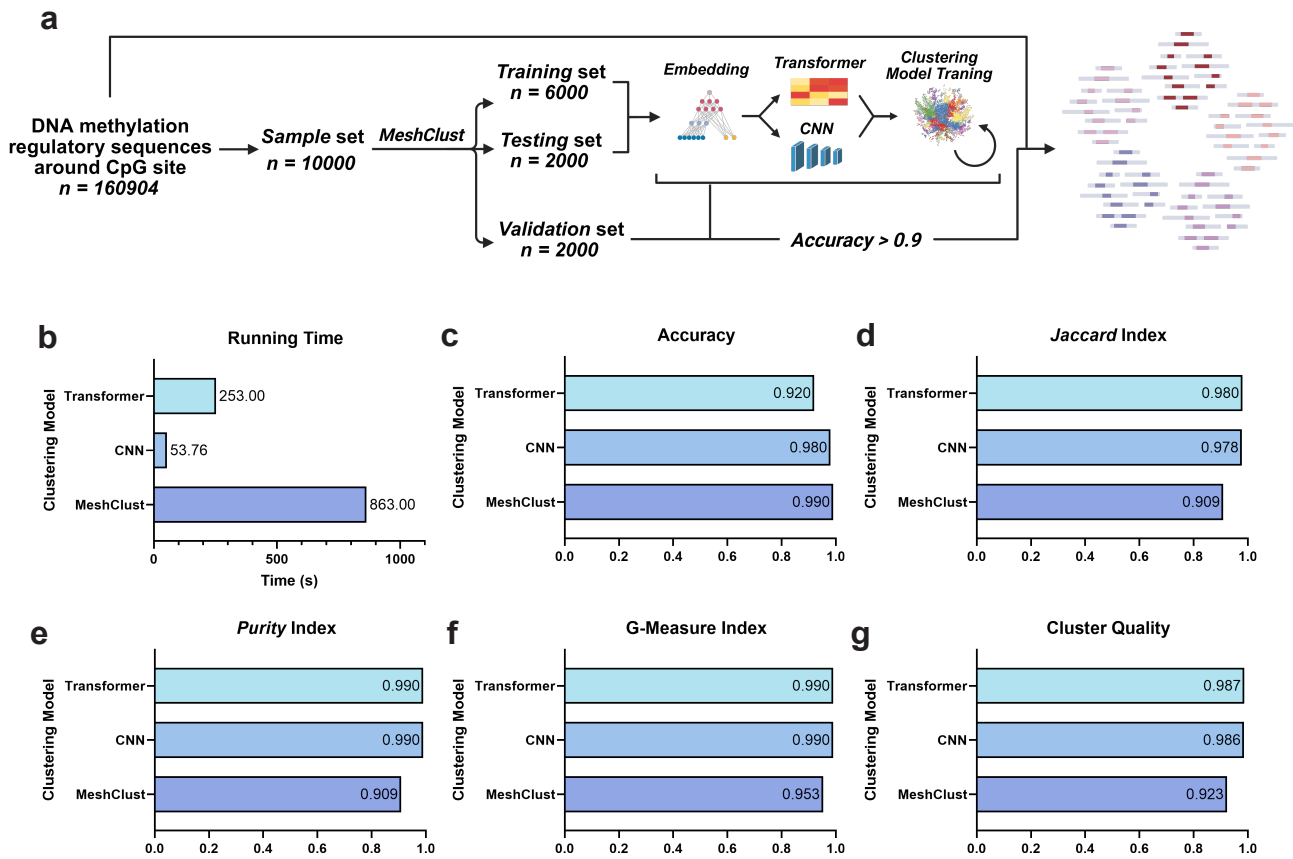


**Fig.S1| Heterogeneity of DNA methylation in pan-cancer dataset.**

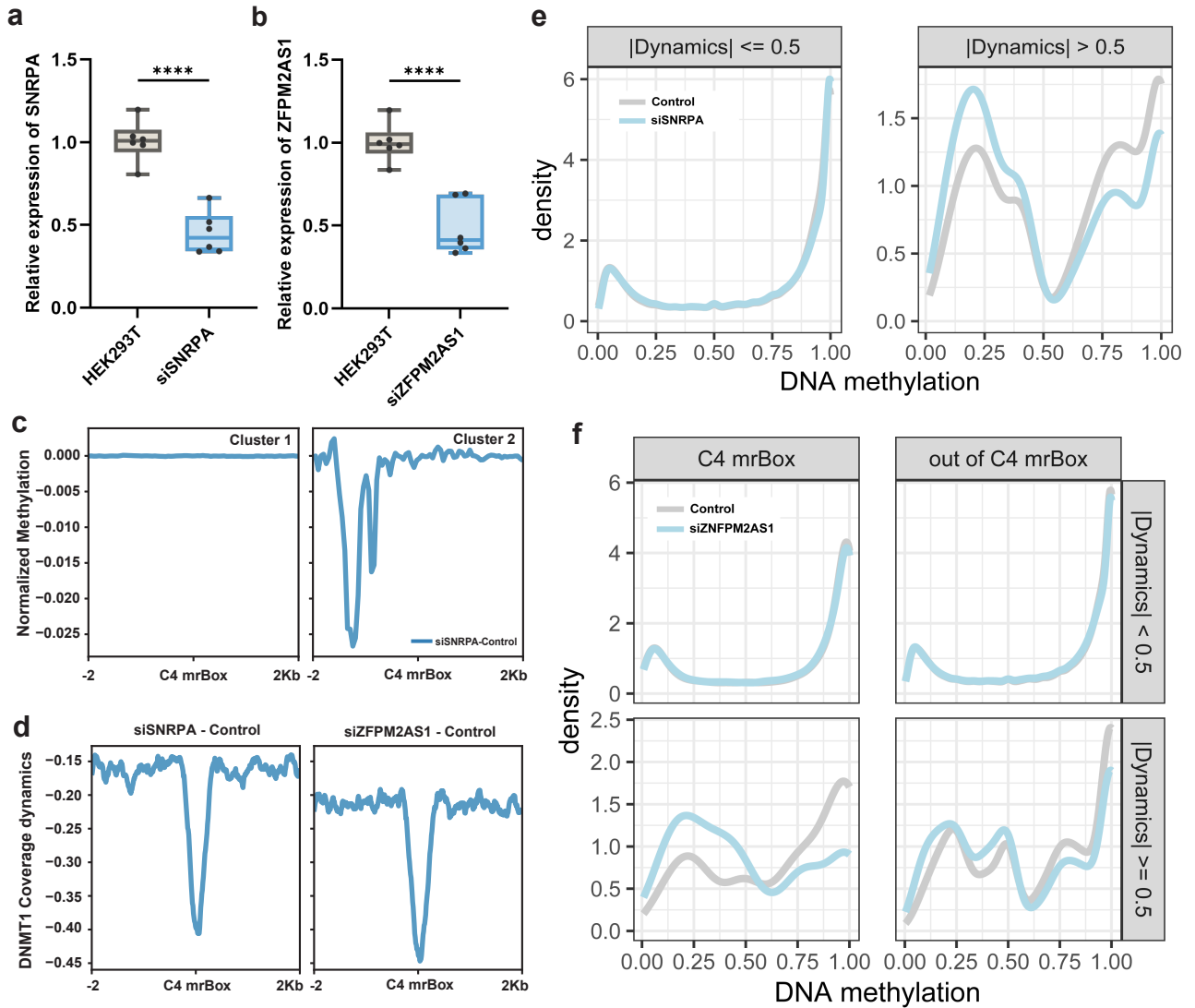
**a.** UMAP plot of DNA methylation distribution of samples from TCGA Pan-Cancer dataset. **b.** UMAP plot of DNA methylation distribution in LUAD patients. **c.** Comparison of DNA methylation landscape distributed in tumor and normal tissues. **d.** Correlation of KRAS methylation and KRAS expression. **e-f.** Pattern of DNA methylation landscape in LUAD patients from TCGA dataset.



**Fig.S2| Estimation of mrBox Clustering algorithm**

**a.** mrBox clustering algorithm pipline, including sampling, modeling, training and validation steps. **b-g.** The Jaccard index, G-measure index, Purity index, Clustering quality and running time of CNN-based clustering model, Transformer-based clustering model and Meshclust.

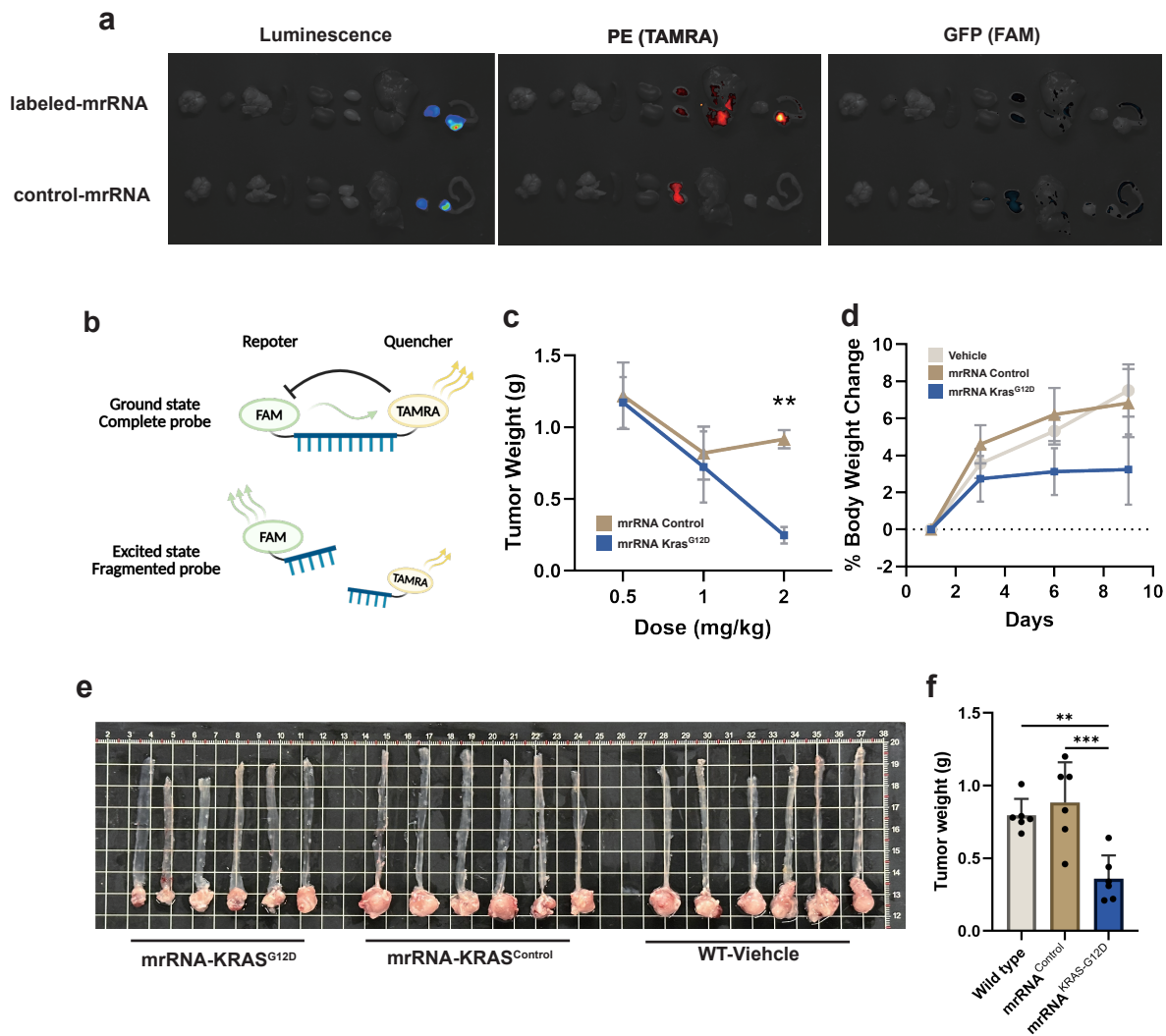




**Fig.S4| Role of SNRPA and ZFPM2AS1 in mrBox-directed DNA methylation.**

**a-b.** Validation of SNRPA and ZFPM2AS1 silencing in HEK293T cell lines with qPCR assay. *Student's t test*, \*\*\*\*  $p < 0.0001$ . Error bars, mean  $\pm$  SEM. **c.** DNA methylation dynamics around C4 mrBox in HEK293T cells treated with SNRPA silencing assay. **d.** DNMT1 enrichment changes on C4 mrBox in HEK293T cells treated with siSNRPA (**Left**) or siZFPM2AS1 (**Right**) assay. **e.** DNA methylation changes across the whole genome in HEK293T cells treated with siSNRPA assay or non-targeting control. **f.** DNA methylation changes on 1k-bp around C4 mrBox and other mrBoxes in HEK293T cells treated with siZFPM2AS1 assay or non-targeting control.





**Fig.S5| OMS therapy in mice orthotopic tumor model.**

**a.** Distribution and stability of methylation regulatory RNA (mrRNA) used in OMS therapy were measured by in vivo imaging based on FAM/TAMRA-labeled mrRNA in mice Ct-26 tumor model. **b.** Schematics of DNA probe integrity validation assay based on fluorescence resonance energy transfer (FERT). **c.** Dose-response assay of OMS therapy targeting KRASG12D mutation in mice orthotopic tumor model. **d.** Body weight changes of mice during OMS therapy. **e-f.** Tumor samples and tumor weight on Balb/c mice after sacrificing on day 15. One-way ANOVA followed by Tukey's multiple comparisons test, \*\*\*\*  $p < 0.0001$ , \*\*\*  $p < 0.001$ , \*\*  $p < 0.01$ , and \*  $p < 0.05$ . Error bars, mean  $\pm$  SEM.