

Supplementary Figure 1. Scatter Plots of Gene Re-expression with Decitabine or Trichostatin-A in Eight Non-Small Cell Lung Cancer Cell Lines. Y-axis is the ratio of gene expression in decitabine (DAC) treated cells to mock-treated cells. X-axis the ratio of TSA treated cells to mock treated cells. DAC-specific re-expression for a gene is defined as a greater than 2.0 fold re-expression on a microarray with DAC treatment compared to mock treated cells, less than 1.4 fold re-expression with TSA treatment compared to mock treated cells, and no basal expression in mock treated cells. DAC-specific upregulation in at least two cell lines occurred in 305 genes.

Supplementary Table 1. List of Infinium 450K Methylation Probes from Figure 1. The table includes probe ID, annotated gene, t-statistic and p-value associated with linear regression analysis of individual probe performance in distinguishing tumor vs. normal samples, frequency of methylation in tumors, and whether the annotated gene is polycomb parked in embryonic stem cells. Bolded are the best performing probes from the top three performing genes, based on methylation array.

Supplementary Figure 2. DNA Methylation of *CDO1*, *HOXA9*, and *TAC1* is Highly Sensitive for Stage I NSCLC in the Cancer Genome Atlas. A single Infinium methylation probe with the best discriminative capacity between tumor and normal samples was selected for each of the 3 genes. A sample is considered methylated for a gene if its β -value was larger than three times the standard deviation of the mean of β -values of normal samples. Methylation of at least one gene-promoter among *CDO1*, *HOXA9*, and *TAC1* by Infinium array identifies 98.7% of stage I NSCLC cases in The Cancer Genome Atlas.

Supplementary Figure 3. Cancer-Specific Hypermethylation Forms Clusters of Non-Small Cell Lung Cancer Cases in The Cancer Genome Atlas. (A) Medoid clustering of 426 stage I and II Non-Small Cell Lung Cancer cases in The Cancer Genome Atlas optimally identifies three clusters based on methylation data from probes listed in supplementary table 1. Rows represent individual Infinium probes and columns represent individual cancer and normal patient samples. Samples cluster into dark blue non-squamous-predominant, green squamous-predominant, and light blue mixed clusters. (B) Kaplan-Meier Survival of the 3 clusters defined in panel A.

Supplementary Figure 4. Kaplan-Meier Survival Curves for Non-Small Cell Lung Cancer for p16 methylation in combination with *APC*, *RASSF1*, or *CDH13*. Overall survival for stage I lung cancers from The Cancer Genome Atlas by methylation status of tumors.