Figure S1

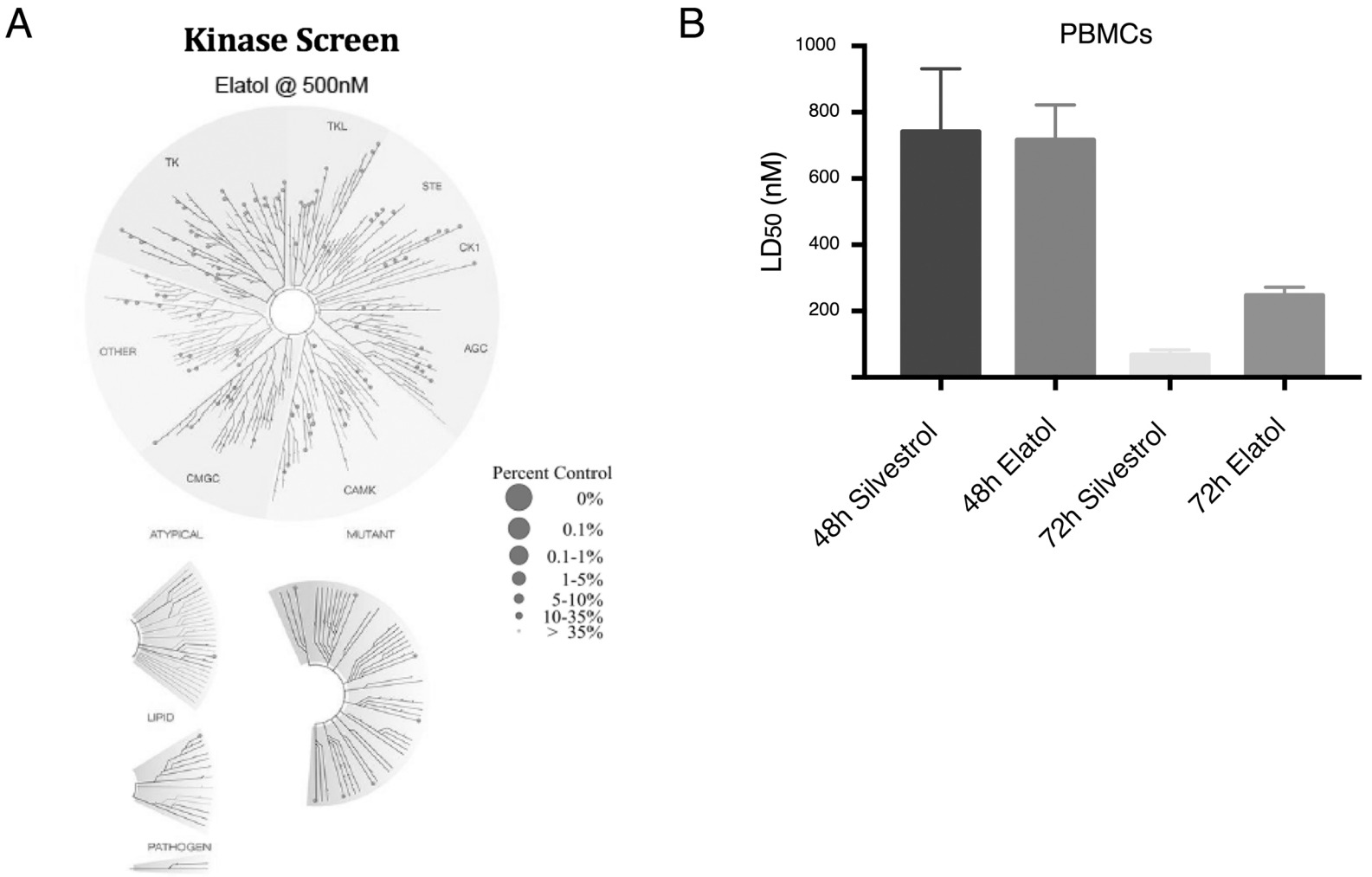
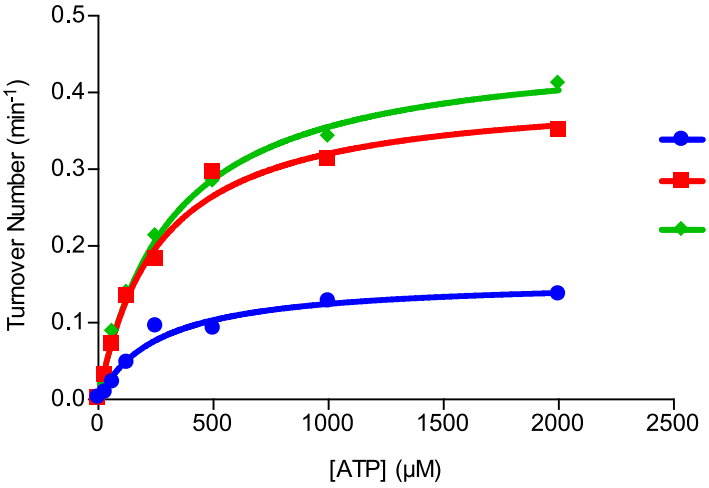


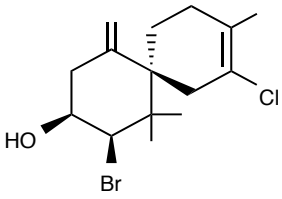
Figure S1. A) Elatol was submitted to a 96-member kinome screen (LeadHunter, DiscoveRx) to evaluate specificity. inhibition of any of the kinases would be indicated by a dot, corresponding to percent inhibition relative to a positive control. B) Sensitivity of normal human peripheral blood mononuclear cells (PBMCs) isolated using hisptopaque-1077 (Sigma) from normal healthy donors. Viability measured after 72-hour treatment using Promega Cell Titer Glo reagent. LD50 calculated using nonlinear regression fit analysis in Graphpad Prism 7. Mean + SEM n=4.

A

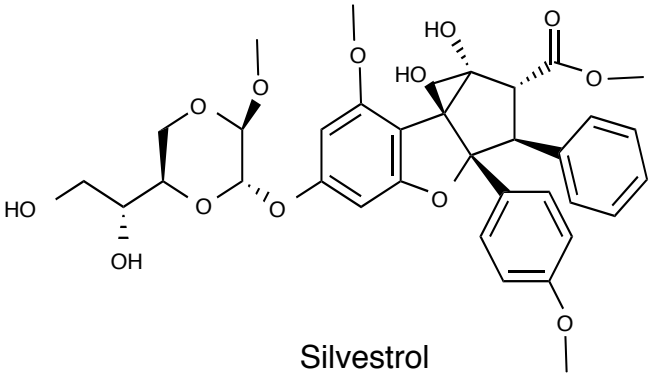


	K_M (μM)	K_{cat} (min^{-1})	K_{cat}/K_M
eIF4A1 WT	258	0.157	0.000608
eIF4A1 K82R	261	0.404	0.00155
eIF4A1 K238E	310	0.465	0.00150

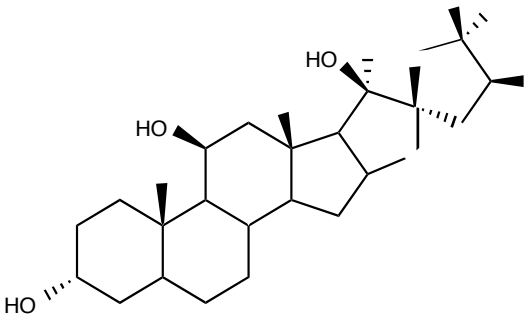
B



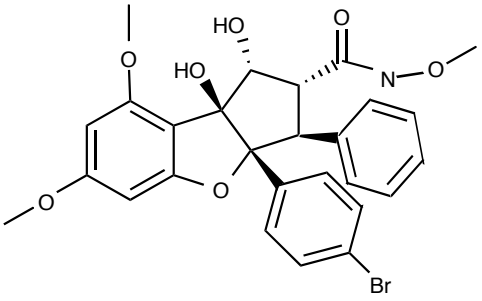
Elatol



Silvestrol



Hippuristanol



Rocaglate

Figure S2. A) Michaelis-Menten curves of eIF4A1 wild type (blue), K82R (red), and K238E (green). Michaelis-Menten constants for eIF4A1 wild type and mutants in table on the left. B) Chemical structures of elatol and three other known eIF4A inhibitors.

Figure S3

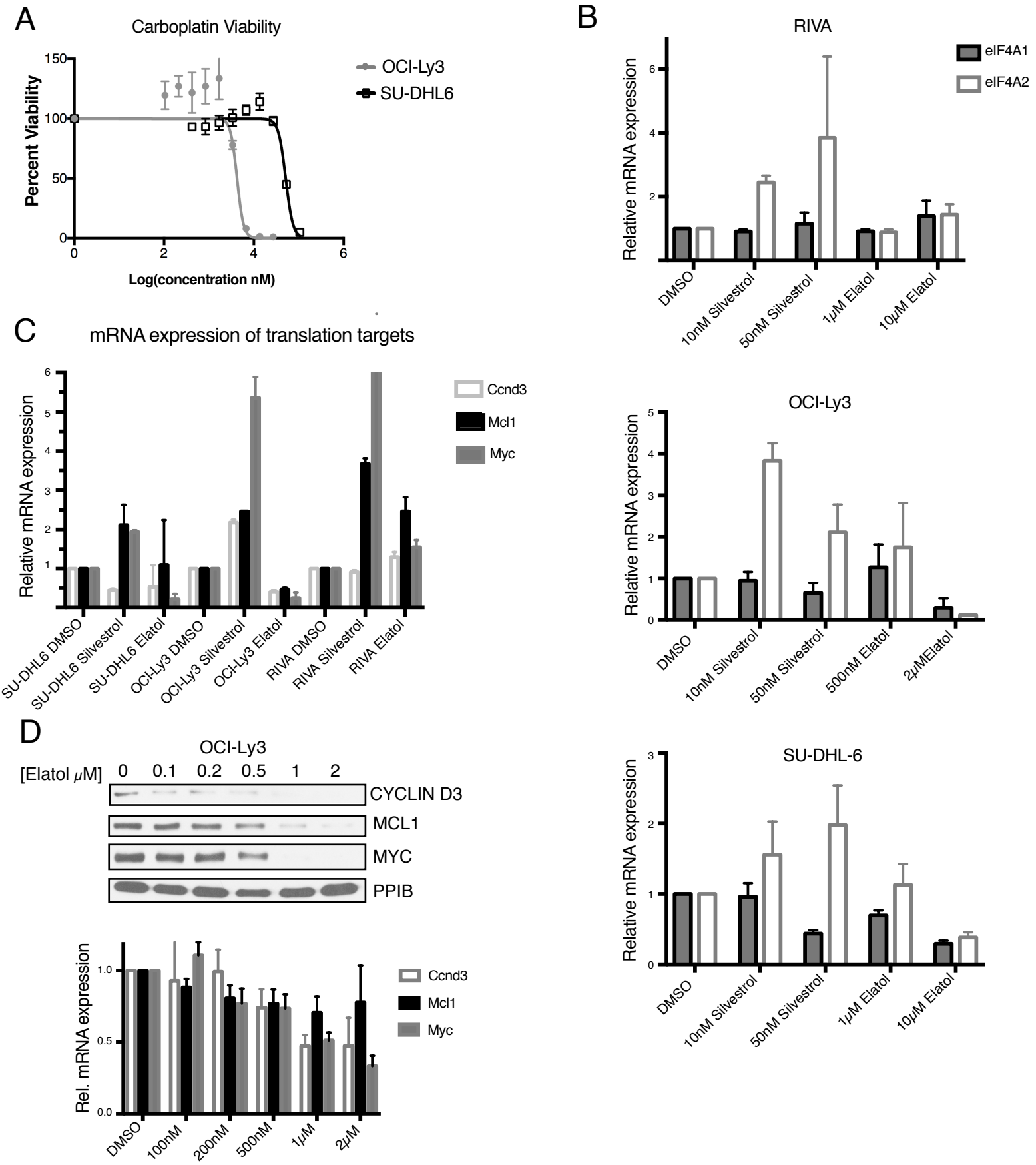


Figure S3. A) Cell viability following 72h carbopaltin treatment measured using Cell Titer Glo. Nonlinear regression fit analysis in Graphpad Prism 7. Mean -/+ SEM N=4. B) Relative mRNA expression of eIF4A1 and eIF4A2 following 24 hour treatment with silvestrol or elatol. Expression calculated using the double delta CT method normalized to DMSO. Mean -/+ SEM, n=3 C) Relative mRNA expression of translationally regulated targets following 24 hour treatment with silvestrol or elatol. Expression calculated using the double delta CT method normalized to DMSO treated cells. Mean -/+ SEM, n=3 D) Protein and relative mRNA expression in OCI-Ly3 cells treated with the indicated concentration of elatol for 24 hours. Expression calculated using the double delta CT method normalized to DMSO. Mean -/+ SEM, n=3.

Figure S4

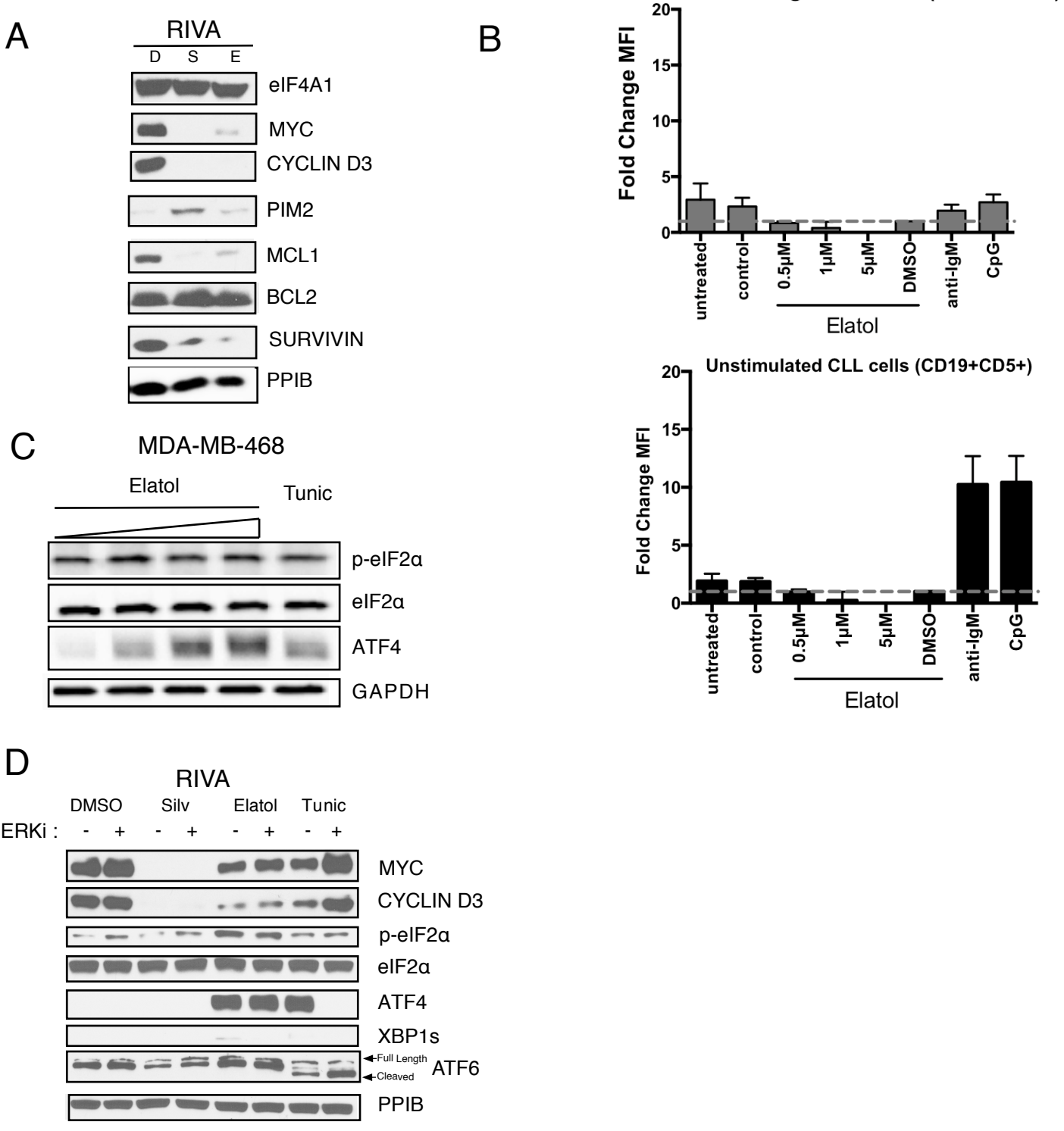


Figure S4. A) Western blot showing protein expression of translationally regulated genes in RIVA cells treated with DMSO (D), 50nM silvestrol (S) or 5 μM elatol for 16h. Representative images, n=3. B) Basal translation measured by OPP incorporation in CD19+CD5+ CLL patient cells (left) and non-malignant CD19-CD5+ T-cells from the same patient samples (right) following elatol treatment. Anti-Ig-M and CpG-ODN stimulation used as a positive control. Mean fluorescent intensity normalized to DMSO treated cells. Mean + SEM n=4. * = p< 0.01, ** = p<0.001. C) Protein expression in MDA-MB-468 cells treated with DMSO (far left), 500nM, 2.5 μ M, 10 μ M elatol or 10 μ M tunicamycin (far right) for six hours. D) Western blot showing protein expression in RIVA cells treated for four hours with DMSO, 100nM silvestrol, 5 μM elatol or 5 μM tunicamycin with or without the combination of 1μ M PERKi. Representative images. n=3.

Figure S5

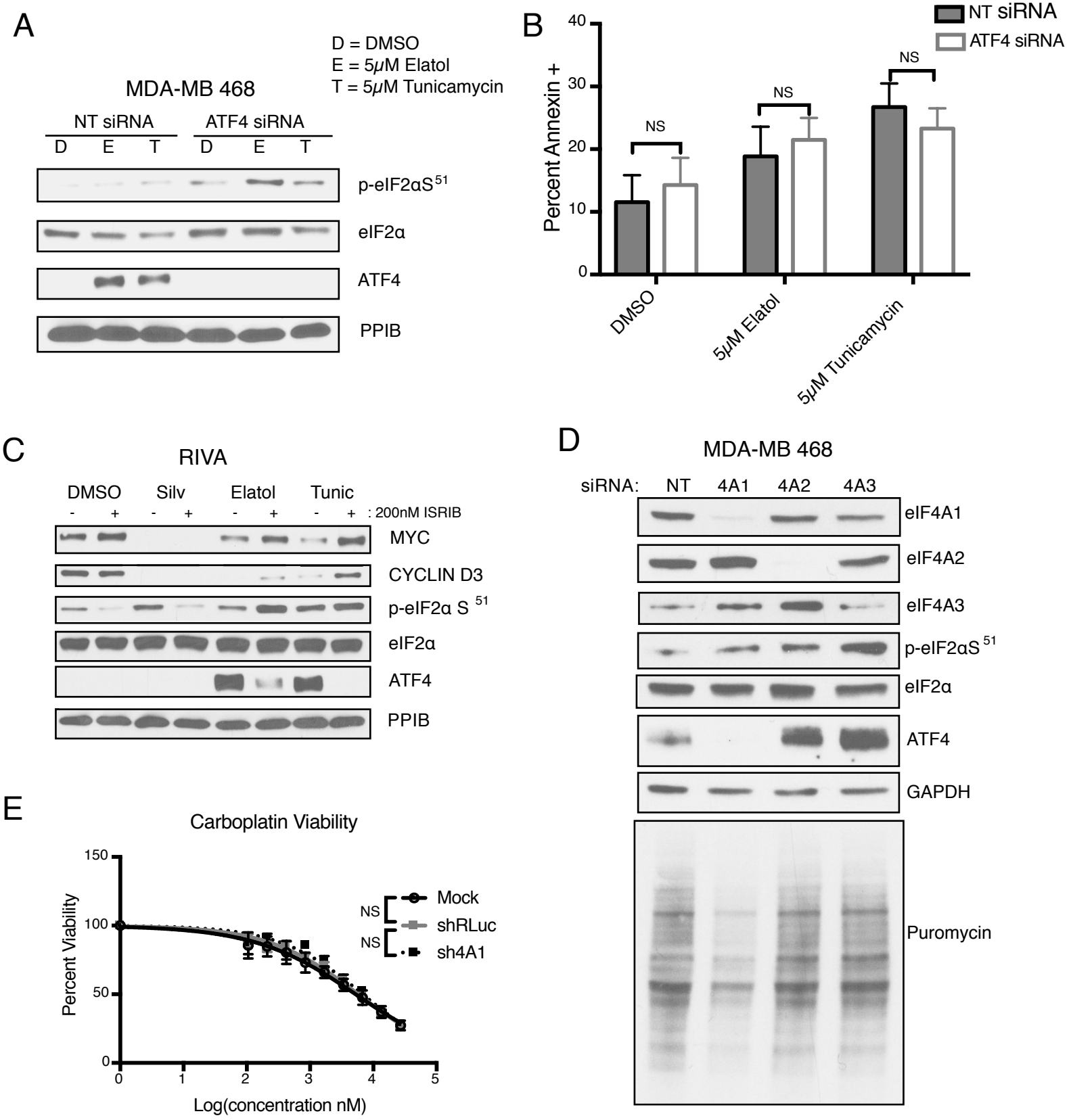


Figure S5. A) Western blot analysis of MDA-MB-468 breast cancer cells transfected with 50nM ATF4 siRNA or a non-targeting control (NT). 48 hours after transfection cells were treated with DMSO, 5 μM elatol or 5 μM tunicamycin for 8 hours and samples were collected for analysis. Representative images, n=2. B) MDA-MB-468 cells were transfected with 50nM ATF4 siRNA or NT control for 48 hours and then treated with DMSO, 5 μM elatol or 5 μM tunicamycin for 24 hours. Then cell death was measured by flow cytometry following annexin V staining. Mean +/- SEM n=3. C) Protein expression in RIVA cells treated for four hours with DMSO, 100nM silvestrol, 5 μM elatol or 5 μM tunicamycin with or without the combination of 200nM ISRIB. Representative images. N=3. D) Western blot analysis of MDA-MB-468 cells transfected with siRNA targeting eIF4A1, eIF4A2, eIF4A3 or a non-targeting control (NT). Cells were pulsed with 10mM puromycin for 30 minutes prior to lysis for detection of global translation by puromycin incorporation. E) 5 day viability of NIH-3T3 cells stably expressing shRNA targeting control (RLuc) or eIF4A1 treated with carboplatin measured using Cell Titer-Glo. Nonlinear regression fit analysis in Graphpad Prism 7. Mean +/- SEM n=4.

Figure S6

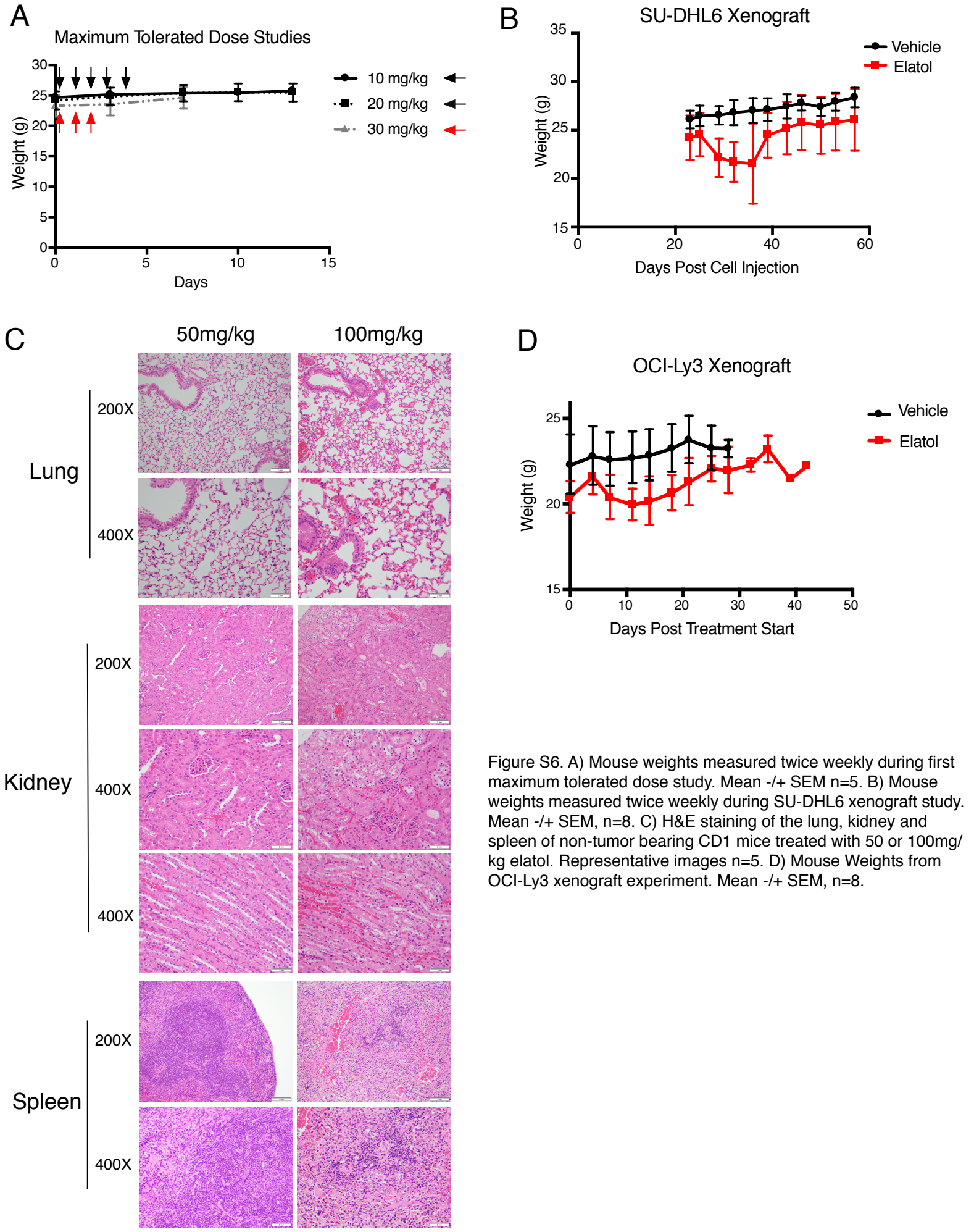


Figure S6. A) Mouse weights measured twice weekly during first maximum tolerated dose study. Mean -/+ SEM n=5. B) Mouse weights measured twice weekly during SU-DHL6 xenograft study. Mean -/+ SEM, n=8. C) H&E staining of the lung, kidney and spleen of non-tumor bearing CD1 mice treated with 50 or 100mg/kg elatol. Representative images n=5. D) Mouse Weights from OCI-Ly3 xenograft experiment. Mean -/+ SEM, n=8.