Supplementary Figure S1 Inactivation of Crebbp in preSC cells.

A, Cartoon showing strategy to delete Crebbp, employing two different sgRNAs directed towards the histone acetyltransferase (HAT) domain.

B, Western Blot showing loss of wild-type CREBBP and reduced expression of E-CADHERIN, with transduction of sgCrebbp-1 and sgCrebbp-2 in preSC cells and in resulting allograft tumors. Related to Main Figure 1.

C, CGRP Immunofluorescence on preSC-sgCrebbp allograft showing neuroendocrine marker positivity. A control neuroendocrine lesion from the Rb1/Trp53/p130 autochthonous SCLC model is shown. Nuclei were stained with DAPI. Scale bar: 100µm
Supplementary Figure S2 Histology of Rb1/Trp53/Crebbp-deleted lung SCLC and liver metastases. A, Low power view with much hemorrhage and necrosis. B, High power image showing classic SCLC morphology. C, Mediastinal lymph node with considerable hemorrhage and increased vascularity. D, Increased vascularity and hemorrhage. E, F, Vascular invasion. G, H, Liver metastasis in Rb1/Trp53/Crebbp (G) and Rb1/Trp53-deleted (H) models. I, Quantification of % with liver metastasis upon histological evaluation. n=12 livers per model analyzed. Scale bar, 50µm.
Supplementary Figure S3 Features of Rb1/Trp53 and Rb1/Trp53/Crebbp GEM models of SCLC. A, Phospho Ser10 histone H3 immunochemistry in Rb1/Trp53 and Rb1/Trp53/Crebbp-mutant SCLC models. Strongly stained mitotic cells (arrows) were included in quantification. Scale bar, 50µm.

B, Quantification of data from 5 independent tumors per model. ns: not significant.

C, RNAseq analyses of c-Myc, N-Myc and L-Myc, as well as neuroendocrine markers Ascl1, Ncam1 and Syp in mouse SCLC tumors from Rb1/Trp53 (RP) and Rb1/Trp53/Crebbp (RPC) GEM models.
Supplementary Figure S4  Pituitary and thyroid tumors with Rb1/Trp53 or Rb1/Trp53/Crebbp inactivation driven by Ascl1Cre-ERT2.
A-B, Pituitary carcinomas from Rb1lox/lox;Trp53lox/lox;Ascl1Cre-ERT2 (Rb1/Trp53) tamoxifen treated mice at time of morbidity showed multifocal invasion of the overlying neural parenchyma.
C, Neoplastic cells invaded the underlying sphenoid bone. Islands of neoplastic cells were present within bone marrow (*).
D-E, The Rb1lox/lox;Trp53lox/lox;Ascl1Cre-ERT2 mice also exhibited thyroid C-cell adenomas (Ad) or hyperplasia (Hyp) characterized by discrete nodular foci composed of well differentiated C cells that compressed adjacent follicles.
F-G, While the pituitary carcinomas in Rb1lox/lox;Trp53lox/lox; Crebbplox/lox;Ascl1Cre-ERT2 (Rb1/Trp53/Crebbp) triple mutant mice arose more rapidly, they were histologically similar to those from the Rb1/Trp53 double mutant model (B).
H-I, The Rb1/Trp53/Crebbp animals exhibited bilateral, large, expansile thyroid medullary C-cell carcinomas (arrows) that invaded adjacent musculature.
J, Higher magnification of C-cell thyroid carcinoma from Rb1/Trp53/Crebbp animal showing vascular invasion (white arrow).
A,D,F,H: Scale bar 500μM. B,C,E,G: Scale bar 100μM. I: Scale bar 200μM. Related to Main Figure 2.
**Supplementary Figure S5.** Gene set enrichment analysis (GSEA) identifies biological processes and pathways regulated by Crebbp. GSEA plots showing the top gene sets enriched in the Crebbp-deficient neuroendocrine tumors, G2M_CHECKPOINT and MITOTIC_SPINDLE in mouse SCLC A, pituitary tumors B, and thyroid tumors C. Related to Main Figure 3.
Supplementary Figure S6. Immunofluorescence showing that SCLC cells with reduced CDH1 or increased VIMENTIN still maintain CGRP expression.

A, CGRP (red channel), E-CADHERIN (green channel), with DAPI nuclear stain and merged image for Rb1/Trp53 (RP) and Rb1/Trp53/Crebbp (RPC) SCLC models.

B, CGRP (red channel), VIMENTIN (green channel), with DAPI nuclear stain and merged image for RP and RPC SCLC models.
Supplementary Figure S7. GSEA analyses showing a trend towards enrichment in Epithelial Mesenchymal Transition related genes in the 11 human SCLC annotated for CREBBP mutation compared to 70 CREBBP wild-type samples. Underlying RNAseq data from George et al, 2017. FDR: False Discovery Rate. NES: Normalized Enrichment Score.
Supplementary Figure S8. Perturbation of CREBBP and CDH1 expression in DMS53 cells.

A, CellTiter-Glo viability assay of sgRNA mediated knockout of CREBBP in DMS53 cells (n=3 independent experiments). Note increased proliferation with CREBBP suppression. ***, p<0.001. The deletion of CREBBP was validated by immunoblotting.

B, CellTiter-Glo viability assay of overexpression of CDH1 in DMS53 cells treated with or without 0.25 mg/ml doxycycline. Inducible lentiviral vector system (pLenti-puro and pLenti CMV TetR Blast) was employed. ***, p<0.001. CDH1 overexpression suppressed proliferation. The overexpression of CDH1 in this cell line was validated by immunoblotting. Related to Main Figure 4.
**Supplementary Figure S9  CREBBP deletion in NCI-H1882 cell line and PDX model LU505.**

**A,** Heat map showing copy number variation analyses from low coverage whole genome sequencing of human SCLC cell lines. Log$_2$ ratio of binned reads in SCLC cell lines relative to normal control is shown. Deletion (blue) in NCI-H1882 is consistent with absent CREBBP expression in this cell line.

**B,** Read density plot in IGV showing reads from a targeted resequencing panel (Ovation Cancer 2.0) including CREBBP exonic sequence. The absence of reads in exon 1 (arrow) is consistent with a genomic deletion in sample LU505 and correlates with absent CREBBP expression in this model (See Figure 6). Sequencing of two additional SCLC PDX models are shown for comparison. Related to Main Figure 5.
**Supplementary Figure S10. Features of PDX model LU505 and cultured cells.**

**A,** Western blot analyses showing absence of CREBBP protein, high expression of MYCL and mesenchymal markers SLUG and ZEB1, and low expression of ASCL1 in LU505 PDX model of SCLC. For comparison, a SCLC PDX model with high ASCL1 expression, FHSC14, is also shown.

**B,** Representative phase contrast image (left) and F-actin/Vimentin immunofluorescence, showing mesenchymal features of LU505 cells when placed in culture. Scale bar: 100µm. Nuclei were stained with DAPI.

**C,** Histology of LU505 PDX model in vivo. This model exhibits classic SCLC histology.
Supplementary Figure S11. Re-expression of Crebbp inhibits tumorigenesis of LU505 cells in NSG mice. Image of tumors derived from LU505-Vector cells 8 weeks after subcutaneous injection of 5.0 x 10^6 cells. For the 5 LU505-Crebbp injected and 5 LU505-CDH1 injected mice, no tumor could be detected at 8 weeks. Related to Main Figure 5.
Supplementary Figure S12. Expression of CREBBP or CDH1 inhibits the migratory abilities of LU505 cells.

A, Representative images of migratory cells of LU505 with or without Crebbp overexpression. Data were presented as migrated cells per field. ***, p<0.001. n= 3 biological replicates.

B, Representative images of migratory cells of LU505 with or without CDH1 overexpression. Data were presented as migrated cells per field. ***, p<0.001. n= 3 biological replicates.

Related to Main Figure 5.
Supplementary Figure S13. Reduced H3K27Ac associated with *Cldn3*, *Cldn6*, *Cldn9*, *Tjp3* and *Sdc4* genes upon loss of *Crebbp* in preSC cells. ChIP-seq read density plots shows reduced H3K27Ac in genomic regions of *Cldn3*, *Cldn6*, *Cldn9*, *Crb3*, *Tjp3* and *Sdc4* in two *Crebbp* knockdown preSC cells (shCrebbp-1 and shCrebbp-2; blue) compared to two control preSC cells (shNS and shEmpty; red). Related to Main Figure 6.
**Supplementary Figure S14. Pracinostat treatment in human SCLC cells results in increased H3K27Ac and decreased E-CADHERIN.**

**A,** Immunoblot analyses of acetylation levels of H3K27 and H3K18 and protein levels of E-CADHERIN and CREBBP in control (Vector) and Crebbp re-expression (Crebbp) LU505 cells treated with DMSO or 125nM pracinostat for 72 hours. H3 and β-ACTIN were used as loading control respectively.

**B,** Immunoblotting analyses of acetylation levels of H3K27 and H3K18 and protein levels of E-CADHERIN and CREBBP in control (sgGFP) and CREBBP-knockout (sgCREBBP) DMS53 cells treated with DMSO or pracinostat for 72 hours. H3 and β-ACTIN were used as loading control respectively.

Related to Main Figure 6.
Supplementary Figure S15. Pracinostat activity in human SCLC cell lines inversely correlates with CREBBP expression. CellMinerCDB was used to analyze drug response and RNAseq expression data from Polley et al, JNCI, 2016. Higher Pracinostat activity is associated with lower CREBBP expression.
Supplementary Figure S16. Strong responses to Pracinostat in 
*Rb1/Trp53/Crebbp*-deleted SCLC model
A, Tumor volume changes (%) in RP and RPC mice treated with saline and pracinostat at 2 weeks as normalized to pre-treatment tumor volume. Data are shown as individual values for volume changes at 2 weeks relative to baseline. 
B, Treatment response divided into PD (progressive disease), SD (stable disease), PR (partial regression) and CR (complete regression) groups in RP and RPC mice treated with saline and Pracinostat at weeks. Data are presented as percentage of total mice in each treatment group. 
Related to Main Figure 7.