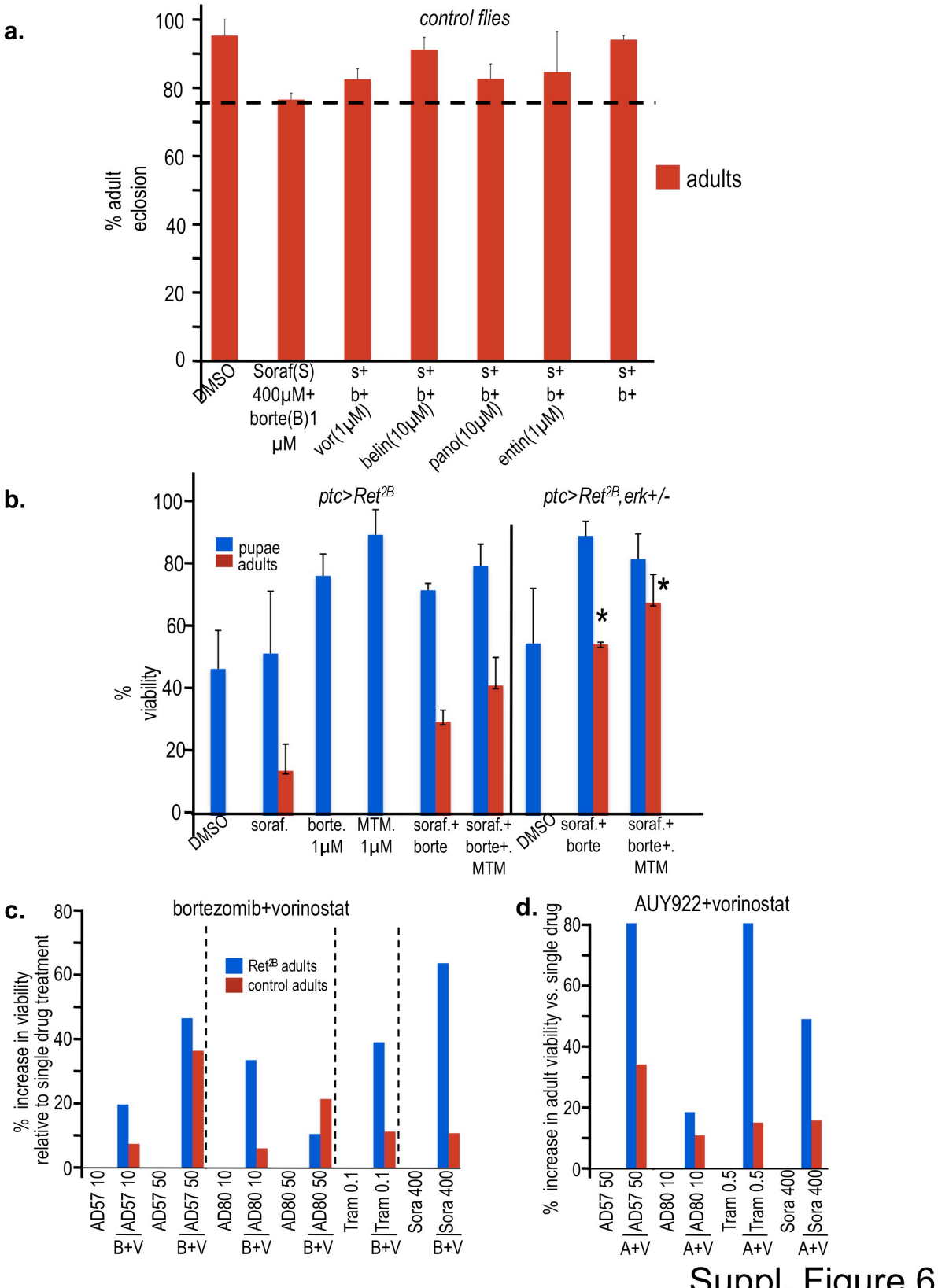

Suppl. Figure 6

Supplemental Figure 6.

Genetic and pharmacological approaches identified additional drugs/cocktails that act as 'network brakes'

(A) Viability studies showing that pan HDAC inhibitors can improve the viability of control flies (*ptc-GAL4*) treated with sorafenib (400 μM)/bortezomib (1 μM). Control flies consuming sorafenib/bortezomib combination on average showed 76% of embryos surviving to adults. When pan HDAC inhibitors were added to this combination there was a consistent increase of viability: i) +vorinostat-82%, ii) +belinostat-90%, iii) +panobinostat-82%, iv) +entinostat-84%, v) CUDC-907-93%. Paired t-tests (PRISM) between sorafenib/bortezomib treated and triple drug treated flies showed p-values <0.05. Approximately 50 flies were analyzed for each treatment.

(B) Viability studies showing that MTM, an inhibitor of the SP1-class of transcription factors, improves viability of *ptc-GAL4>Ret^{2B}* flies treated with sorafenib (400 μM)/bortezomib (1 μM) (asterisk). Effect on adult viability is further improved by reducing *erk* gene dosage (double asterisk).

(C) Bortezomib/vorinostat improved viability of *ptc>Ret^{2B}* and control flies fed with polypharmacological inhibitors that target Ret pathway components. Flies were fed either kinase inhibitors alone (AD57, AD80, trametinib, or sorafenib) or as a 3-drug cocktail with bortezomib/vorinostat (B+V). All kinase inhibitors showed improved viability in the presence of bortezomib/vorinostat. Total number of animals tested per treatment: control- AD57 (n=75), AD57+B+V (n=116); AD80 (n=114), AD80+B+V (n=112); trametinib (n=123), trametinib+B+V (n=131); sorafenib (n=118), sorafenib (n=120). *ptc>Ret^{2B}*- AD57 (n=205), AD57+B+V (n=186); AD80 (n=78), AD80+B+V (n=92); trametinib (n=115), trametinib+B+V (n=89); sorafenib (n=97), sorafenib (n=89).

(D) Presence of vorinostat/AUY922 also improved viability of *Ret^{2B}* (*ptc>Ret^{2B}*) and *control* (*ptc-GAL4*) flies fed with Ret-pathway kinase inhibitors. *Ret^{2B}* and control flies were fed either kinase inhibitors alone (AD57, AD80, trametinib, or sorafenib) or as a 3-drug cocktail with vorinostat/AUY922 (V+922). Represented on the right hand side is the relative improve in viability of the 3-drug cocktail compared to kinase inhibitor treatment alone in both models tested. All the kinase inhibitors showed improved viability in the presence of vorinostat/AUY922 in both models.