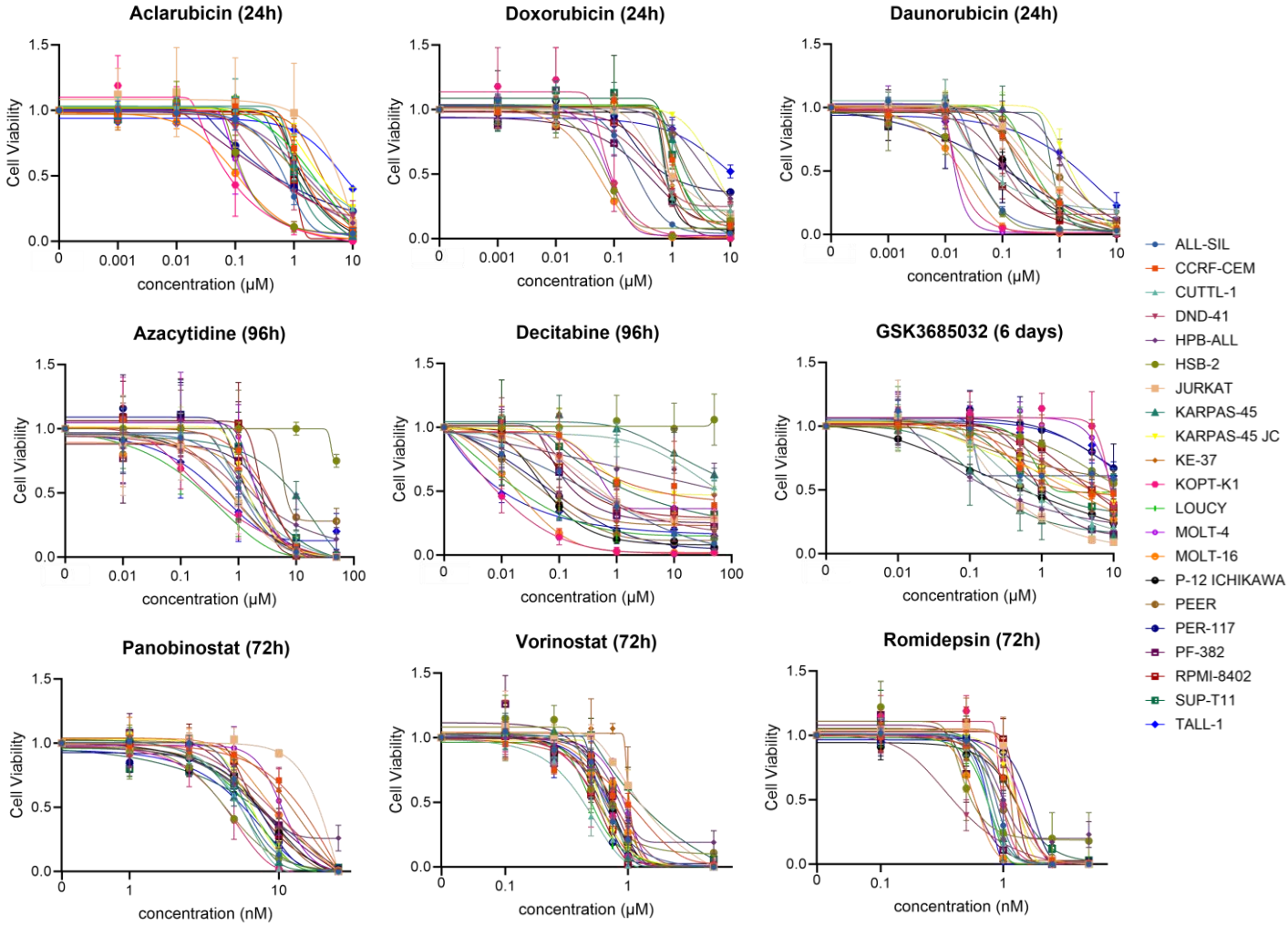
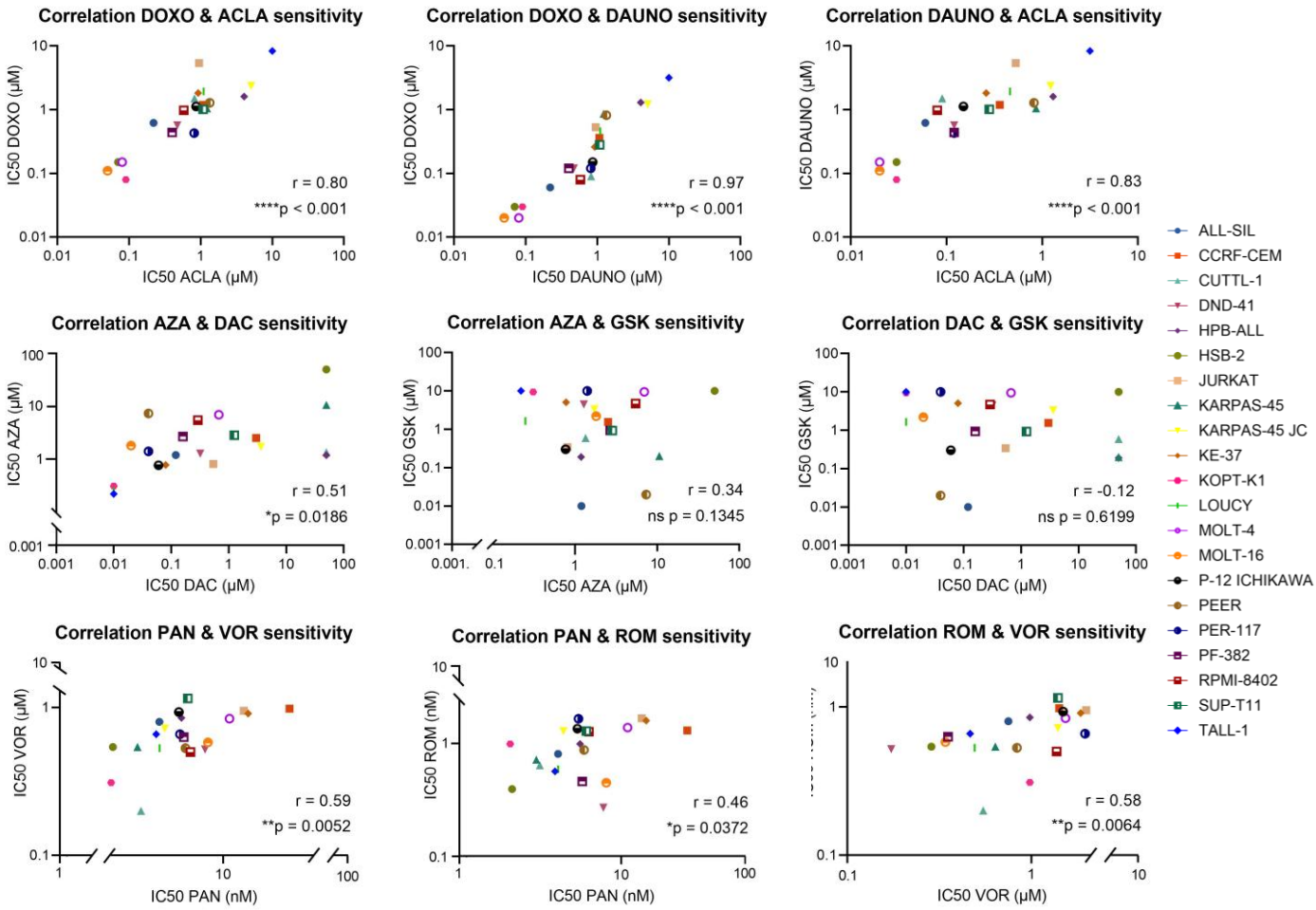
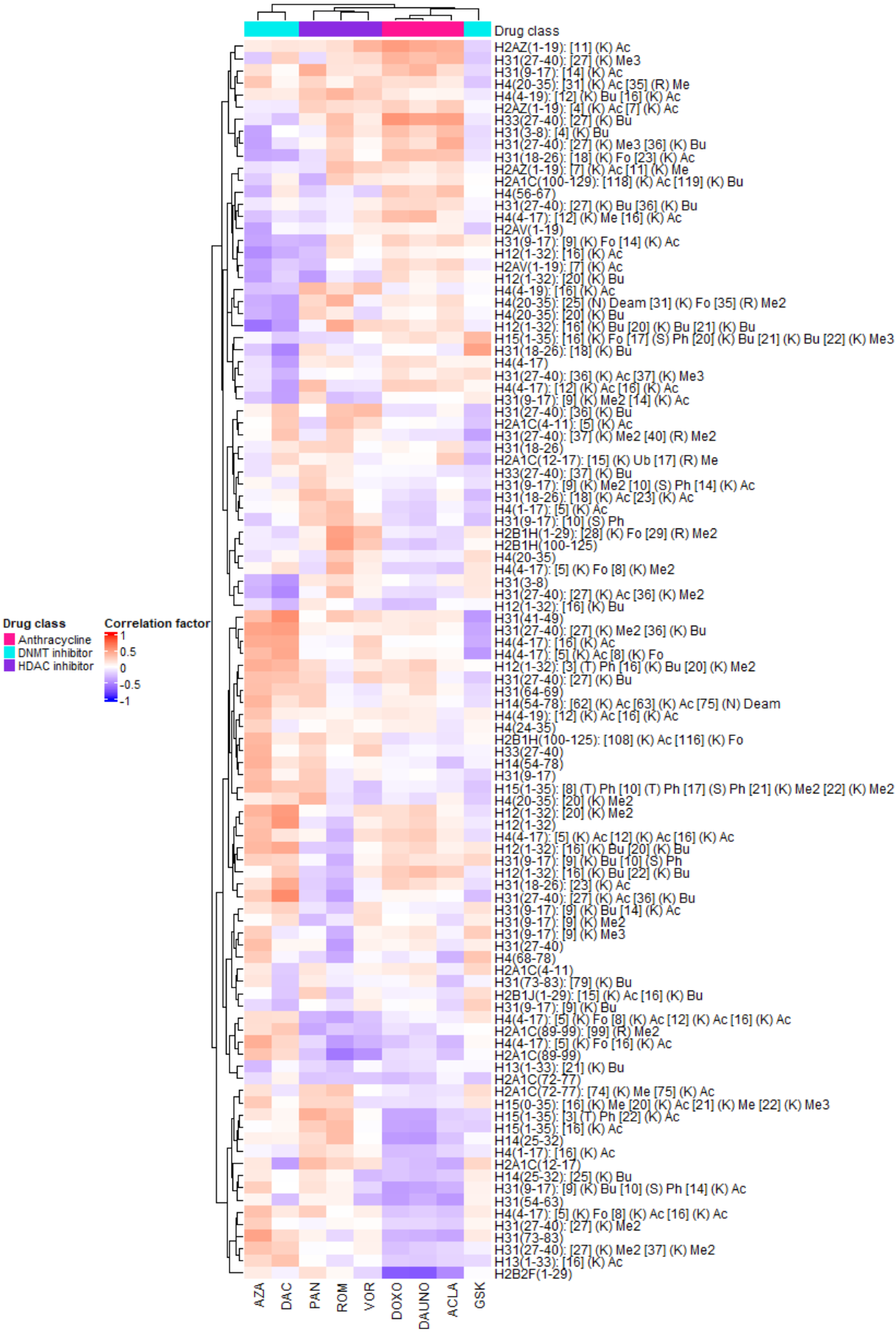


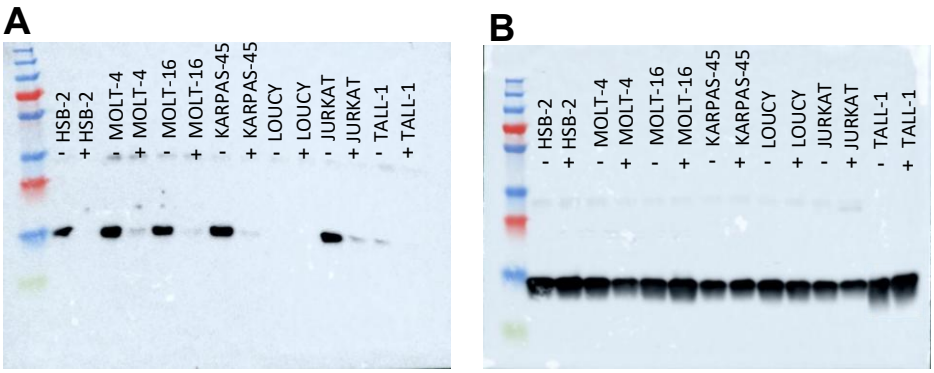
Supplementary Figure 1. Dose-response curves showing the cell viability of 21 T-ALL cell lines (colors) after in vitro treatment with a dilution series of nine epidrugs. Each data point represents the mean of three independent experiments.



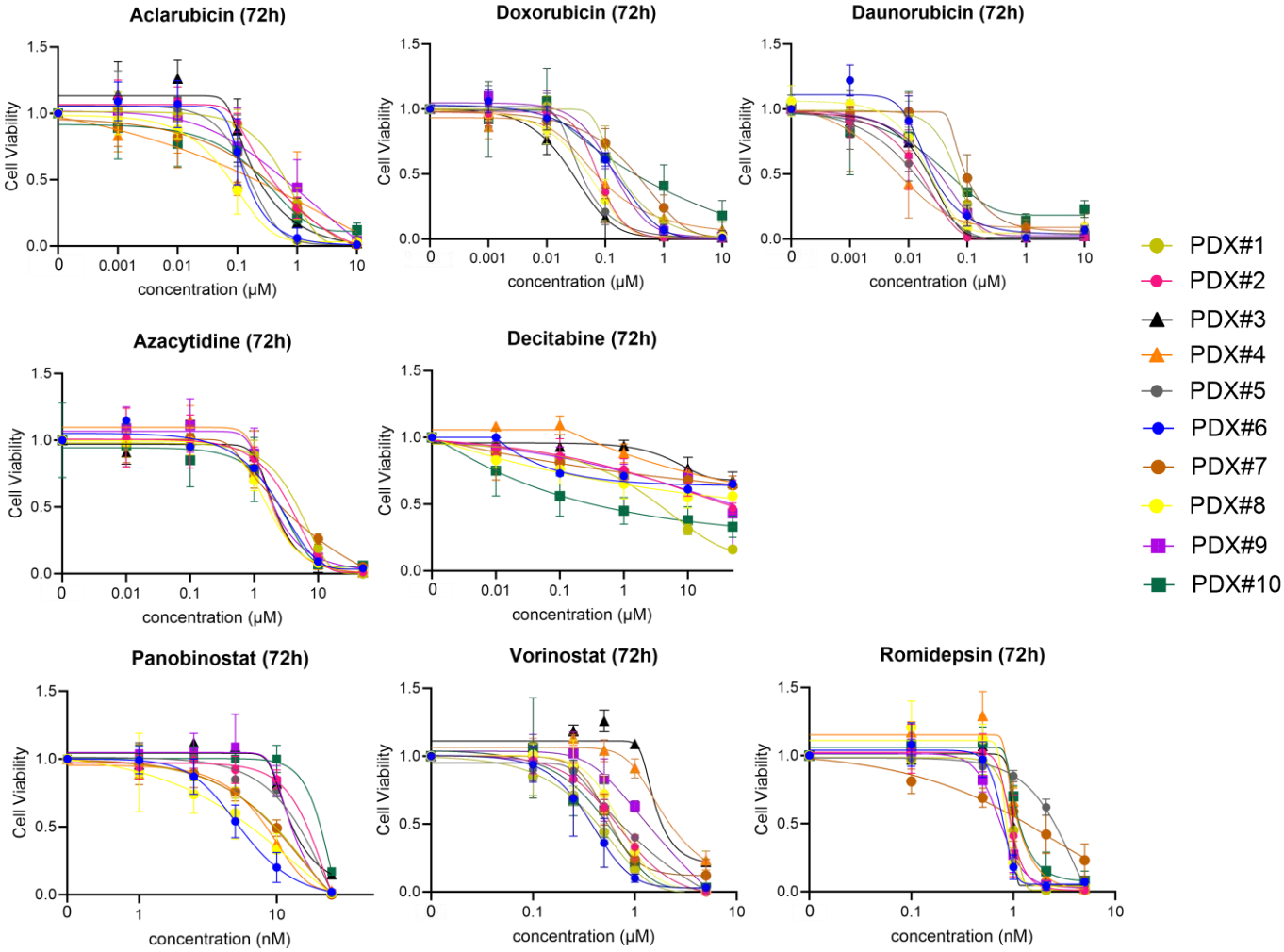
Supplementary Figure 2. Scatter plots showing the Pearson correlation between the IC50s of 21 T-ALL cell lines (colors) within drug classes.



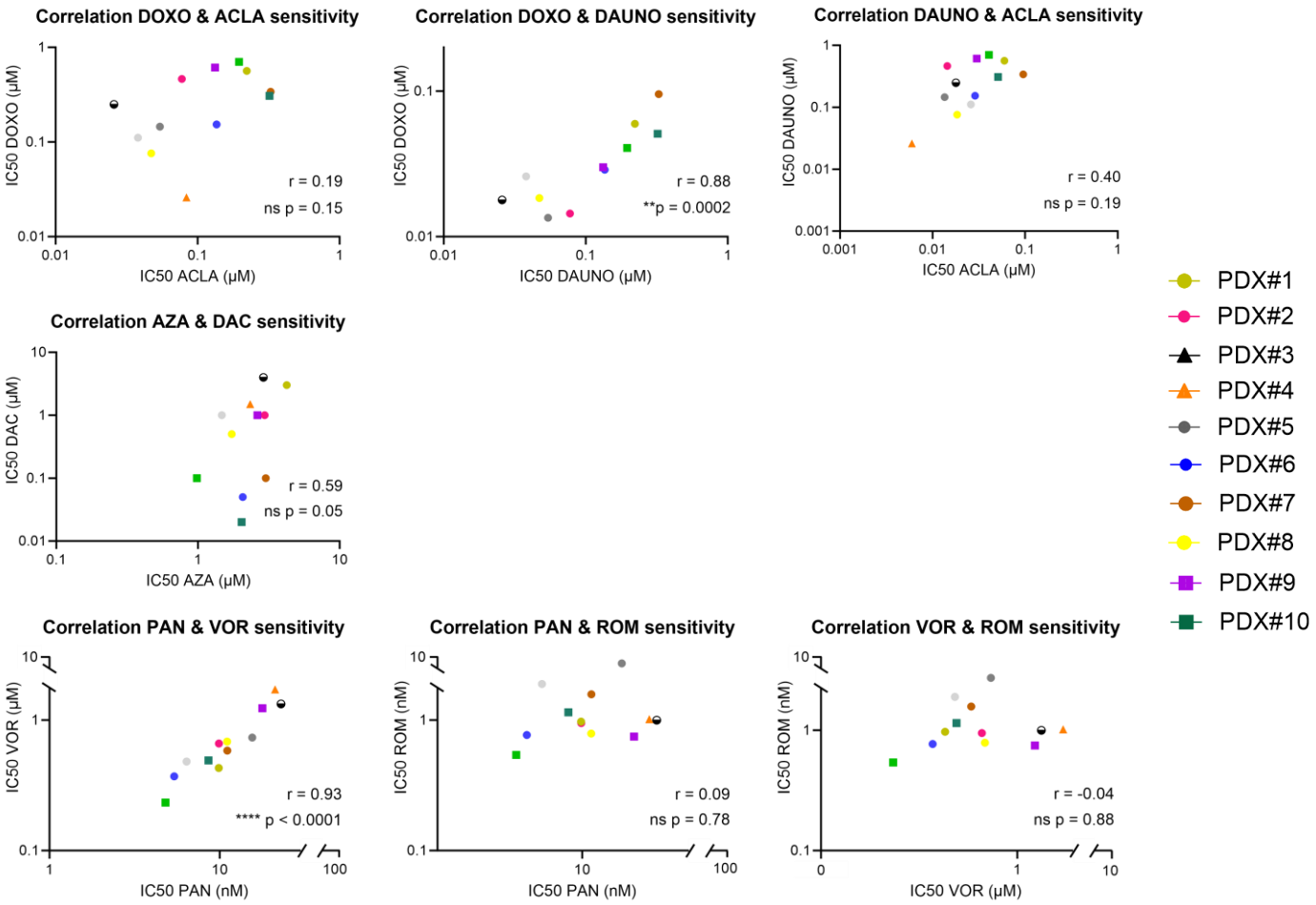
Supplementary Figure 3. Clustered heatmap showing the Spearman correlation factors between histone peptidoforms (rows) and IC50 values (columns) over the 21 cell lines. Positive correlation coefficients (red) indicate that higher hPTM levels are associated with higher IC50 values, suggesting a link to lower sensitivity. Conversely, negative correlation coefficients (blue) imply that high hPTM levels are associated with lower IC50 values, indicating a potential association to higher sensitivity.



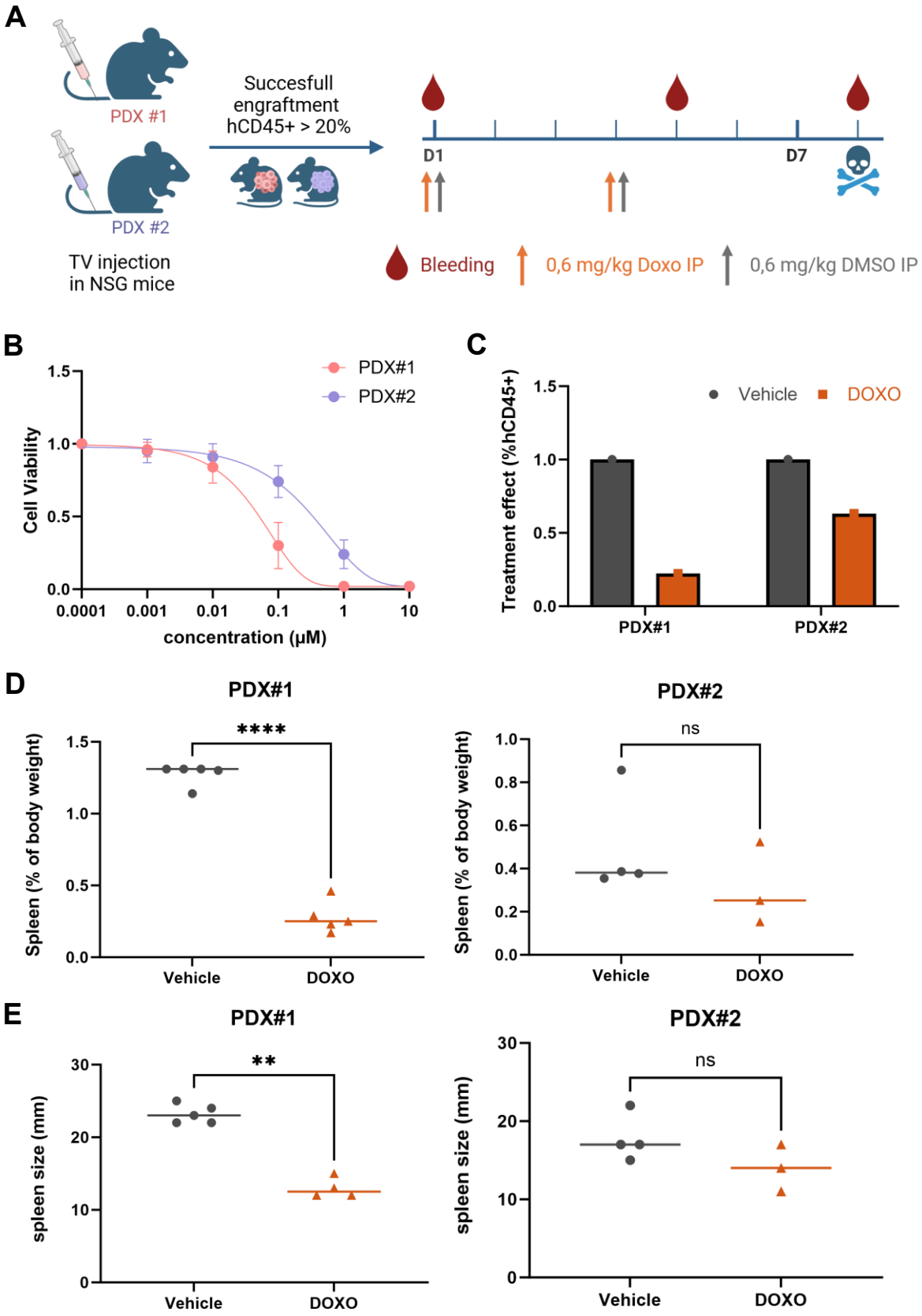
Supplementary Figure 4. Western blot images showing H3K27me3 **(A)** and H3 **(B)** levels after 24-hour aclarubicin treatment in a subset of seven cell lines with or without 72-hour pre-treatment with the EZH2 inhibitor GSK126.



Supplementary Figure 5. Dose-response curves showing the cell viability of 10 T-ALL PDX models (colors) after in vitro treatment with a dilution series of eight epidrugs. Each data point represents the mean of three independent experiments.



Supplementary Figure 6. Scatter plots showing the Pearson correlation between the IC50s of 10 T-ALL PDX models within drug classes.



Supplementary Figure 7. In vivo doxorubicin treatment aligns with ex vivo drug response predictions. (A) NSG mice were engrafted with malignant bone marrow material of T-ALL patients. Once engraftment percentage in the blood was higher than 20%, mice were treated with vehicle (DMSO, grey) or doxorubicin (0.6 mg/kg body weight, orange) for two times with an interval of three days. Blood was collected on day one, day five and day eight to assess %hCD45. Mice were sacrificed on day eight for the collection of leukemic blasts. Figure created with BioRender.com. **(B)** Dose-response curve showing the cell viability of both PDX models after ex vivo treatment with a dilution series of doxorubicin. Each data point represents the mean of three independent experiments. PDX#1 is more susceptible to doxorubicin compared to PDX#2. **(C)** The treatment effect of 1 cycle of doxorubicin on hCD45+ cells in the peripheral blood is shown by normalizing tumor growth (average #hCD45+ cells on day 5/average #hCD45+ cells on day 1) in doxorubicin treated mice to tumor growth in vehicle treated mice. **(D)** Spleen weight as a percentage of body weight and **(E) s**pleen size of the mice treated with a vehicle (grey) or doxorubicine (orange) for both PDX models.

Supplementary Figure 8. Clustered heatmap showing the Spearman correlation factors between histone peptidoforms (rows) and IC50 values (columns) over the 10 PDX models. Positive correlation coefficients (red) indicate that higher hPTM levels are associated with higher IC50 values, suggesting a link to lower sensitivity. Conversely, negative correlation coefficients (blue) imply that high hPTM levels are associated with lower IC50 values, indicating a potential association to higher sensitivity.