



Fig. S1 A core DNA repair genetic network and ERCC6L2 deficient cell lines.

a Clustering tree of 414 DNA repair gene knockouts and 36 DNA damage chemicals. Red rectangles label the NHEJ clusters. Heat map of Z-scores is plotted with a legend at top-left. **b** ERCC6L2 knockout strategies in CH12F3 cells. The resulting clones were genotyped by PCR on genomic DNA. RNA-Seq data of *Ercc6l2* gene are showed with zoom-in views of the knockout-regions at bottom. For each panel: genome annotation is showed on top tract, sgRNA targeting sites are illustrated as arrows with a pair of sgRNAs labeled with same color, genome coordinates (mm10) are labeled at the bottom. **c** Cell viability curves of ERCC6L2-deficient or LIG4-deficient CH12F3 B cells upon different treatments. **d** Cell viability curves of ERCC6L2-deficient and isogenic *v-Abl* pro-B cells to Zeocin treatment are showed. **e** *ERCC6L2* knockout strategy in U2OS cells with a pair of sgRNAs is illustrated on top. The resulting clones were genotyped by PCR from genomic DNA. RNA-Seq data of *ERCC6L2* gene are showed with zoom-in views of the knockout-regions at bottom left. Cell viability curves of ERCC6L2-deficient and isogenic U2OS cells to Zeocin treatment are showed (bottom right). Data are represented as mean \pm SD in Panels (c), (d) and (e). A *t*-test was applied as described in the method for Panels (d) and (e).
***: $p < 0.001$.