Supplementary Fig 1: CRISPR screen cells survival, sgRNA reads and gene ontology of enriched themes (Related to Fig 1). (A) The chart shows cell counts while undergoing treatment with etoposide or DMSO for 14 days from the CRISPR KO screen experiment. **(B)** Comparison of cumulative frequency of sgRNA for the Brunello library plasmid used for generating the lentiviral particles (sgRNA library red), puromycin selection (Day 0 blue), and etoposide treated cells replicates 1 (Day 14 Etoposide # Rep 1). **(C)** Pie chart shows that within the gene ontology themes related to the translation machinery, the most genes were related to ribosomal subunit proteins (n=70), followed by mitochondrial ribosomal proteins (n=30) and tRNA synthetase (n=25). **(D)** Violin plot shows genes (KEAP1 p=0.013, TOP2A p=0.00039, PRMT7 p=0.00093, UVRAG p=0.002971, ARID1A p=0.05, PHB p=9.84E-05, MNAT1 p=0.02, ERCC2 p=0.000683, SMARCB1 p=0.0226, ELF4A1 p=0.02, SLC2A1 p<0.005, SMURF1 p=0.01) known to contribute to etoposide susceptibility were enriched in etoposide (day 14) compared to DMSO (day 14). However, TP53, CHEK2, SLC7A6, THAP7 and SMARCE1 were not enriched.

Supplementary Fig 2: Loss of FANCB confers resistance to etoposide, doxorubicin and DNA damage lesion and repair processes at play under etoposide in GBM (Related to Fig 2). (A) List of distinct DNA damage and repair processes implicated by genes whose KO was selected by etoposide. **(B)** Cleavage assay editing in the on-target FANCB but no off-target cleavage on the AP000282.2, including positive control cells edited at other sites with TALEN. **(C)** Immunofluorescence for γH2AX staining on wild type SNB19 and FANCB edited cells and the non-targeting controls treated with etoposide or DMSO, quantified in Fig **2H**. **(D)** The viability assay quantified shows significant survival of FANCB edited cells under 5μM doxorubicin treatment for 72hrs compared to wild type cells (***p=0.001). **(E)** Bar charts showing 53BP1 positive foci in WT and SgFANCB edited cells treated with DMSO or Etoposide (***p=0.001). **(F)** Immunofluorescence images of SNB19 WT and SgFANCB treated with DMSO and etoposide and stained with 53BP1 and DAPI.

Supplementary Fig 3: Expression of Ribosomal subunit proteins correlates with IC50 and AUC etoposide for glioma and many cancers, sgRPS11 edits efficiently (Related to Fig 3). (A) The figures show the correlation of the predicted biomarkers RPS11 (***p=0.0001), RPS16 (*** p=0.0001), RPS18 (***p=0.0001), mRNA levels (TPM) vs the area under the curve for dose-response curve (AUC) for etoposide (inverse spearman's correlation) across 36 glioma CCLE cell lines. **(B)** The gel shows cleavage assay of sgRPS11 edited cells with 50% cleavage at target sites. The cleavage was confirmed with three independent primer sets. **(C)** Western blot showing the overexpression of RPS11 in GBM6 compared to empty vector and to wildtype GBM6. **(D)** Viability of the GBM6 overexpressing RPS11 compared to wild type GBM6 and empty vector control treated with etoposide DMSO.

Supplementary Fig 4: BID shows differential expression in GBM susceptibility to TOP2 poison committed to apoptosis (Related to Fig 5). (A) Histogram shows the effect of 5μM etoposide treatment for 24hrs on protein synthesis across cell lines with variable degree of susceptibility (**refer to** Fig**. 3C top- bottom**). Cells are arranged in order of susceptibility (left most susceptible, intermediate susceptible, right most resistant, unpaired t-test, treated vs untreated). **(B)** Histogram shows BID expression in glioma cell lines following etoposide, in which cell lines were ranked based on susceptibility to this drug (left most susceptible and right most resistant). The median fluorescence intensity for BID expression quantified **(C)** (**** p<0.0001, unpaired t-test). **(D)** Histograms shows

APAF1 expression on susceptible (SNB19) and resistant (GBM12) cell lines with and without etoposide treatment for 24hrs.

Supplementary Fig 5: BCL2 shows differential expression in GBM susceptibility to TOP2 poison committed to apoptosis, and effect of RPS11 loss on 53BP1 foci following etoposide. (A) Histogram shows BCL2 expression in GBM cell lines treated by etoposide for 24hrs arranged from susceptible (left) to resistant (right) **(B)** The median fluorescence intensity quantified (* p=0.02, **p=0.0014, ***p=0.0001, **** p=0.0001, unpaired t-test). **(C)** Immunofluorescence images of 53BP1 stained cells of WT MES83, SgNT and SgRPS11 treated with etoposide and DMSO and quantified in bar charts (*** p=0.001).