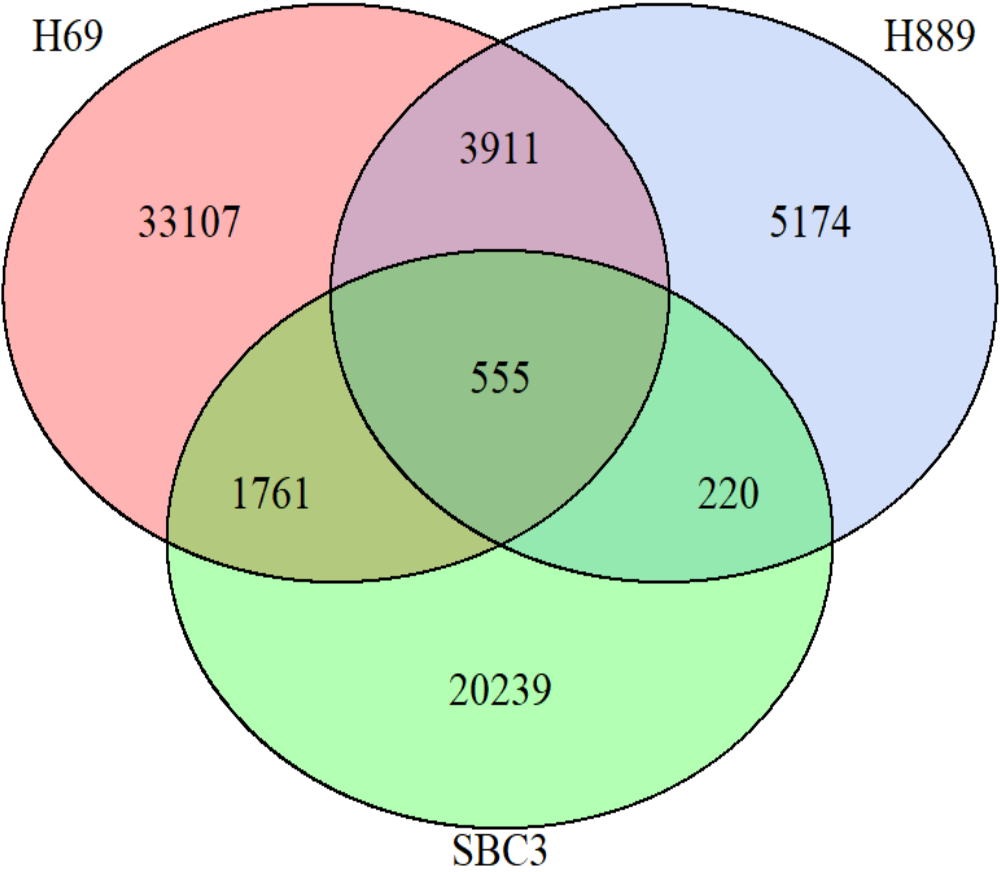
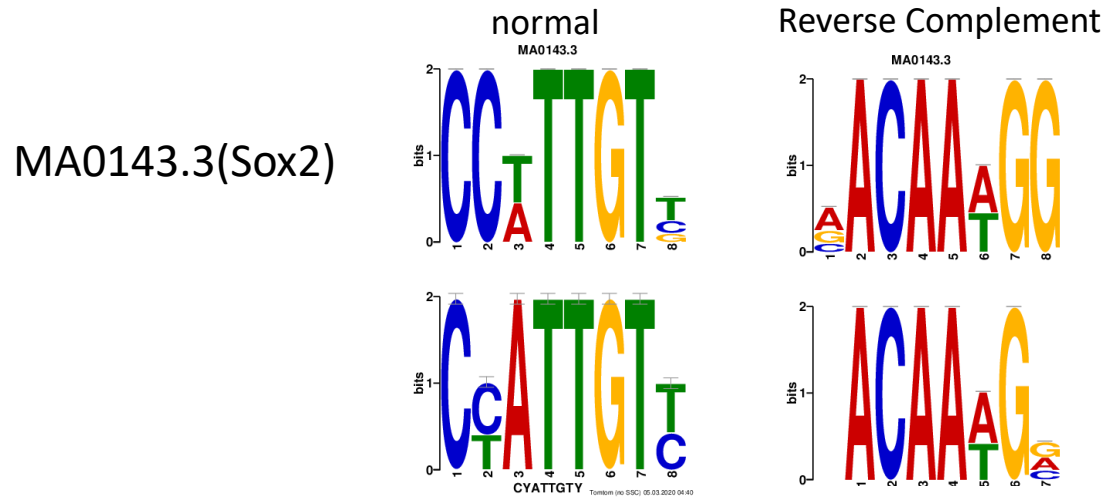
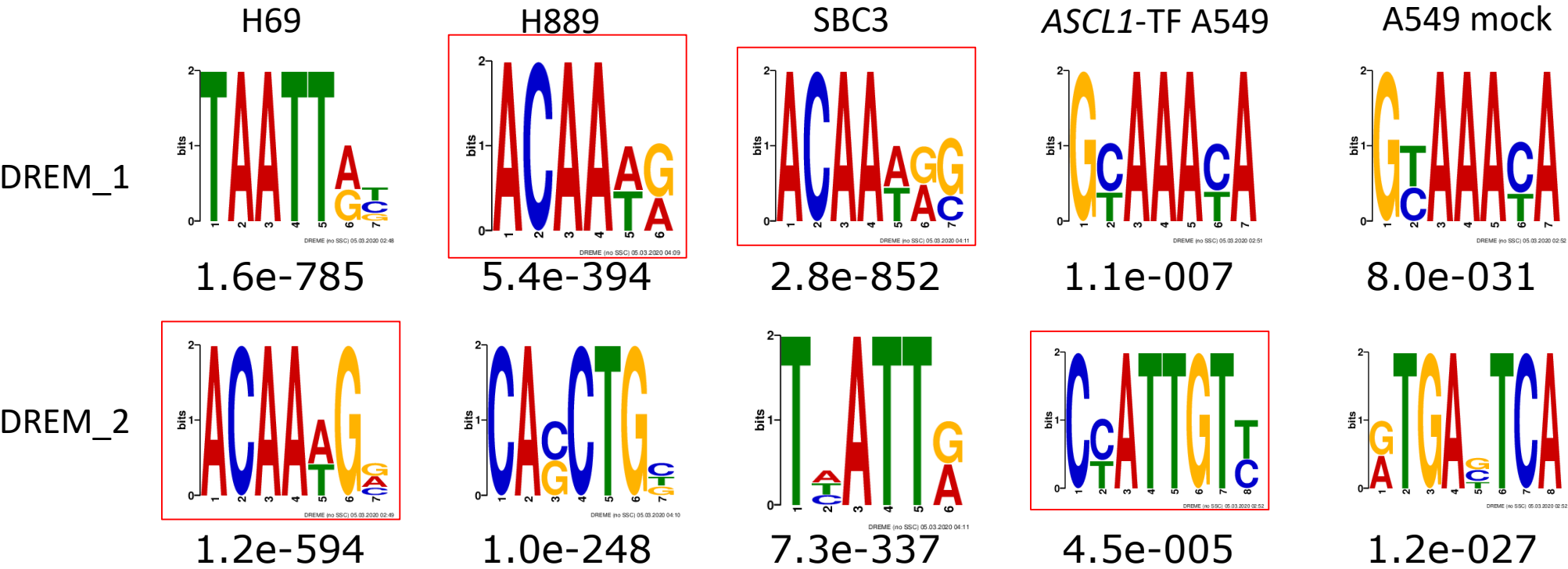


Supplementary Figure S1

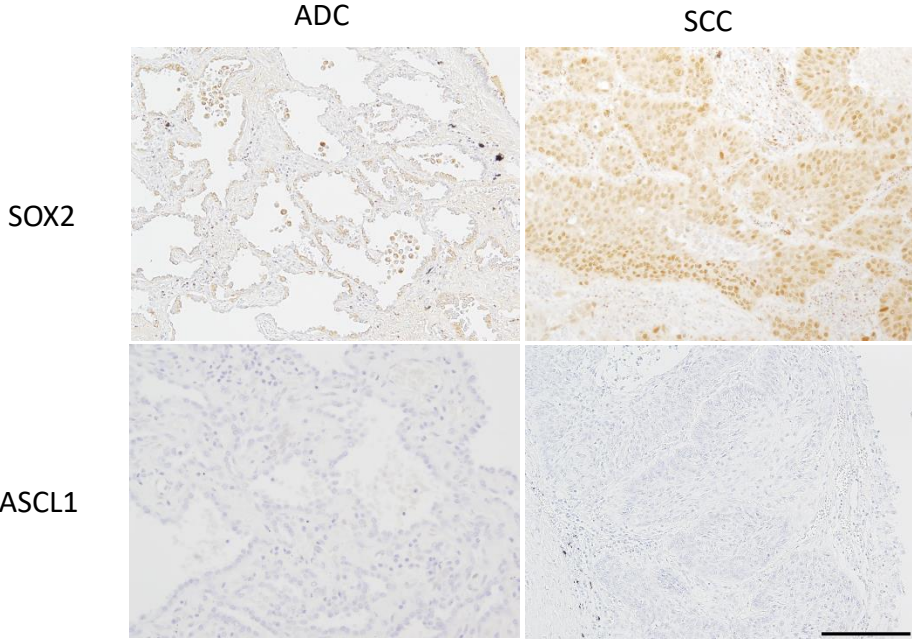


Supplementary Figure S2

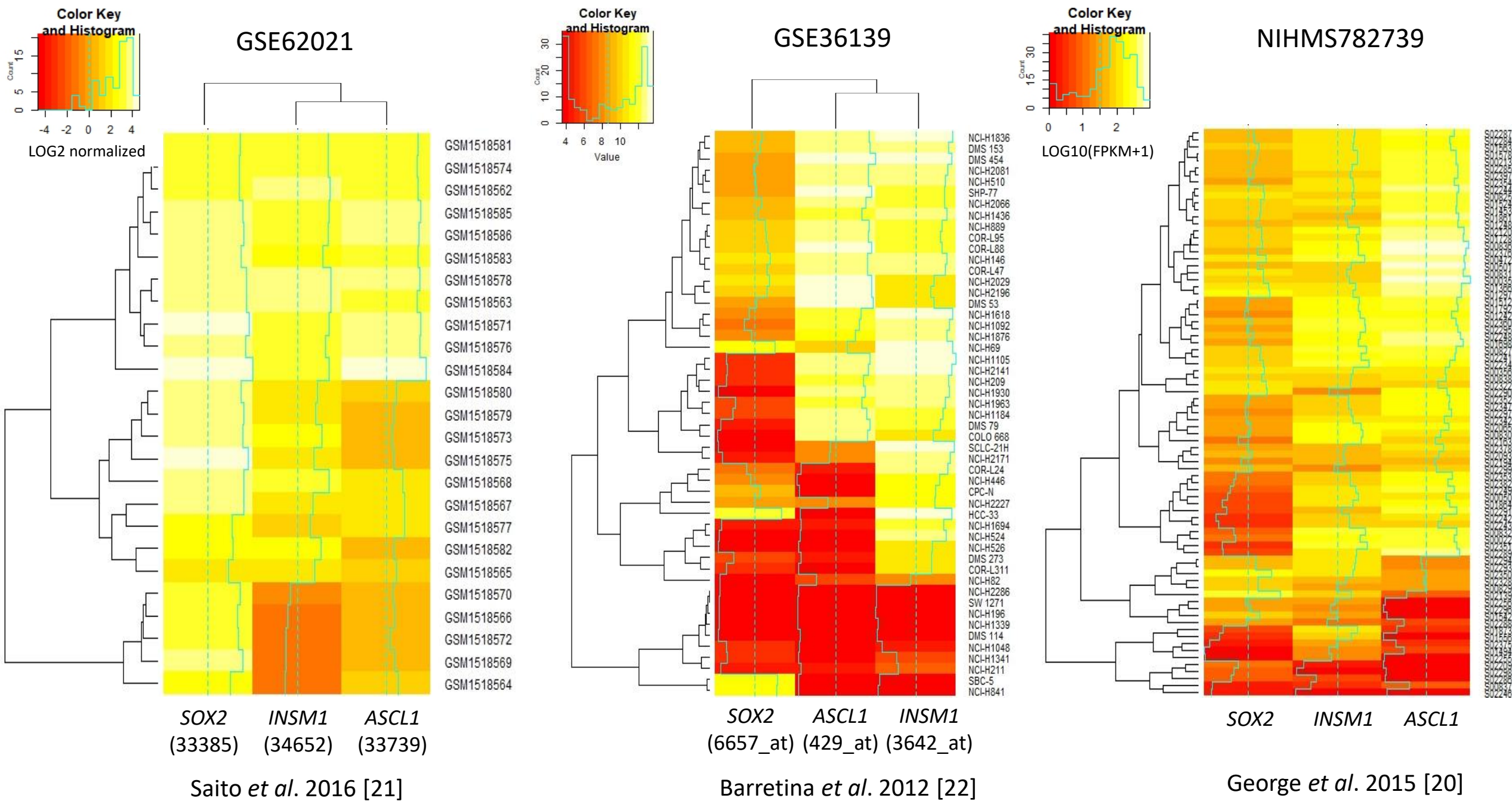
DREME (Discriminative Regular Expression Motif Elicitation) motif top2



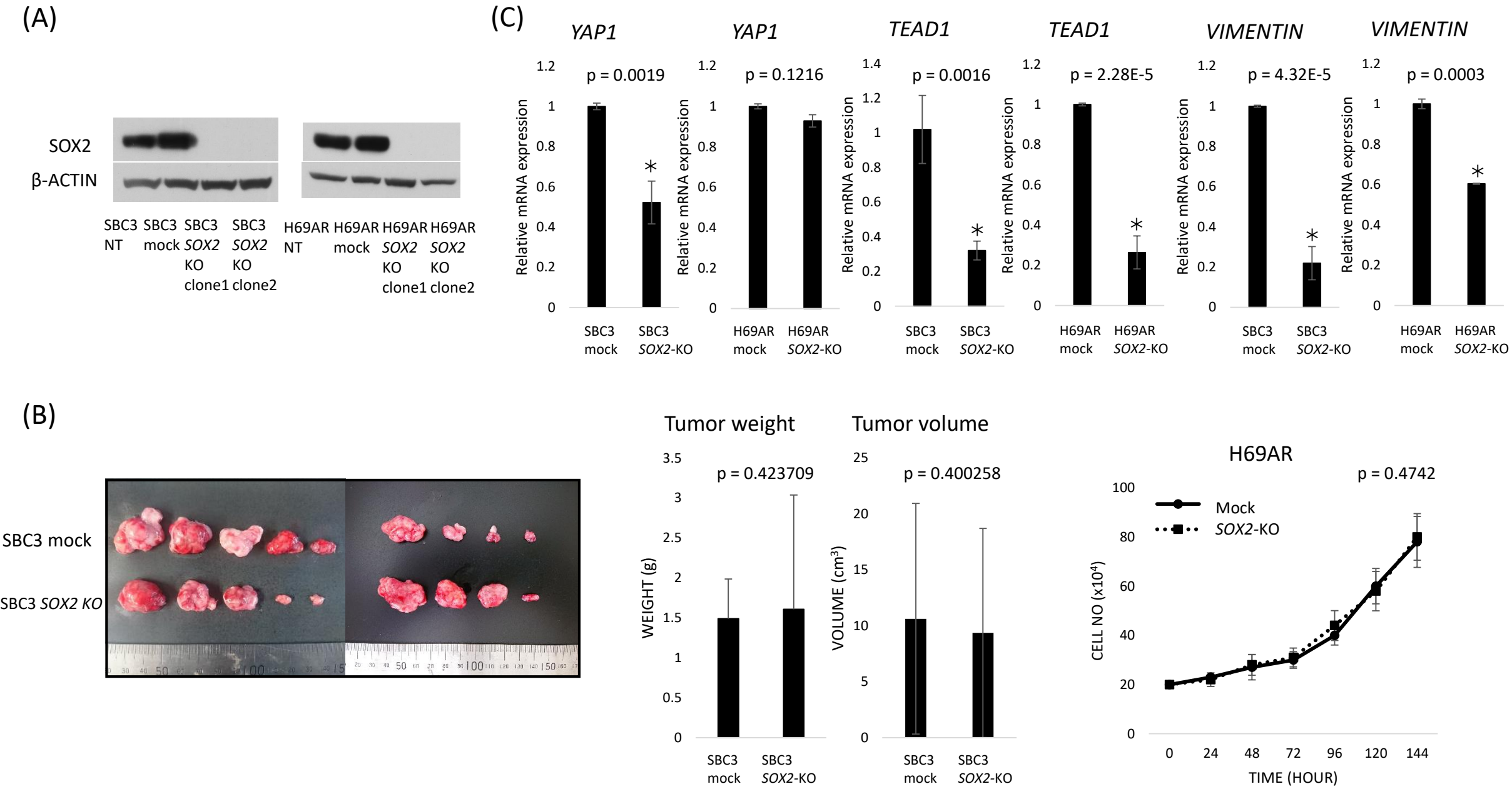
Supplementary Figure S3



Supplementary Figure S4



Supplementary Figure S5



Supplementary Fig. S1: To evaluate the overlaps between the SOX2 peaks, we applied the function 'findOverlapsOfPeaks' of ChIPpeakAnno (Bioconductor). As shown, the result clearly indicated differential binding peaks between the SCLC-A and SCLC-Y subtypes cells. We utilize this data to indicate the differential binding of SOX2 in each subtype.

Supplementary Fig. S2: We performed motif analysis using MEME-Chip website (<http://meme-suite.org/tools/meme-chip>). We found that the SOX2 binding motif was enriched in ChIP-seq peaks of H69, H889, SBC3 and *ASCL1*-TF A549 as shown, which is indicative of successful ChIP-seq experiments. In contrast, no enrichment of SOX2 motif was found in ChIP-seq peaks of the A549 mock, indicating no significant enrichment of SOX2 binding sites due to its low level of SOX2 expression as found in Fig 2A and 2B.

Supplementary Fig. S3: IHC images of surgically resected non-SCLC tissues for SOX2 and ASCL1. SOX2 was expressed in tumor cell nuclei. Representative images are shown. Scale bar = 200 μ m.

Supplementary Fig. S4: Positive correlations of *ASCL1*, *SOX2* and *INSM1* expression in SCLC tissue samples and SCLC cell lines. (A) Expression levels of *ASCL1*, *SOX2*, and

INSM1 in microarray or RNA-seq datasets of SCLC tissues samples or SCLC cell lines.

Spearman correlation coefficients (ρ) and P values are indicated. GSE62021 (n=25) [21], GSE36139 (n=51) [22], and NIHMS782739 (n=81) [20] datasets were analyzed. The results confirmed the coordinated expression of *ASCL1* and *SOX2* in these samples (GSE62021: $\rho=0.416923077$, $p=0.037284808$, GSE36139: $\rho=0.369321267$, $p=0.0075568$, and NIHMS782739: $\rho=0.417389$, $p=0.000103927$). In the same manner, we confirmed the coordinated expression of *ASCL1* and *INSM1* (GSE62021: $\rho=0.717692308$, $p=4.32243E-5$, GSE36139: $\rho=0.476199095$, $p=0.000398$, and NIHMS782739: $\rho=0.550023$, $p=9.8392E-8$).

Heatmap data focusing on *SOX2*, *ASCL1*, and *INSM1* was obtained using these datasets.

Supplementary Fig. S5: *SOX2*-knockout in the SCLC-Y subtype cells, SBC3 and H69AR, using the CRISPR/Cas9 system. *SOX2* protein expression was completely diminished (A), whereas tumor proliferative capacity was not diminished after *SOX2* knockout in SBC3 and H69AR cells (B). *YAP1*, *TEAD1*, or *VIMENTIN* mRNA expression decreased in *SOX2* knockout SBC3 and H69AR cells (C). The analysis was performed in triplicate. Data are shown as the mean $\pm$ SD. Asterisks indicate a significant difference; *, $p<0.05$.