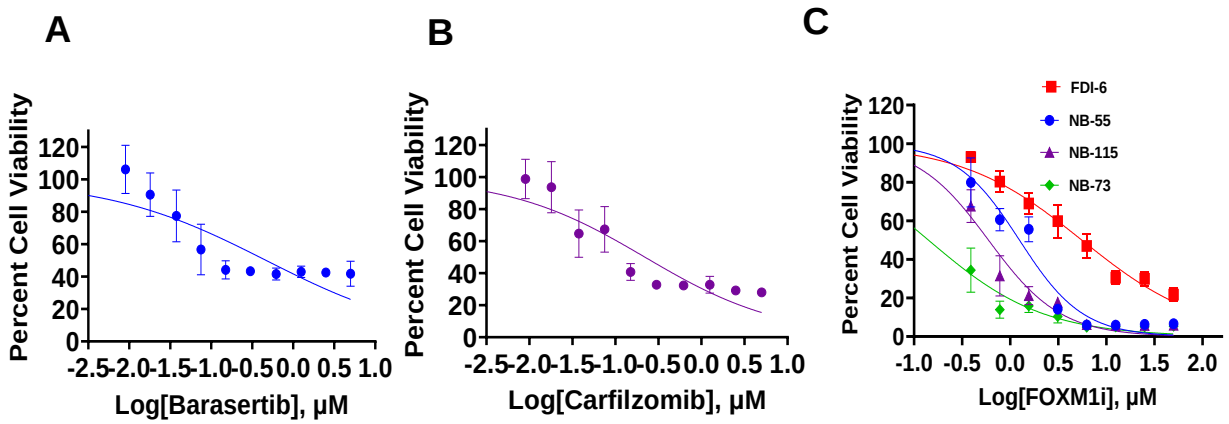


Supplementary Fig. S9: pH3 IHC experiment performed on SBC3 xenograft tumor sections showed a reduction in pH3 staining. IHC staining carried out on xenograft tumors showed difference in pH3 staining in different treatment groups.

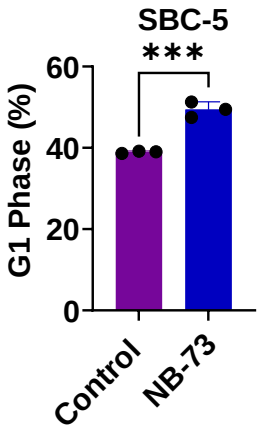


Supplementary Figure S10: ChIP-PCR experiment performed on FOXM1 ChIP samples shows multiple genes that are under the regulation of FOXM1. ChIP-PCR experiment using SBC3–FOXM1 ChIP lysate revealed that FOXM1 is transactivating Aurora Kinase B, CDC25B and RRM2.

Supplementary S11-S12

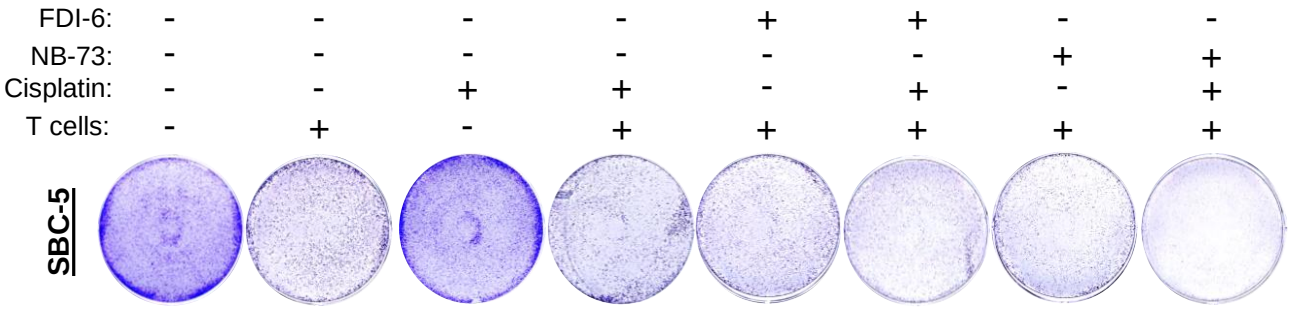


Supplementary Figure S11: Aurora Kinase B inhibitor Barasertib and non-specific FOXM1 inhibitor Carfilzomib reduced the viability of SBC-3 SCLC cells. **A**) Barasertib potently decreased the viability of SBC-3 cells with an IC-50 value of 0.53 µM . **B**) Non-specific FOXM1 inhibitor carfilzomib is capable of adversely affecting viability of SCLC cells; SBC-3 cell viability goes down substantially after carfilzomib treatment (IC50 value: 230 $\pm$ 70 nM) **C)** Effectiveness of FOXM1 inhibitors on SBC-3 cell viability.



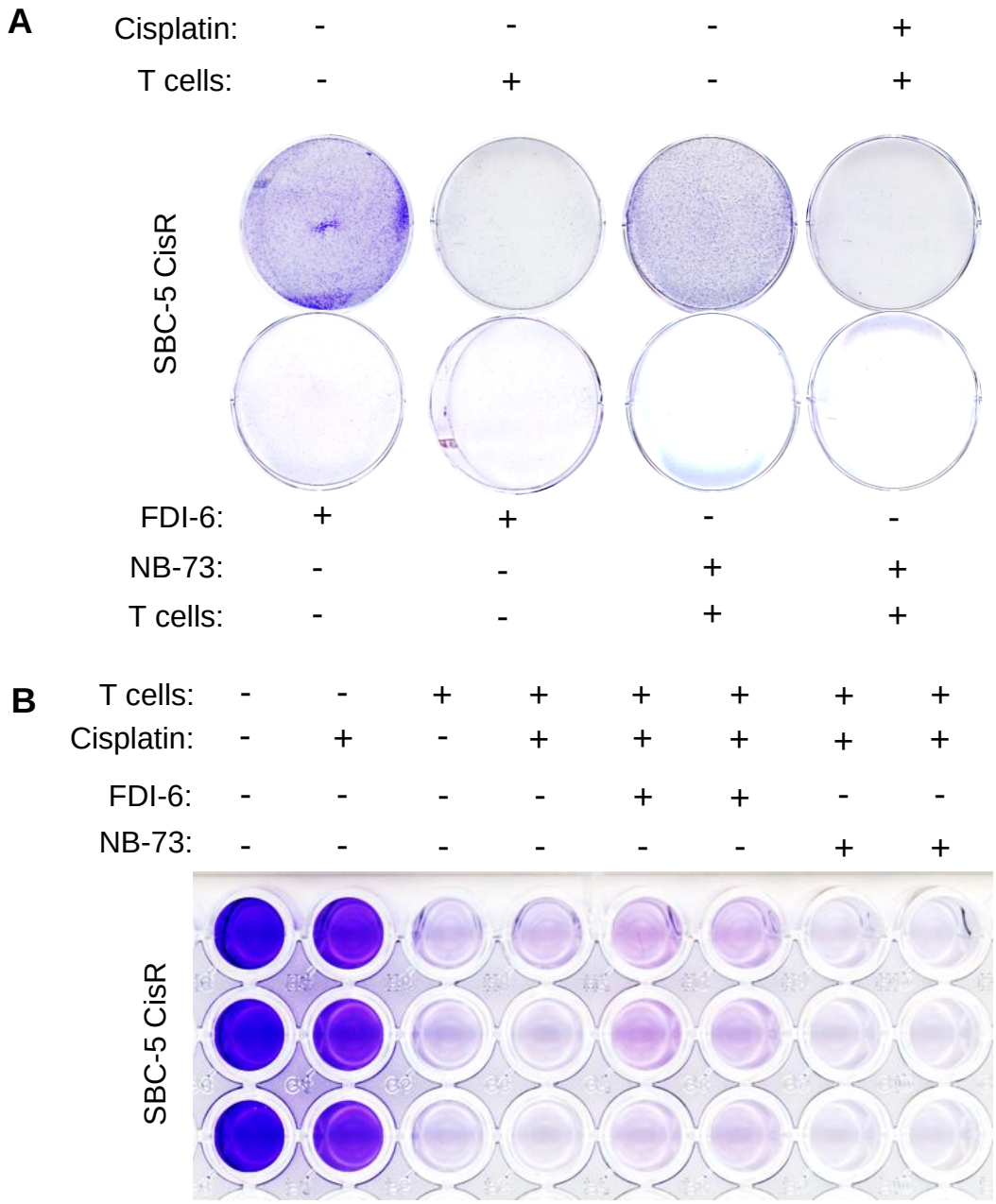
Supplementary Figure S12: FOXM1 inhibition by NB-73 leads to cell cycle arrest in SBC-5 cells. NB-73 treatment is inducing cell cycle arrest in SBC-5 cell line model in G1 phase of cell cycle.

Supplementary S13



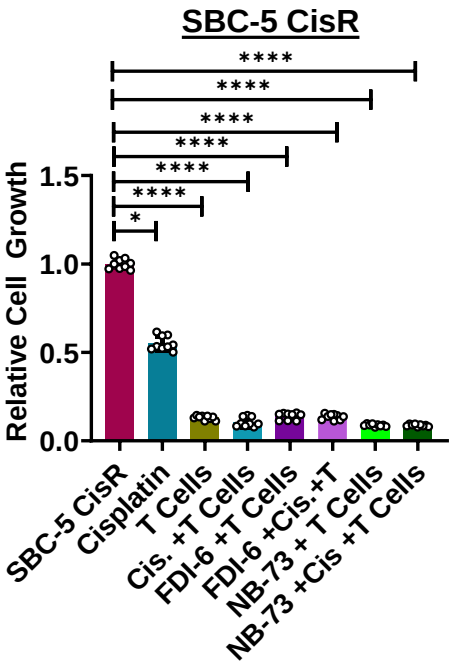
Supplementary Figure S13: Representative image of T cell mediated killing of SBC-5 cells after using different treatment conditions.FOXM1 inhibition alone or in combination with cisplatin enhances T cell mediated of cancer cells.

Supplementary S14



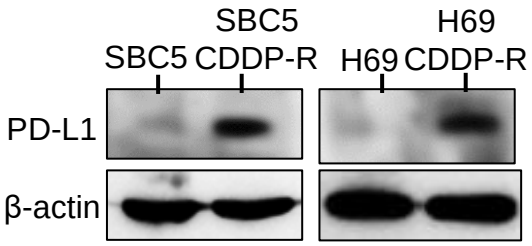
Supplementary Figure S14: Graphical representation of T cell mediated killing of chemo-resistant SCLC cells. **A)** FOXM1 inhibitors enhance T cell mediated killing of chemo-resistant SBC-5 CisR cells. **B)** Comparison of crystal violet staining in different treatment condition after dissolution.

Supplementary S15



Supplementary Figure S15: Relative growth analysis of T cell killing experiment showed substantial reduction in cancer cell population in different treatment conditions. FOXM1 inhibitors enhance T cell mediated killing of chemo-resistant SBC-5 CisR cells.

Supplementary S16

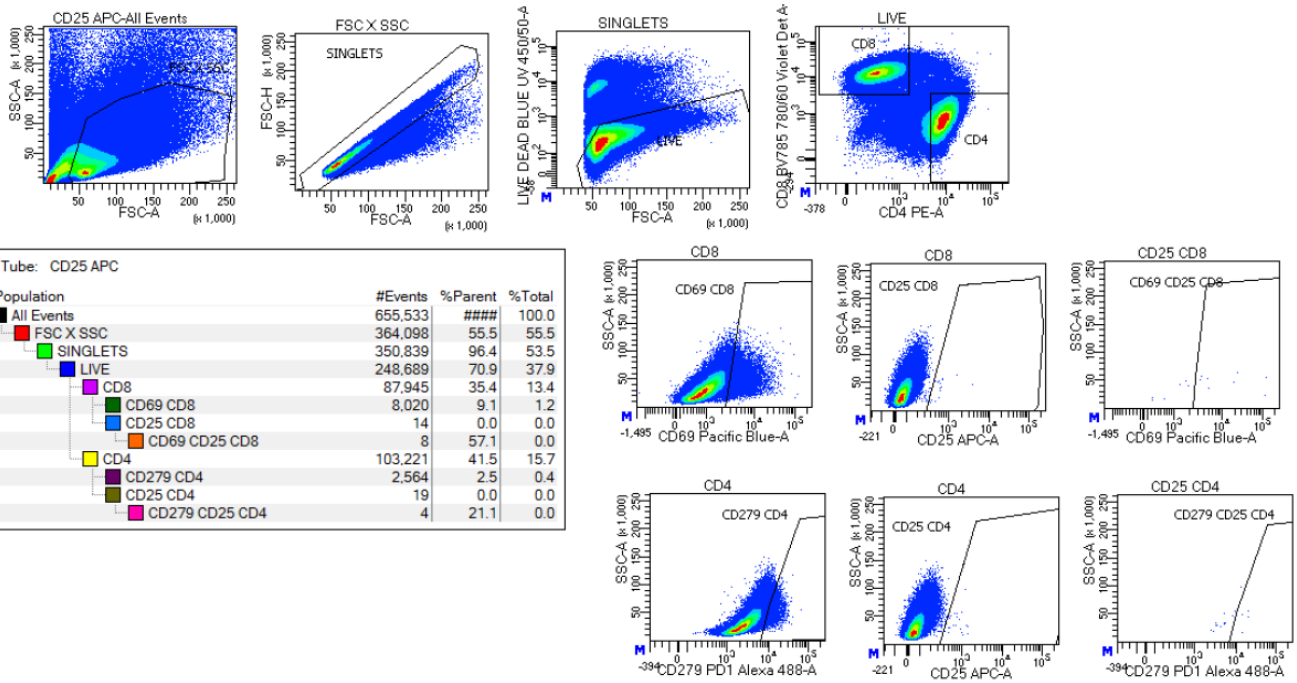


Supplementary Figure S16: PD-L1 expression increases with FOXM1 expression. B) PD-L1 expression increases in chemo-resistant SCLC cell lines SBC-5 CisR and H-69 CisR.

Supplementary S17

A

FMO CD25 APC

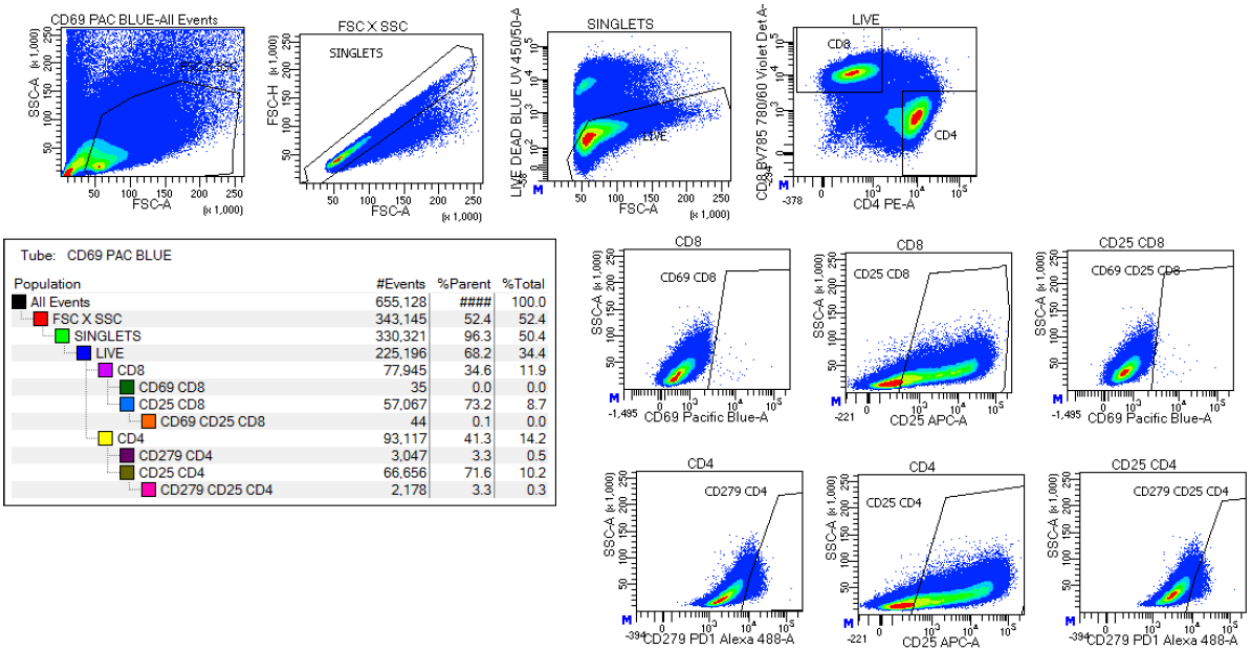


Tube: CD25 APC

Population	#Events	%Parent	%Total
All Events	655,533	####	100.0
FSC X SSC	364,098	55.5	55.5
SINGLETS	350,839	96.4	53.5
LIVE	248,689	70.9	37.9
CD8	87,945	35.4	13.4
CD69 CD8	8,020	9.1	1.2
CD25 CD8	14	0.0	0.0
CD69 CD25 CD8	8	57.1	0.0
CD4	103,221	41.5	15.7
CD279 CD4	2,564	2.5	0.4
CD25 CD4	19	0.0	0.0
CD279 CD25 CD4	4	21.1	0.0

B

FMO CD69 PACIFIC BLUE



Tube: CD69 PAC BLUE

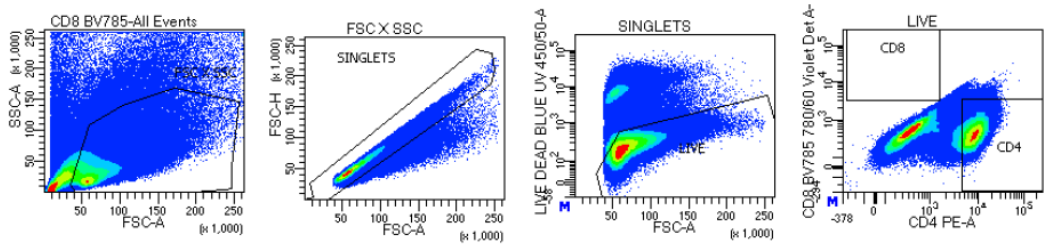
Population	#Events	%Parent	%Total
All Events	655,128	####	100.0
FSC X SSC	343,145	52.4	52.4
SINGLETS	330,321	96.3	50.4
LIVE	225,196	68.2	34.4
CD8	77,945	34.6	11.9
CD69 CD8	35	0.0	0.0
CD25 CD8	57,067	73.2	8.7
CD69 CD25 CD8	44	0.1	0.0
CD4	93,117	41.3	14.2
CD279 CD4	3,047	3.3	0.5
CD25 CD4	66,656	71.6	10.2
CD279 CD25 CD4	2,178	3.3	0.3

Supplementary Figure S17: Representative images of FMOs and gating strategy for T cells. A) FMO and gating strategy for CD25-APC. B) FMO and gating strategy of CD69 Pacific Blue.

Supplementary S18

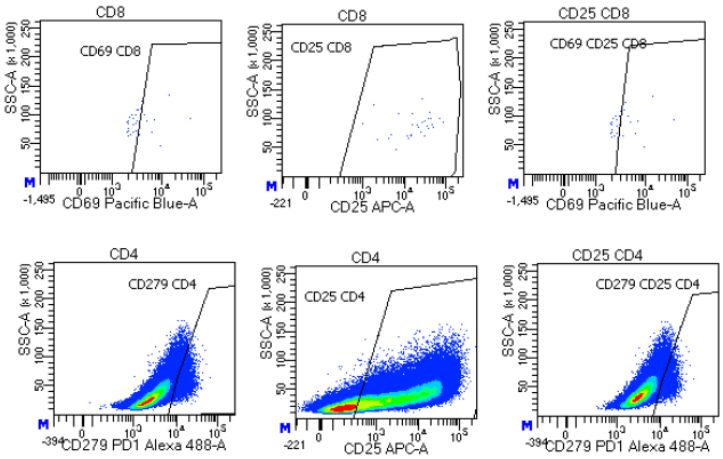
A

FMO CD8 BV 785



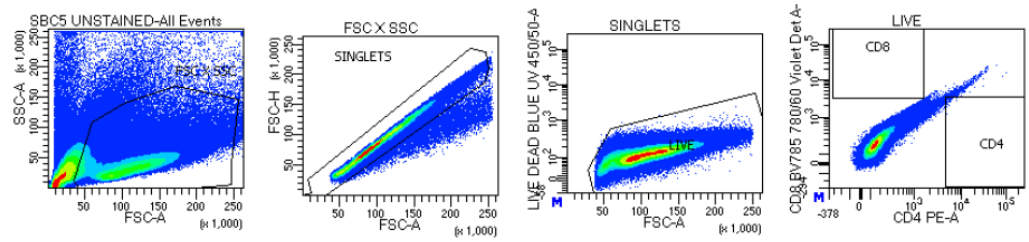
Tube: CD8 BV785

Population	#Events	%Parent	%Total
All Events	678,402	####	100.0
FSC X SSC	368,286	54.3	54.3
SINGLETS	353,830	96.1	52.2
LIVE	247,402	69.9	36.5
CD8	29	0.0	0.0
CD69 CD8	8	27.6	0.0
CD25 CD8	29	100.0	0.0
CD69 CD25 CD8	10	34.5	0.0
CD4	95,430	38.6	14.1
CD279 CD4	3,472	3.6	0.5
CD25 CD4	68,408	71.7	10.1
CD279 CD25 CD4	2,459	3.6	0.4



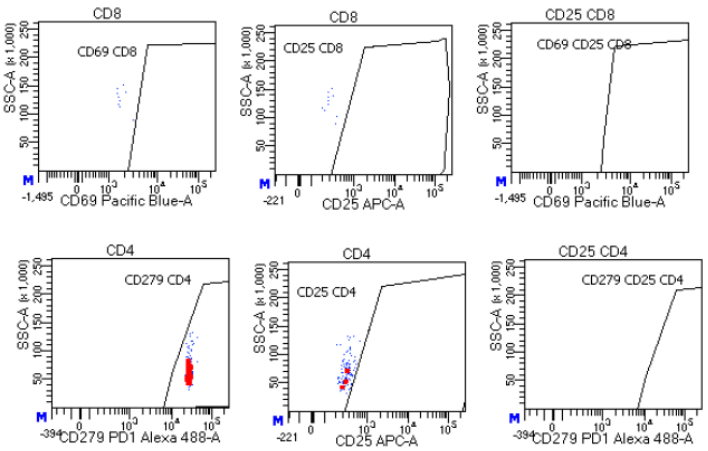
B

SBC-5 Unstained T Cells



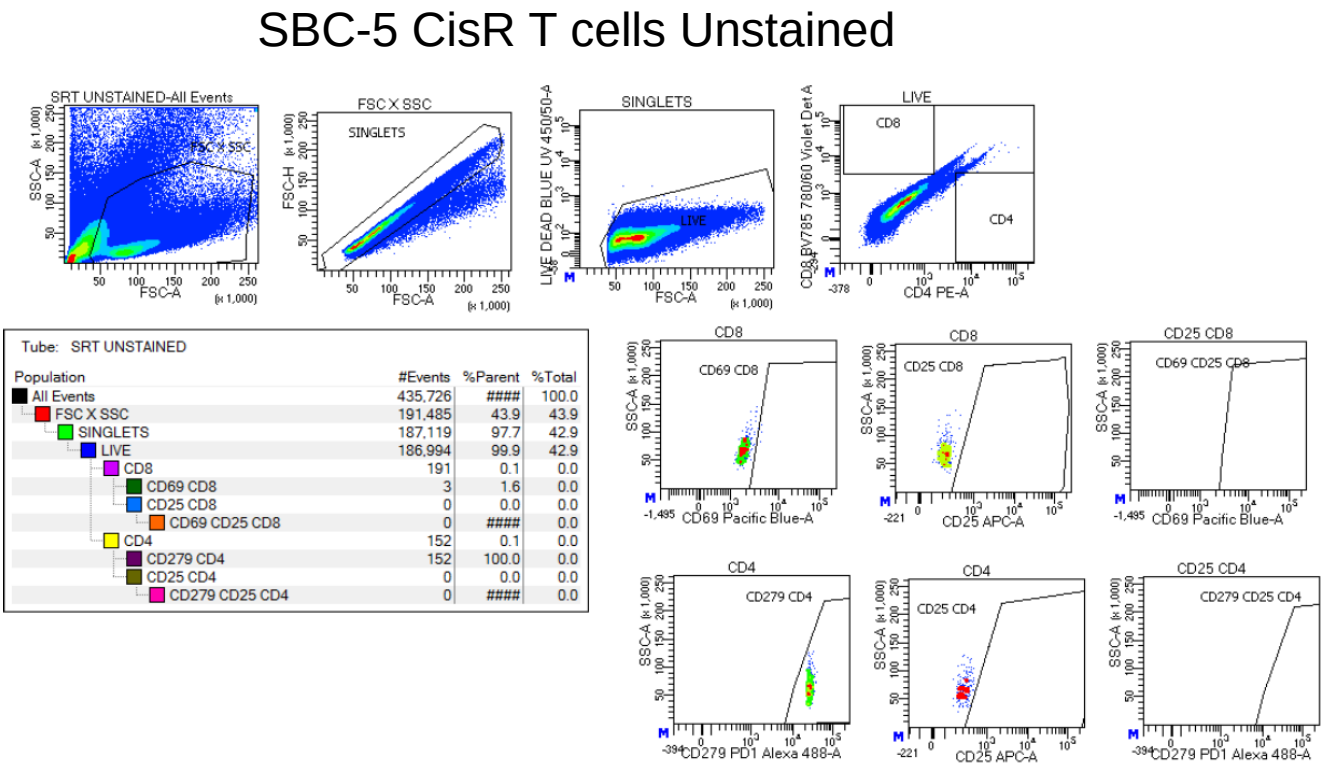
Tube: SBC5 UNSTAINED

Population	#Events	%Parent	%Total
All Events	332,613	####	100.0
FSC X SSC	172,737	51.9	51.9
SINGLETS	166,347	96.3	50.0
LIVE	166,277	100.0	50.0
CD8	10	0.0	0.0
CD69 CD8	0	0.0	0.0
CD25 CD8	0	0.0	0.0
CD69 CD25 CD8	0	####	0.0
CD4	110	0.1	0.0
CD279 CD4	109	99.1	0.0
CD25 CD4	0	0.0	0.0
CD279 CD25 CD4	0	####	0.0



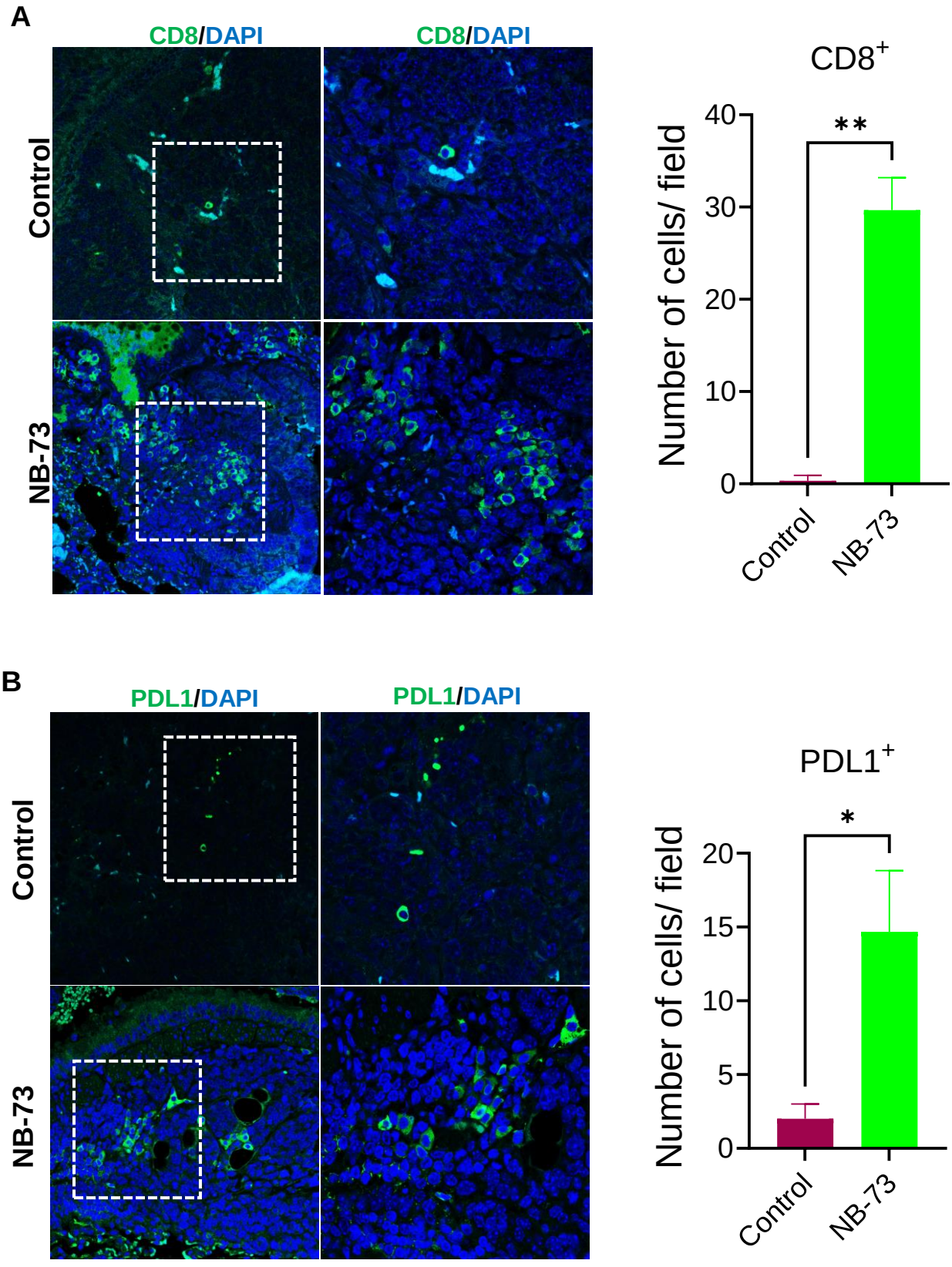
Supplementary Figure S18: Representative images of FMOs and gating strategy for unstained and stained T cells. **A)** FMO for CD8 brilliant violet shows no positive CD8 positive T cells. **B)** FMO and gating strategy FOR unstained T cells culture with SBC-5 cells.

Supplementary S19



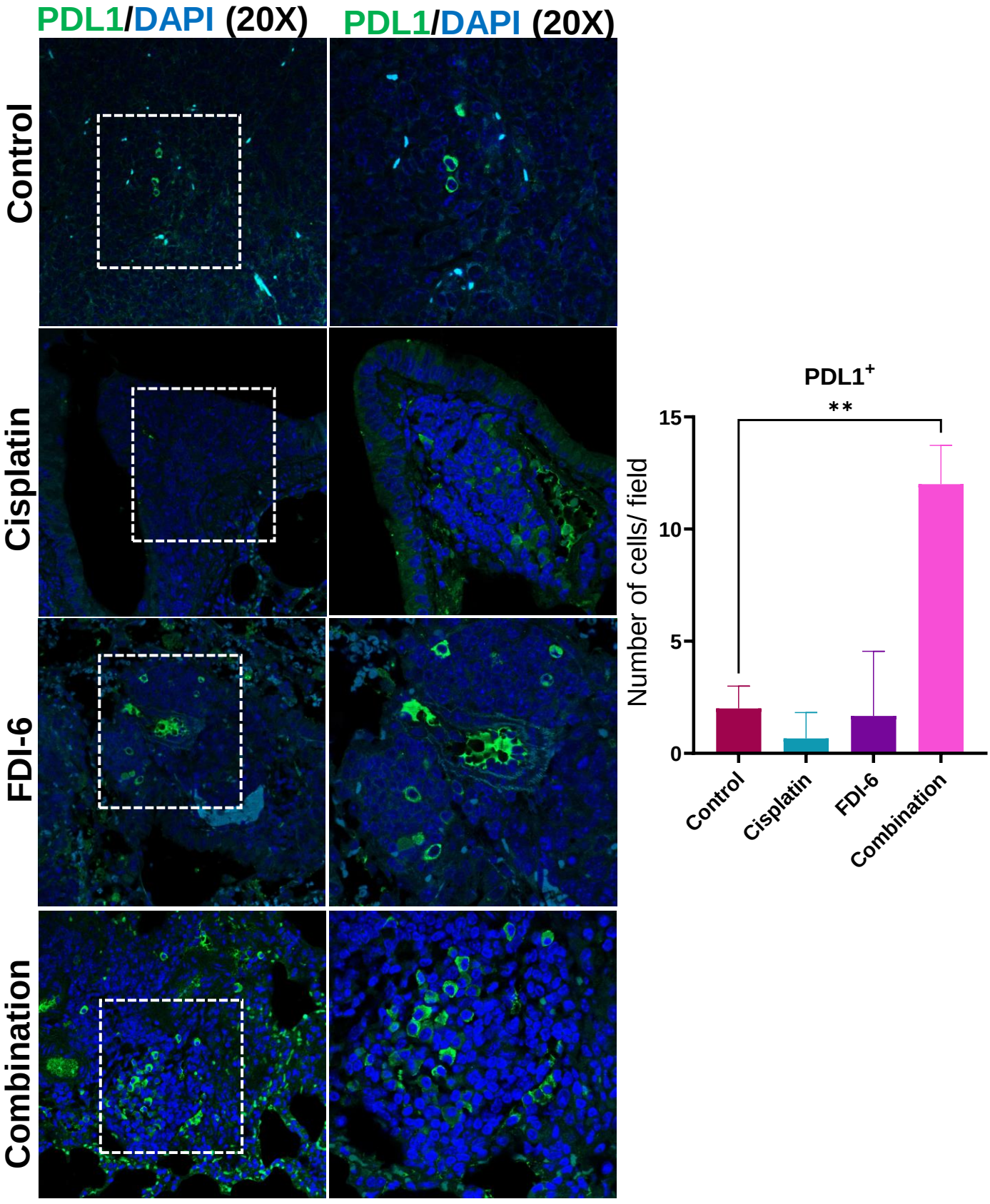
Supplementary Figure S19: Representative images of unstained T cells with gating strategy. Unstained T cells co-cultured with SBC-5 CisR cells with gating strategy.

Supplementary S20



Supplementary Figure S20: Immunofluorescence staining for CD8+ cytotoxic T cells and PD-L1 expression on RPM tumor microenvironment. **A)** FOXM1 inhibitor NB-73 treatment showed an enhanced level of CD8+ T cell infiltration in the spontaneous RPM tumors. **B)** An increase in PD-L1 expression was observed in NB-73 treated RPM cells.

Supplementary S21



Supplementary Figure S21: Immunofluorescence staining for PD-L1 expression on RPM spontaneous tumor cells. An increase in PD-L1 expression was observed in FOXMi (alone or in combination with cisplatin) treated RPM tissues.