Description of Additional Supplementary files

Supplementary Data 1: Summary of the isogenic aneuploid RPE1-hTERT cell line library
Low-pass whole-genome sequencing (lp-WGS) based karyotyping of the 199 single-cell derived clones that were propagated successfully to give rise to RPE1 clones. Trisomies are denoted with the value '1', monosomies are denoted with the value '-1'. The clones that were selected for omics profiling, perturbation screens and mechanistic studies are highlighted in yellow.

Supplementary Data 2: Mutation profiling of RPE1-hTERT clones

Supplementary Data 3: Gene copy number alteration profiling of RPE1-hTERT clones
Log2CN values are provided for each clone.

Supplementary Data 4: Differential gene expression analysis of highly-aneuploid vs. pseudo-diploid RPE1-hTERT clones
DESeq2 differential gene expression analysis of highly-aneuploid (SS51/SS111) versus pseudo-diploid clone SS48. p-values were obtained from a Wald test, and q-values were generated by FDR multiple test correction.

Supplementary Data 5: Differential gene expression analysis of aneuploid vs. pseudo-diploid RPE1-hTERT clones
DESeq2 differential gene expression analysis of all aneuploid clones (SS6/SS119/SS51/SS111) versus pseudo-diploid clone SS48. p-values were obtained from a Wald test, and q-values were generated by FDR multiple test correction.

Supplementary Data 6: miRNA profiling results of RPE1-hTERT clones
miRNA RPM expression values of RPE1-SS48 and SS31 (WT), RPE1-SS77 (p53-mutated clone), RPE1-SS6 and SS119 (single-trisomy clones), and RPE1-SS51 and SS111 (multiple-trisomy clones). p53-targeting miRNAs are indicated in the last column.

Supplementary Data 7: Proteomics of RPE1-hTERT clones
Mass-spectrometry expression values of RPE1-SS48 and SS31 (WT), RPE1-SS77 (p53-mutated clone), RPE1-SS6 and SS119 (single-trisomy clones), and RPE1-SS51 and SS111 (highly-aneuploid clones).

Supplementary Data 8: CRISPR/Cas9 screen results of RPE1-hTERT clones
CERES essentiality scores for each gene in each RPE1 clones. Values<-1 represent gene essentiality.

Supplementary Data 9: Pharmacological screen results of RPE1-hTERT clones
Relative viability (%), determined by normalizing signal to the signal window of (DMSO control - inhibitor control), of each RPE1 clone upon exposure to 5,336 compounds. Shown are the average values of two technical duplicates. Compounds activity was defined by comparing the signal to 3SD of DMSO control. Compounds were defined as "active" if the mean of both replicates was equal or less than the activity threshold, as "inactive" if neither of the replicates was equal or less than the activity threshold, or "inconclusive" if one of the two replicates was equal or less than the activity threshold but the mean of both replicates was above the activity threshold. See **Methods** for more details.

Supplementary Data 10: Extended table of aneuploidy scores for human cancer cell lines
Aneuploidy scores (AS) for 1742 human cancer cell lines. AS were determined as the number of chromosome arms that were gained or lost in each cell lines.

Supplementary Data 11: Genes associated with high proliferation in highly-aneuploid, but not near-euploid, human cancer cell lines
List of genes whose overexpression is significantly associated with high proliferation (i.e., low doubling time) in highly-aneuploid (AS≥21) cancer cell lines, but not in near-euploid (AS≤8) cancer cell lines. p-values were obtained from a Wald test using DESeq2.

Supplementary Data 12: PRISM screen results of human cancer cell lines treated with selumetinib, in the absence or presence of reversine
Comparison of the EC50 values of selumetinib in human cancer cell lines in the absence or presence of a sub-lethal dose (250nM) of reversine (or vehicle control) for 5 days.