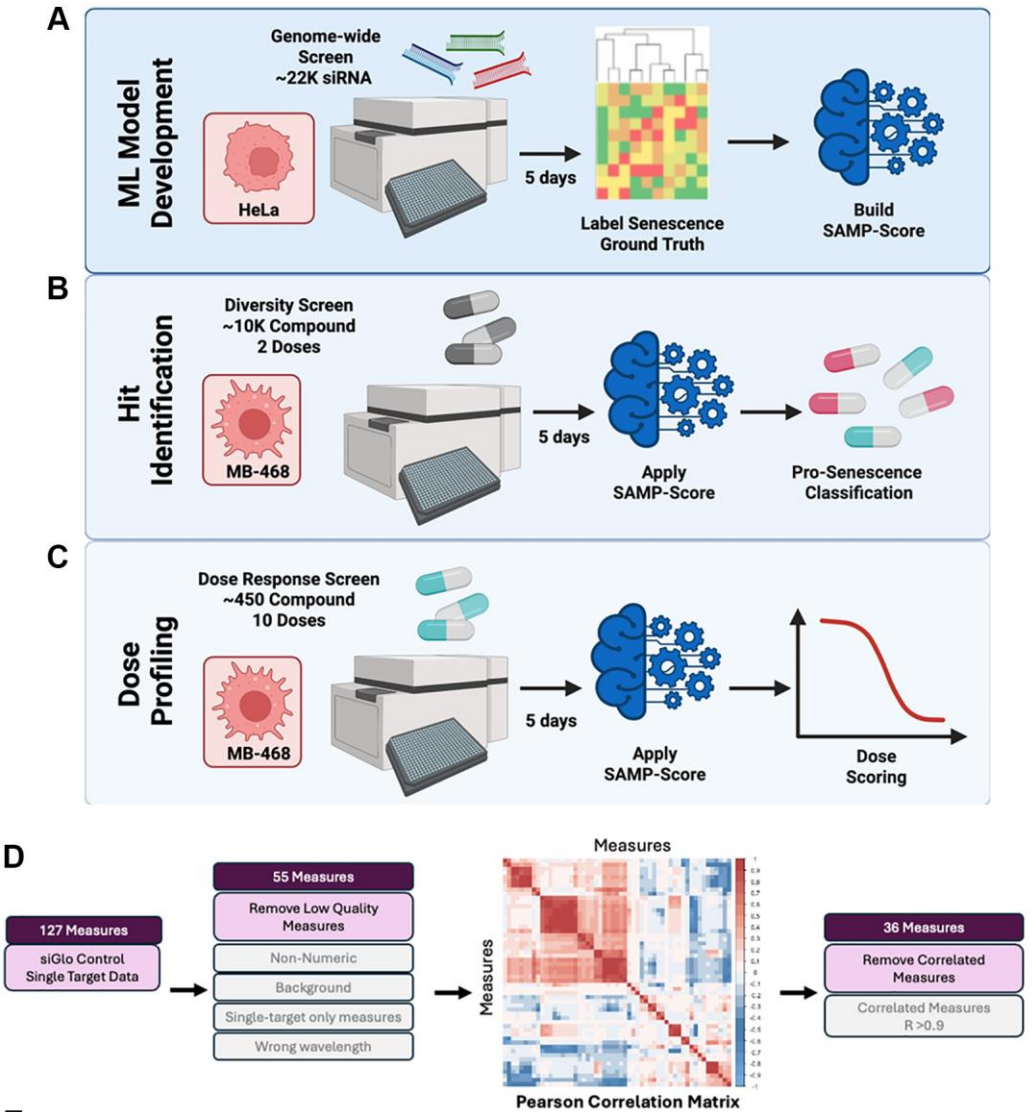
## SUPPLEMENTARY FIGURES

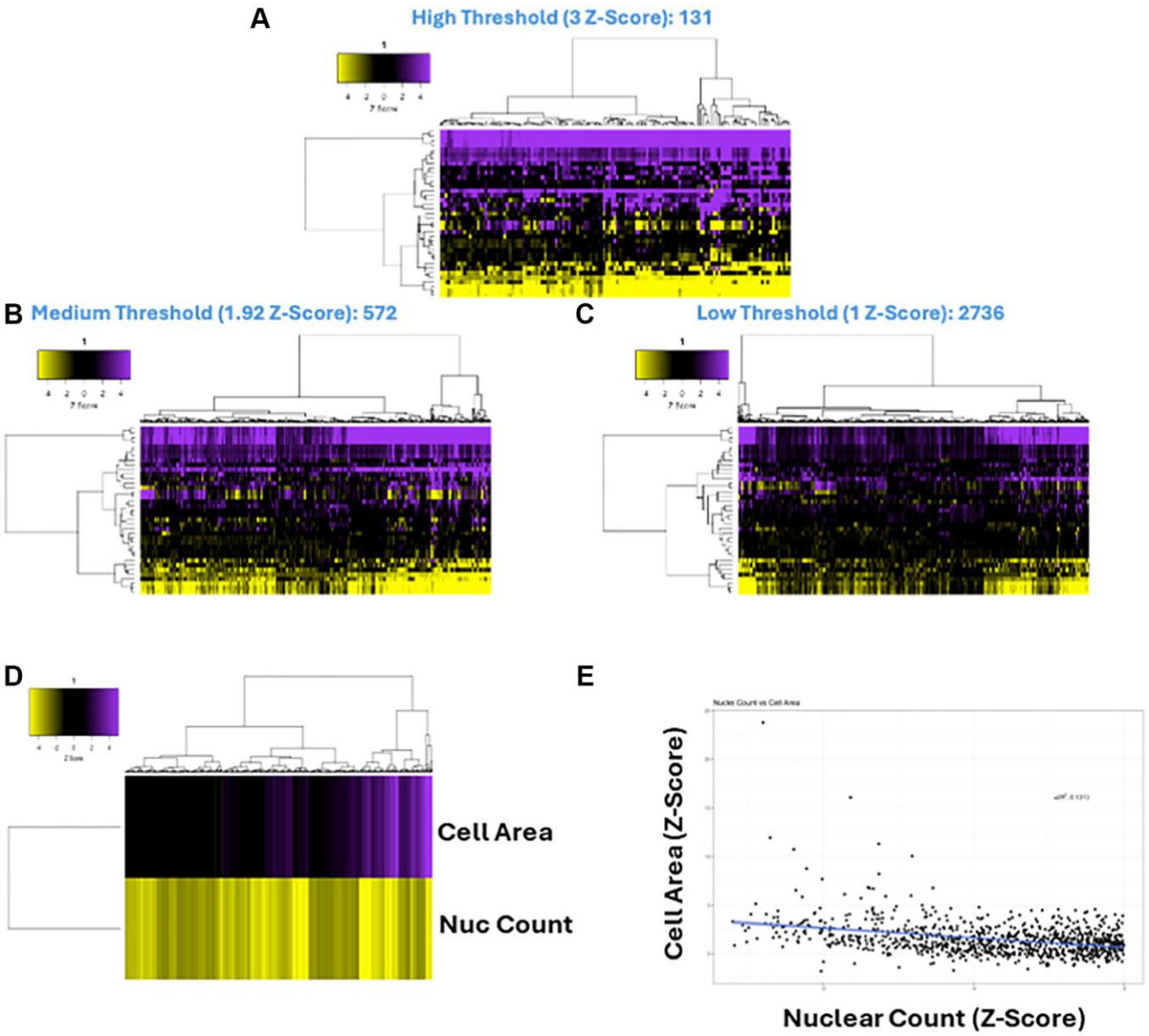



**E**

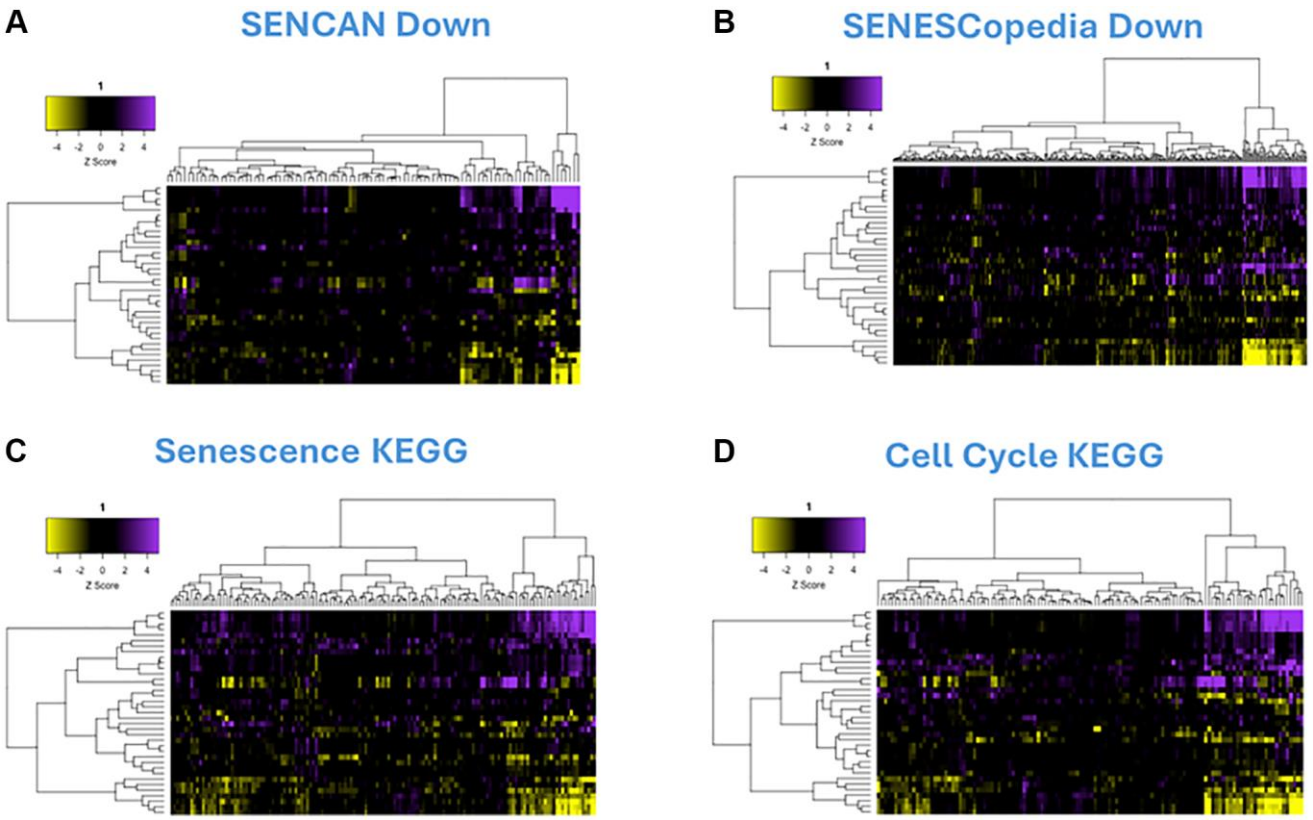
| Measures Retained | | | | | | | |
|---|---|---|---|---|---|---|---|
| 1 | Nuclei.Form.Factor | 11 | Nuclei.Neighbor.Count..SOI.. | 21 | Cells.Area | 31 | Cells.Max.Intensity |
| 2 | Nuclei.Elongation | 12 | Nuclei.Spacing..MIN.. | 22 | Cells.Form.Factor. | 32 | Cells.Major.Axis |
| 3 | Nuclei.Compactness | 13 | Nuclei.Neighbor.Count..MIN. | 23 | Cells.Elongation | 33 | Cells.Minor.Axis |
| 4 | Nuclei.Chord.Ratio | 14 | Nuclei.Spacing..Gabriel.. | 24 | Cells.Compactness | 34 | Cells.Skewness |
| 5 | Nuclei.Displacement | 15 | Nuclei.Neighbor.Count..Gabriel.. | 25 | Cells.Chord.Ratio. | 35 | Cells.Kurtosis |
| 6 | Nuclei.Intensity | 16 | Nuclei.Spacing..Lune.. | 26 | Cells.Nuc.Cell.Area | 36 | Cells.Energy |
| 7 | Nuclei.Total.Intensity | 17 | Nuclei.Neighbor.Count..Lune.. | 27 | Cells.Total.Intensity..Cyto.. | | |
| 8 | Nuclei.Intensity.CV | 18 | Nuclei.Skewness | 28 | Cells.Intensity.CV..Cyto.. | | |
| 9 | Nuclei.Major.Axis.Angle | 19 | Nuclei.Kurtosis | 29 | Cells.Intensity.Spreading. | | |
| 10 | Nuclei.Spacing..SOI.. | 20 | Nuclei.Energy | 30 | Cells.Intensity.SD..Cyto. | | |

| Measures Removed | | | |
|---|---|---|---|
| 1 | Cells.Gyration.Radius | 11 | Nuclei.Entropy |
| 2 | Cells.Diameter | 12 | Cells.Entropy |
| 3 | Cells.Perimeter | 13 | Cells.Intensity.CV..Cell.. |
| 4 | Cells.Light.Flux. | 14 | Cells.Nuc.Cyto.Intensity. |
| 5 | Nuclei.Light.Flux. | 15 | Cells.Total.Intensity..Cell.. |
| 6 | Nuclei.Diameter | 16 | Cells.Intensity.SD..Cell. |
| 7 | Nuclei.Major.Axis | 17 | Cells.Intensity..Cyto. |
| 8 | Nuclei.Gyration.Radius | 18 | Cells.Intensity..Cell. |
| 9 | Nuclei.Perimeter | 19 | Nuclei.Intensity.SD |
| 10 | Nuclei.Area | | |

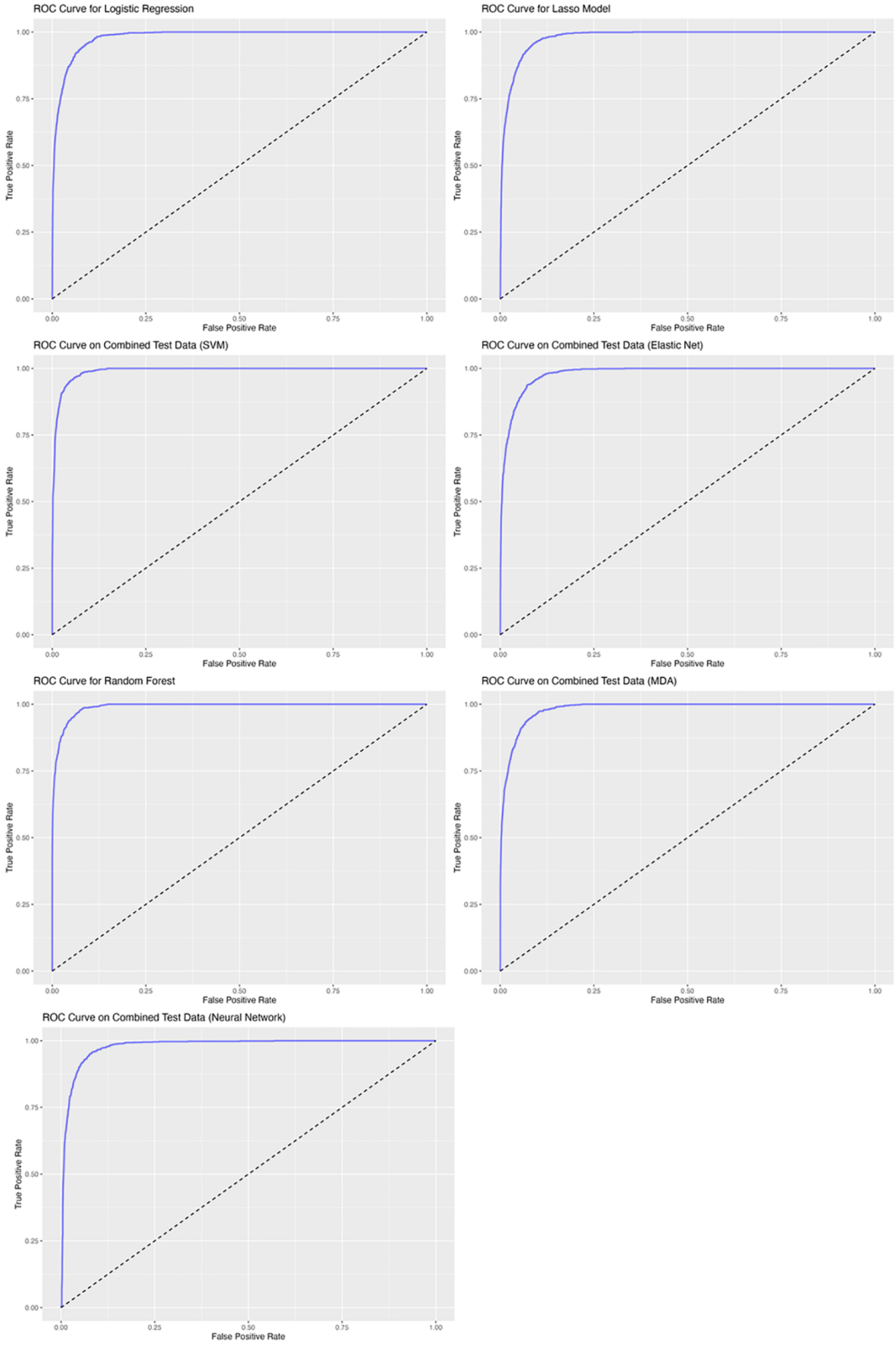
**Supplementary Figure 1. High content screening overview and feature selection.** (**A**–**C**) Overview of high three high content screens ((**A**) genome-wide siRNA screen in HeLa cells to establish ground truth for model development; (**B**) compound diversity screen for senescent hit identification; (**C**) dose profiling of senescent hits). (**D**) Feature dimensionality reduction strategy via Pearson correlation assessment. (**E**) List of final features which comprise SAMP profiles.



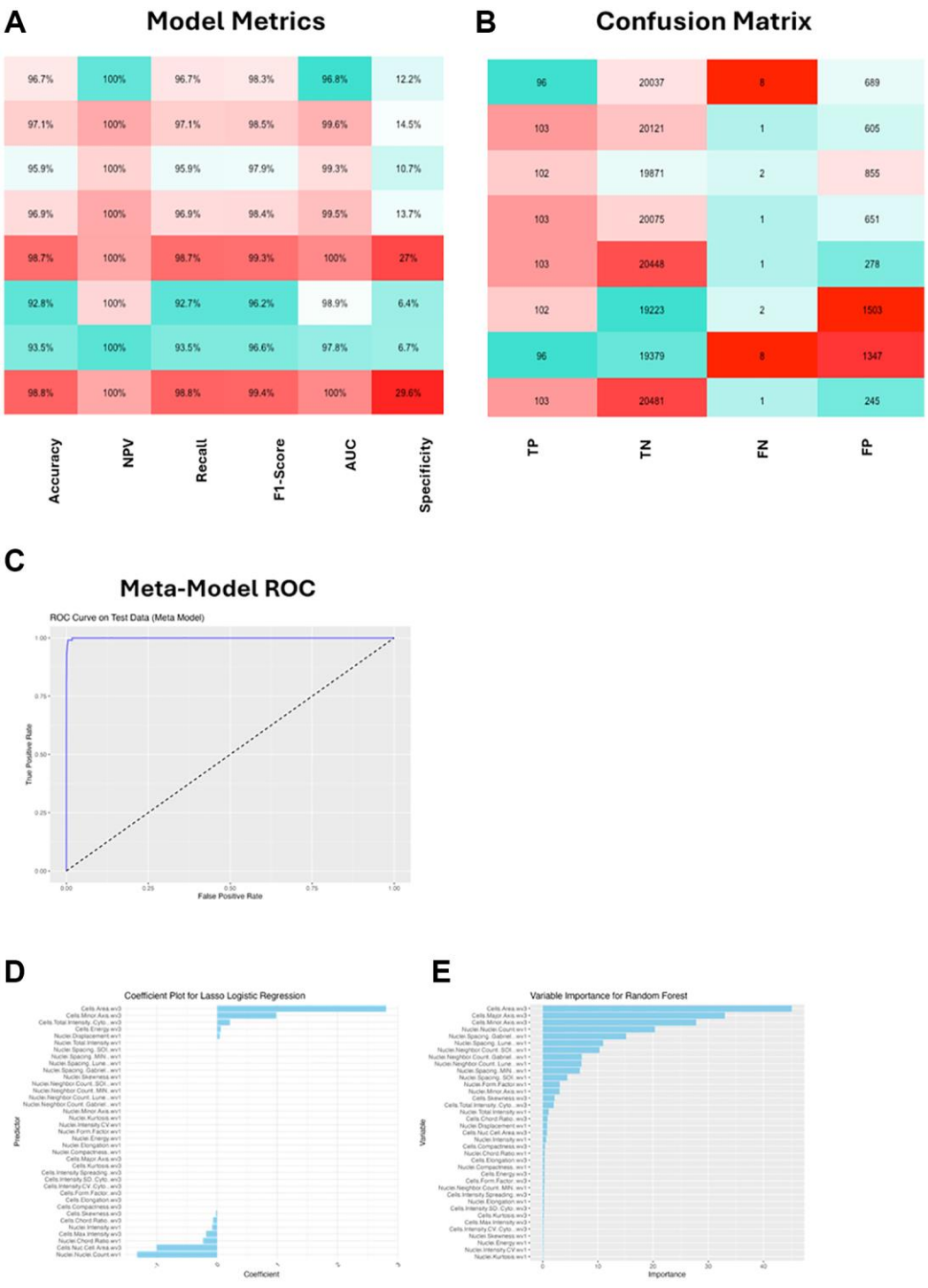

**Supplementary Figure 2. Genome-wide siRNA HeLa screen – traditional screening readouts.** (**A**–**C**) Heatmaps representing high content analysis feature (HCA; y-axis) profiles of a genome-wide siRNA screen treatments (siRNAs; x-axis) that reduce nuclear count and increase nuclear area by high, medium and low stringency thresholds. (**D**) Heatmap profile showing cell area and nuclear count Z-scores for all treatments. (**E**) Scatter plot showing nuclear count vs cell area Z-scores. In all heatmaps, purple indicates positive modulation and yellow negative modulation of greater than 1.96 Z-scores from siGLO control. Black indicates no change.




**Supplementary Figure 3. Genome-wide siRNA HeLa screen – biased pathway labelling.** (**A**–**D**) Heatmaps representing high content analysis feature (HCA; y-axis) profiles of a genome-wide siRNA screen treatments (siRNAs; x-axis) selected through identification as downregulated in SENCAN and SENESCopedia database or Senescence/Cell Cycle KEGG pathway analysis terms. In all heatmaps, purple indicates positive modulation and yellow negative modulation of greater than 1.96 Z-scores from DMSO vehicle control. Black indicates no change.

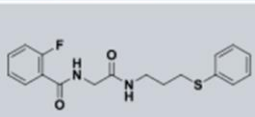


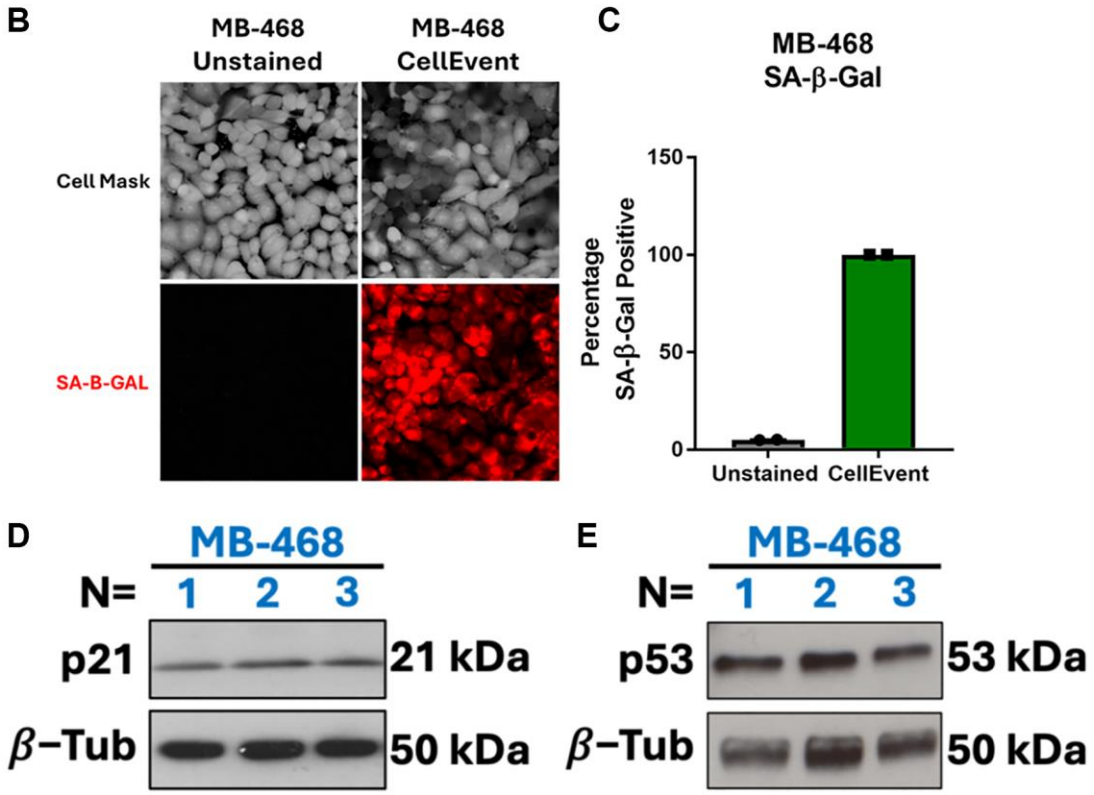

**Supplementary Figure 4. Receiver operating characteristic (ROC) curves for all composite models of SAMP-Score.**



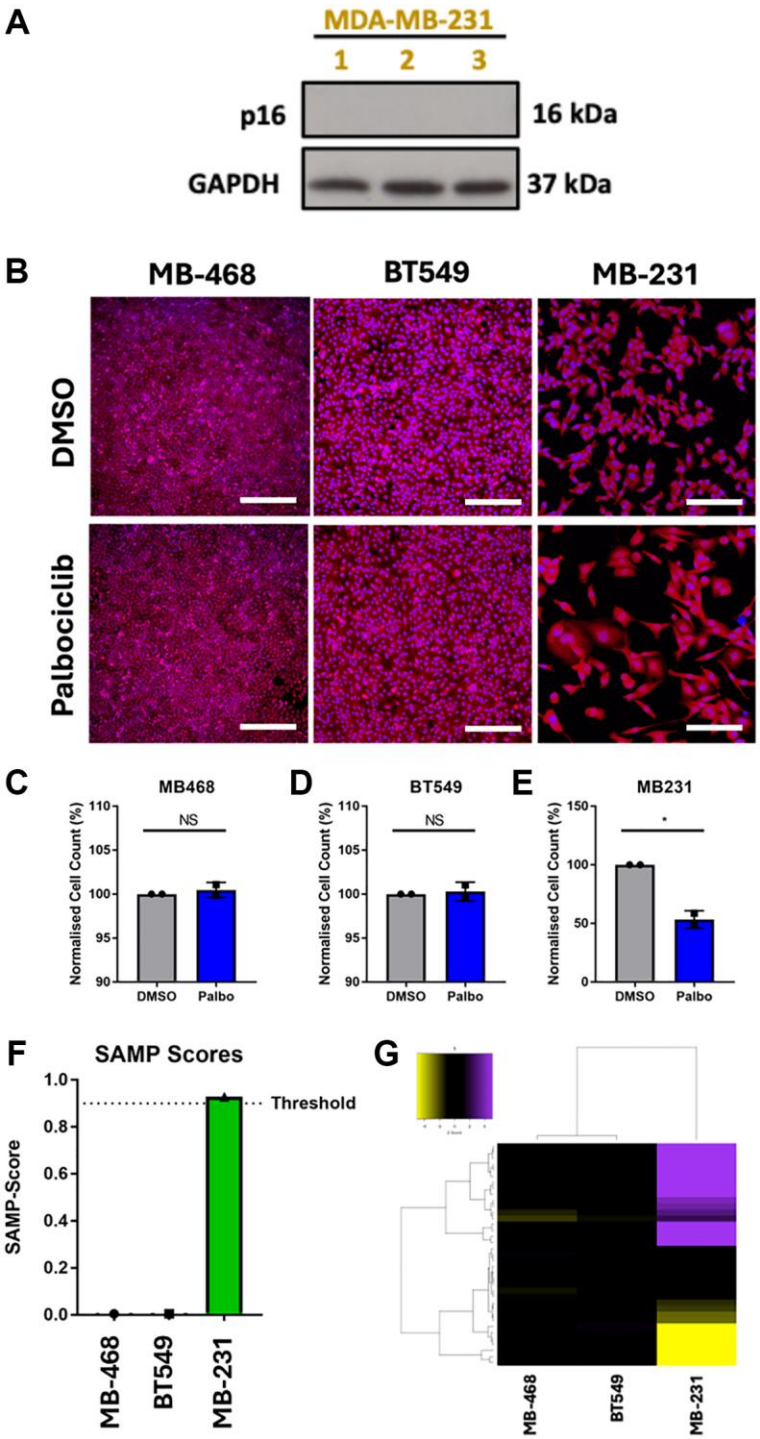

**Supplementary Figure 5. Model Development and Metric Assessment using traditional threshold-based senescence labelling of training data.** (**A**, **B**) Machine learning (ML) model assessment metrics and confusion matrix for all individual ML models and stacked meta-model (SAMP-Score). Abbreviations: NPV: Negative Prediction Value; AUC: Area under curve; PPV: Positive Prediction Value; TP: True Positive; TN: True Negative; FN: False Negative; FP: False Positive. (**C**) Receiver operating characteristic (ROC) curve for stacked meta model. (**D**, **E**) Model feature contributions to Lasso and Random Forest models.

A

| | | QM0005928 |
|---|---|---|
| | |  |
| Toxicity | HepG2 pIC50 | 4.4 |
| Solubility | ReaSol (uM) | 180 |
| DMPK | Clearance (ml/min/g) | 8.3 |
| | MDCK (Papp, nm/s) | 235 |
| Physiochemical Properties | MWt | 346.42 |
| | logP/CHI-logD | 2.6/2.6 |
| | tPSA | 58 |
| Metrics | LE/LLE | 0.30/ 2.6 |
| | IFI | 0.1 |




**Supplementary Figure 6. QM0005928 physicochemical properties and SenMark+ cancer cell senescence markers.** (**A**) Standard chemical assessment panel for QM5928. (**B**, **C**) Senescence-associated beta galactosidase staining of MB-468 cells. *N* = 1 with 2 technical replicates. (**D**, **E**) Immunoblotting of MB-468 cells for p21 and p53. *N* = 3.




**Supplementary Figure 7. SAMP-Score assessment of BLBC response to CDK Inhibition.** (**A**) Immunoblotting of MB-231 cells for p16. N-3. (**B–E**) Response to 1 uM palbociclib treatment or vehicle control (DMSO) in MB-468, BT549 and MB-231 BLBC lines. (**F**) SAMP-Score classification coefficient for MB-468, BT549 and MB-231 BLBC lines treated with palbociclib. (**G**) Heatmap representing high content analysis feature (HCA; y-axis) profiles of MB-468, BT549 and MB-231 BLBC lines treated with palbociclib (x-axis). In all heatmaps, purple indicates positive modulation and yellow negative modulation of greater than 1.96 Z-scores from DMSO vehicle control. Black indicates no change.