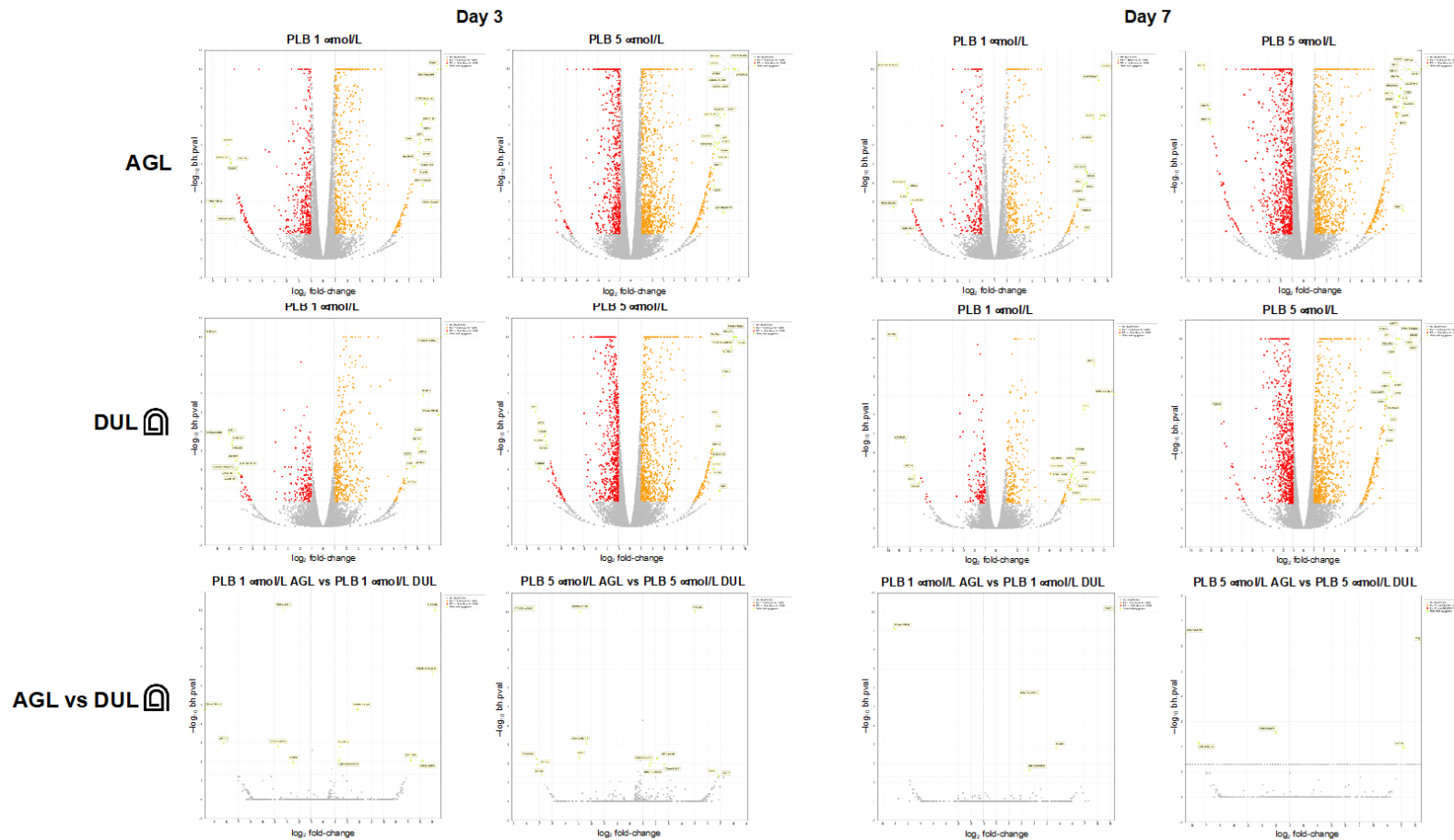


Cellular Senescence in the Absence of Galactic Cosmic-Ray Muons

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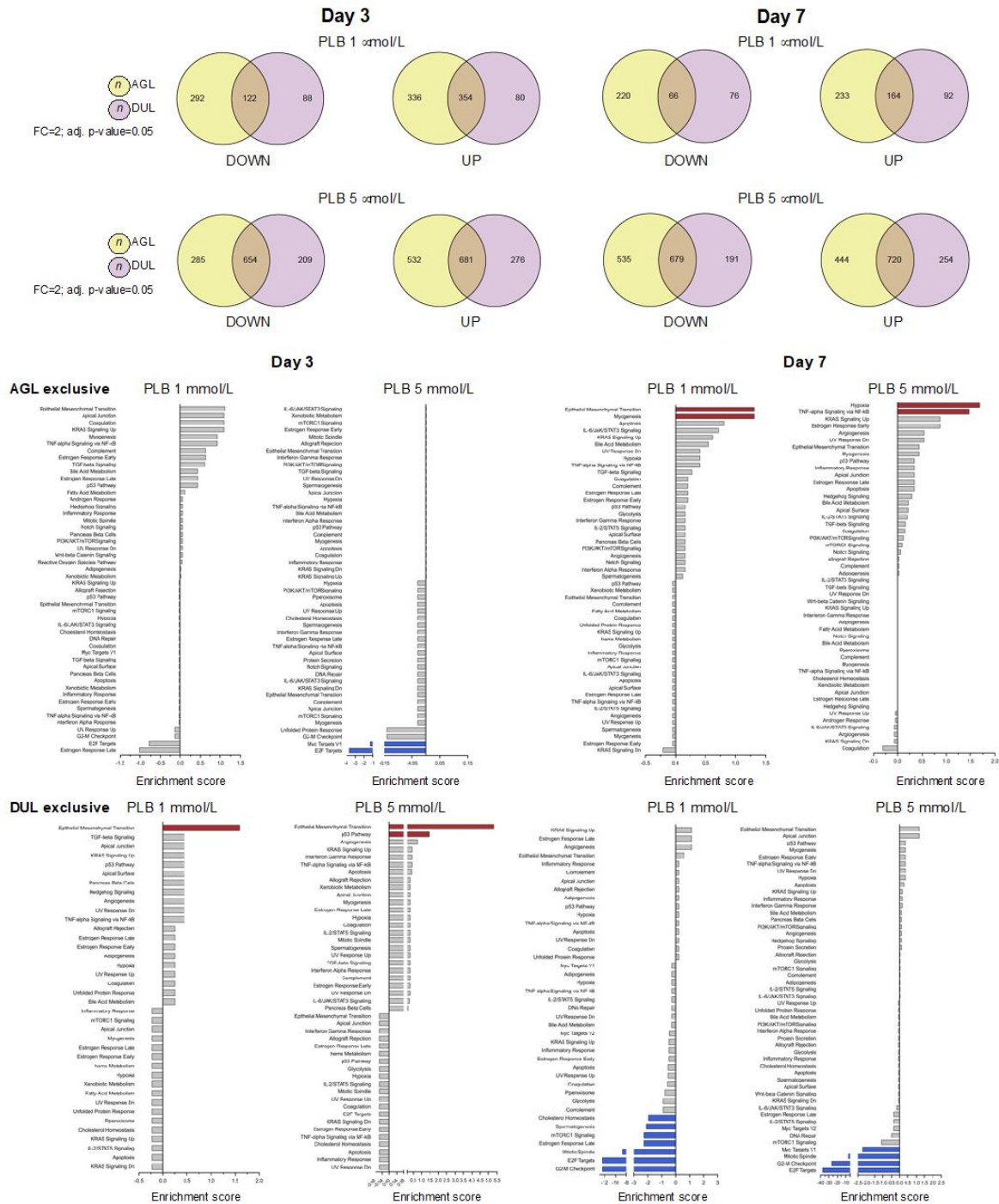
SUPPLEMENTARY DATA



Supplementary Figure 1. Palbociclib elicits dose- and time-dependent transcriptional remodeling that is highly concordant between AGL and DUL environments.

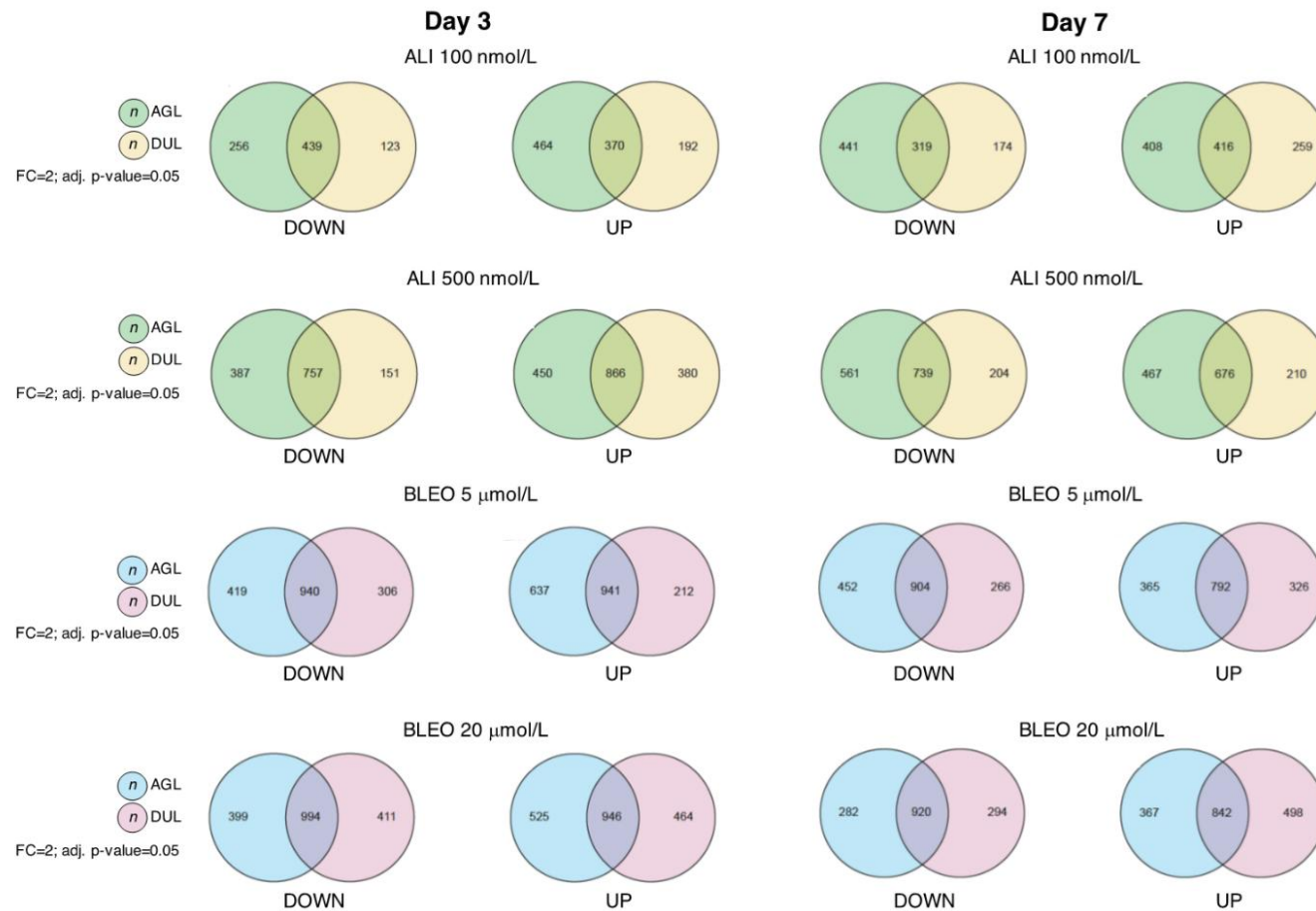
The volcano plots display \log_2 fold-change (x-axis, palbociclib versus vehicle) against $-\log_{10}$ Benjamini-Hochberg-adjusted p value (y-axis) for RNA-seq on days 3 and 7 following treatment with low (1 $\mu\text{mol/L}$) and high (5 $\mu\text{mol/L}$) concentrations of palbociclib (PLB) in the AGL (top panels) and DUL (middle panels) environments. The bottom panels compare AGL vs. DUL at matched doses and times. Despite the clear PLB-induced differential expression within each environment, the AGL and DUL profiles largely overlap under matched conditions. This results in few site-specific DEGs and indicates that the treatment and time variables explain most of the variance. DEGs are highlighted according to the labeled code: Grey points mark genes that were tested but did not meet the criteria for significant differential expression (e.g., BH-adjusted $p \geq 0.05$ and/or $|\log_2\text{FC}|$ below the preset threshold). These genes serve as the background. Red and orange points denote significantly down- and up-regulated DEGs, respectively. Green labels highlight a selected set of top genes (by effect size) to guide interpretation.

SUPPLEMENTARY DATA



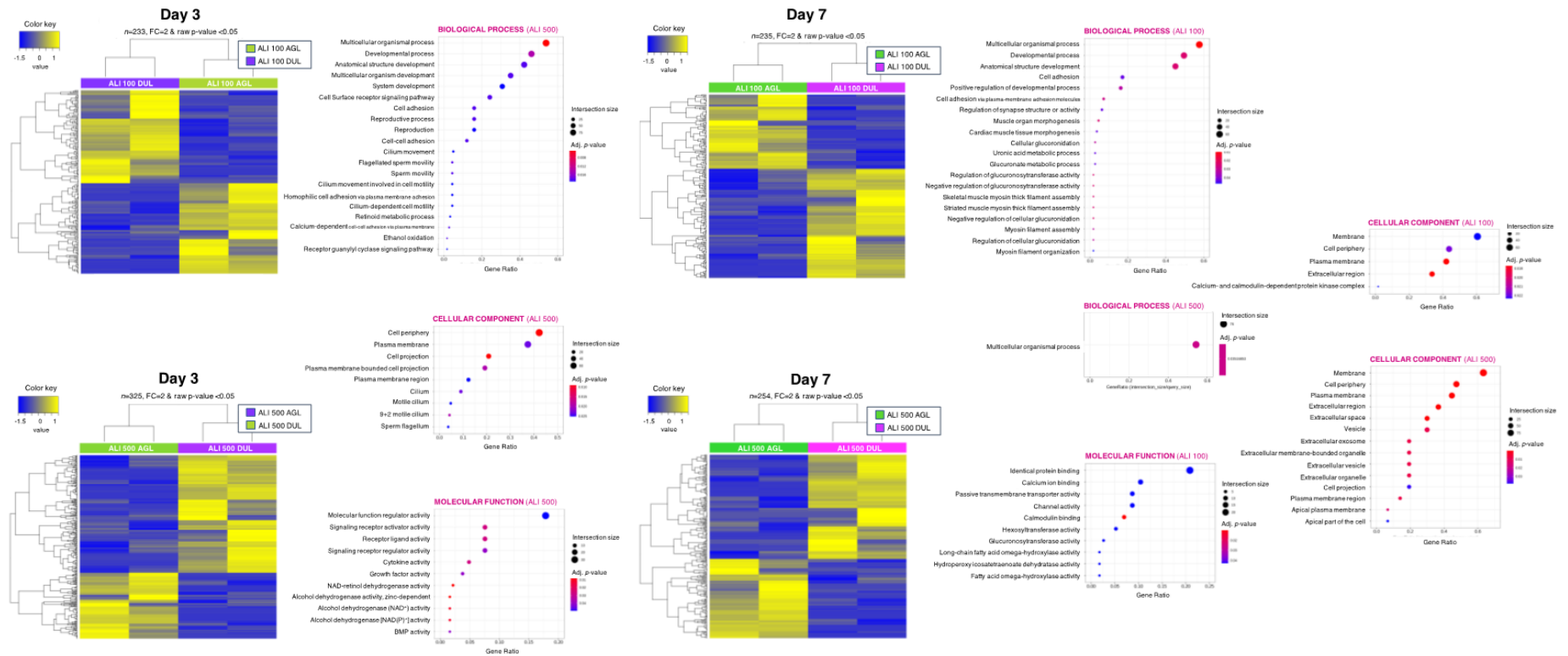
Supplementary Figure 2. Dose-, time-, and muonic environment-dependent transcriptional programs induced by palbociclib. *Top.* Venn diagrams summarizing the overlap between AGL (left circles) and DUL (right circles) differentially expressed genes (DEGs) for each condition. The columns indicate the time points (day 3 and day 7), and the rows indicate the palbociclib (PLB) concentrations (1 and 5 $\mu\text{mol/L}$). Within each condition, DEGs were identified within the environment (palbociclib versus the matched untreated control) and stratified by direction (down or up). Numbers denote the unique gene count in each set or overlap. The inclusion criteria for all DEGs were $|\text{fold-change}| \geq 2$ and Benjamini-Hochberg adjusted $p < 0.05$, using \log_2 -based expression values. Directionality was assigned based on the signed fold-change. The overlaps in the Venn diagrams represent DEGs that are common to both environments (AGL and DUL) at the specified dose and time point, while the non-overlapping segments indicate environment-specific responses. *Bottom.* Pathway enrichment of the exclusive core gene sets –DEGs only in AGL or only in DUL for each matched condition (day 3/day 7 \times PLB 1 $\mu\text{mol/L}/5 \mu\text{mol/L}$). Enrichment was performed with EnrichR v3.2, and the top 25 results are displayed as ranked bar plots according to the EnrichR-reported enrichment score and p -value (the shortest bars represent the lowest significance), and the longest bars represent the highest significance). Only terms that passed EnrichR's default multiple testing procedure (adjusted $p < 0.05$) are highlighted in color.

SUPPLEMENTARY DATA



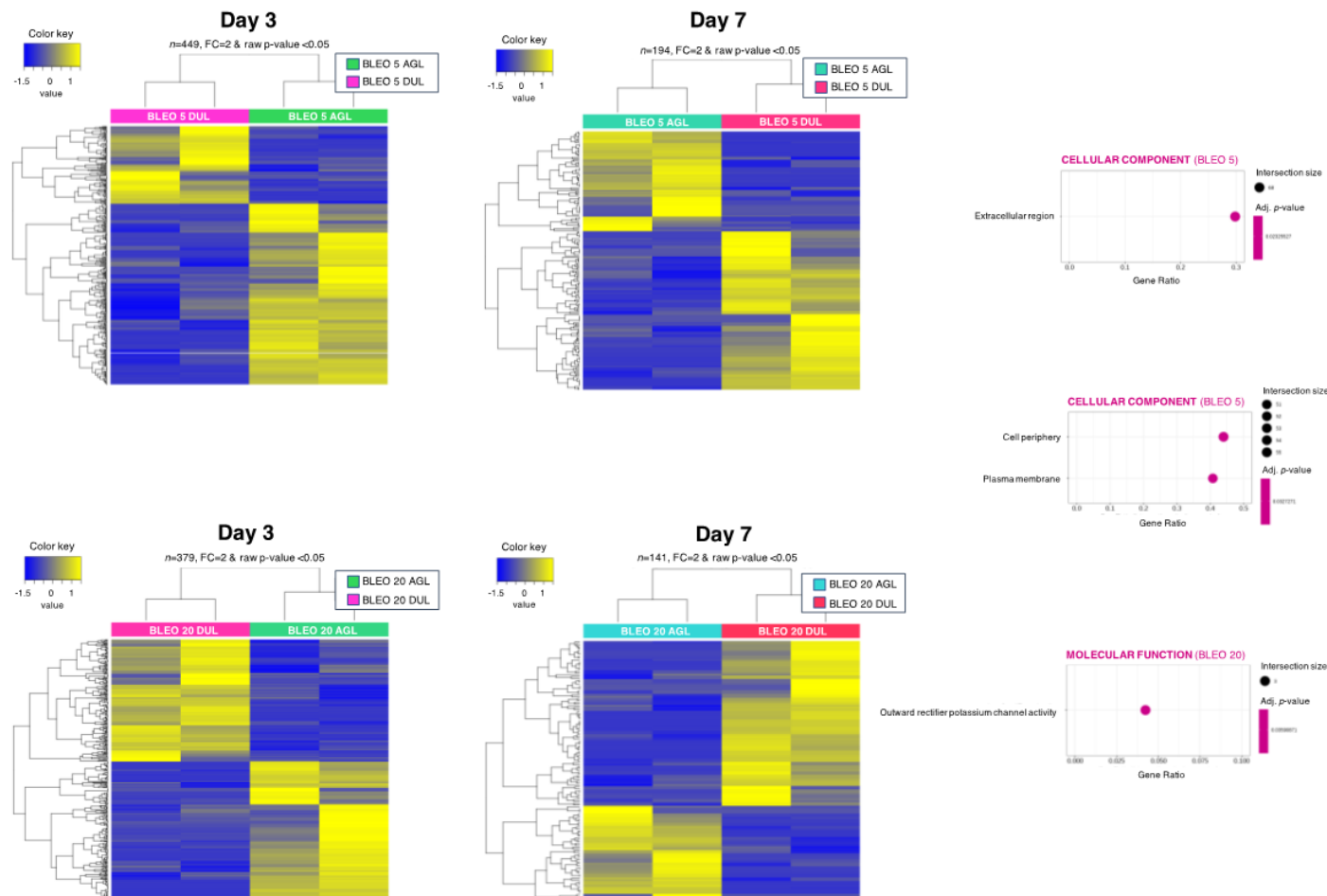
Supplementary Figure 3. Dose-, time-, and muonic environment-dependent transcriptional programs induced by alisertib and bleomycin. Venn diagrams summarizing the overlap between AGL (left circles) and DUL (right circles) differentially expressed genes (DEGs) for each condition. The columns indicate the time points (day 3 and day 7), and the rows indicate the alisertib (ALI) and bleomycin (BLEO) concentrations (100 and 500 nmol/L, 5 and 20 mmol/L, respectively). Within each condition, DEGs were identified within the environment (alisertib/bleomycin versus the matched untreated control) and stratified by direction (down or up). Numbers denote the unique gene count in each set or overlap. The inclusion criteria for all DEGs were $|\text{fold-change}| \geq 2$ and Benjamini-Hochberg adjusted $p < 0.05$, using \log_2 -based expression values. Directionality was assigned based on the signed fold-change. The overlaps in the Venn diagrams represent DEGs that are common to both environments (AGL and DUL) at the specified dose and time point, while the non-overlapping segments indicate environment-specific responses.

SUPPLEMENTARY DATA



Supplementary Figure 4. Differential transcriptomic responses to alisertib in AGL and DUL environments. Figure shows two-way, unsupervised, hierarchical heatmaps of DEGs identified in each contrast (rows, genes; columns, samples). The values are z-scores per gene computed from log₂-based expression values. Only genes with a |fold-change| ≥ 2 and a raw $p < 0.05$ were included ($n = 2$ independent biological replicates). The four gene sets comprise ALI 100 nmol/L day 3 ($n = 233$), ALI 500 nmol/L day 3 ($n = 325$), ALI 100 nmol/L day 7 ($n = 235$), and ALI 500 nmol/L day 7 ($n = 254$), comparing AGL vs. DUL conditions. The sample labels above each heatmap indicate the treatment (PLB 1 or 5 $\mu\text{mol/L}$), the time point (day 3 or 7), and the environment (AGL or DUL). Color keys denote relative expression (low to high) after z-score normalization. Gene Ontology (GO) enrichment analyses were performed on the DEG sets and are summarized by the three GO domains: Biological Process, Cellular Component, and Molecular Function. For each contrast, the most significantly enriched terms within each domain are displayed and ranked by significance within the category.

SUPPLEMENTARY DATA



Supplementary Figure 5. Differential transcriptomic responses to bleomycin in AGL and DUL environments. Figure shows two-way, unsupervised, hierarchical heatmaps of DEGs identified in each contrast (rows, genes; columns, samples). The values are z-scores per gene computed from log₂-based expression values. Only genes with a |fold-change| ≥ 2 and a raw p < 0.05 were included (n = 2 independent biological replicates). The four gene sets comprise BLEO 5 mmol/L day 3 (n = 449), BLEO 20 mmol/L day 3 (n = 379), BLEO 5 mmol/L day 7 (n = 194), and BLEO 20 mmol/L day 7 (n = 141), comparing AGL vs. DUL conditions. The sample labels above each heatmap indicate the treatment (PLB 1 or 5 μmol/L), the time point (day 3 or 7), and the environment (AGL or DUL). Color keys denote relative expression (low to high) after z-score normalization. Gene Ontology (GO) enrichment analyses were performed on the DEG sets and are summarized by the three GO domains: Biological Process, Cellular Component, and Molecular Function. For each contrast, the most significantly enriched terms within each domain are displayed and ranked by significance within the category.