SUPPLEMENTAL FIGURE LEGENDS

Figure S1. Engineering Doxycycline-inducible eIF4E shRNAs in the Col1AI Locus; Related to Figure 1. A. Configuration of the Col1A1 allele in CTGM-targetted ES cells. **B.** Suppression of eIF4E in CTGM targeted ES cells exposed to 1 μg/ml DOX for the indicated time and analyzed by Western blotting. **C.** Immunohistochemical analysis of representative tissues from untreated and DOX-treated (14 days) *4E.389/rtTA* mice probed with anti-EGFP or anti-eIF4E antibodies and counterstained with hematoxylin. Bar, represents 50 μm. In DOX-treated *4E.389/rtTA* mice, eIF4E expression is suppressed in liver hepatocytes, red and white pulp of the spleen, skin keratinocytes and crypt cells and villi of the intestine. **D.** Western blot of MEFs harvested from a *4E.389/rtTA* embryo and treated *ex vivo* with 1 μg/ml DOX for 3 days.

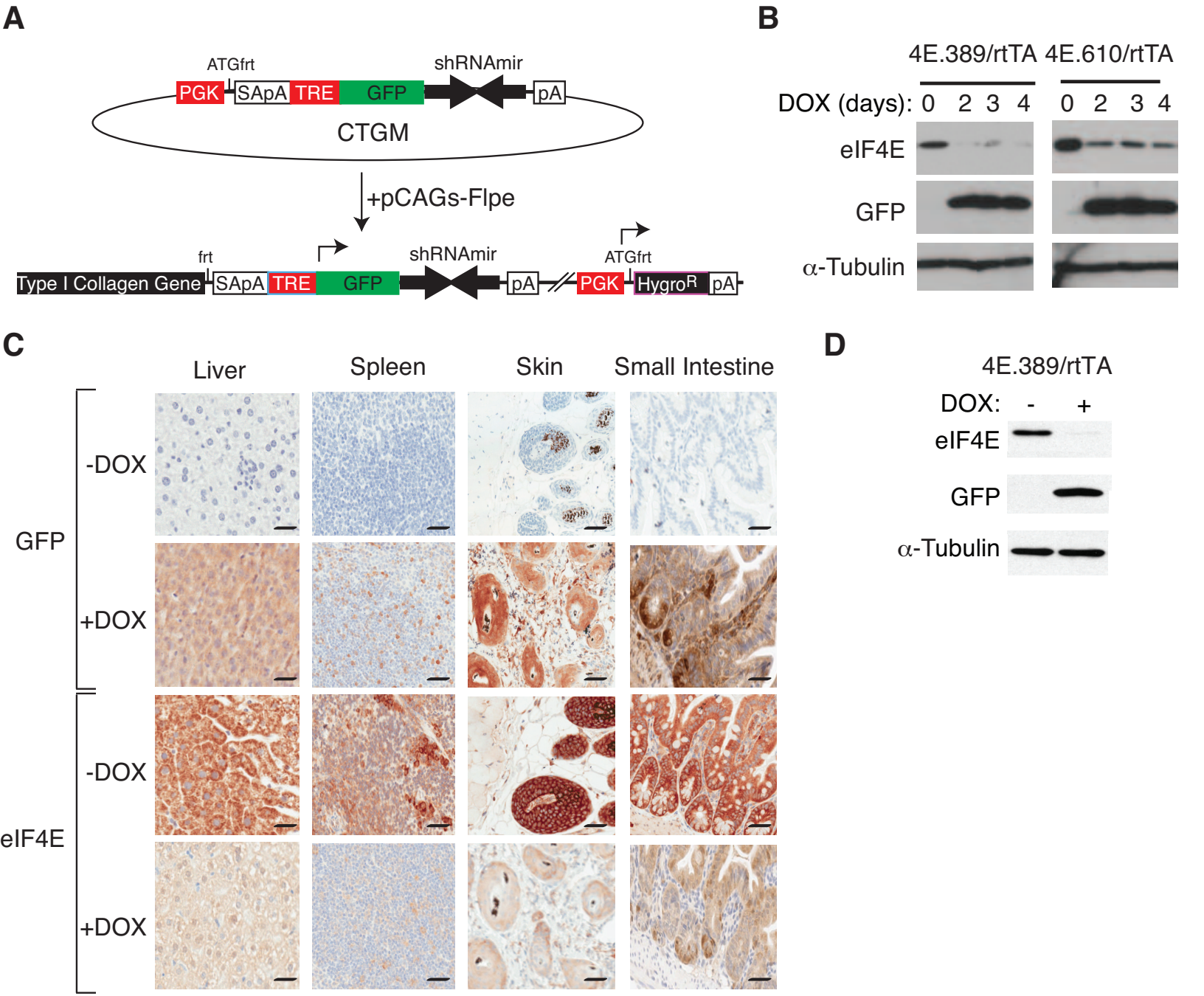
Figure S2. Suppression of eIF4E Causes a Proliferative Disadvantage in MYC Over-expressing Cells; Related to Figure 2. A. Flow cytometry analysis of bone marrow derived $B220^+$ cells from 6 wk old transgenic mice that had been treated with vehicle or DOX for 2 wks. Error bars denote SEM; n=3. **B.** Schematic diagram illustrating two-color FACs assay to assess the consequences of eIF4E depletion and Myc over-expression. In this setting, Myc expression is linked to GFP and shRNAmir expression is linked to turboRFP (tRFP). **C.** Quantitation of flow cytometry analysis of $\%GFP^+$, $\%RFP^+$, and $\%GFP^+RFP^+$ in NIH-3T3 and hTert-BJ cells two days post-infection with MSCV-GFP or MSCV-Myc-GFP and LMS-tRFP-shRNAmir harboring the indicated shRNA. n=3. Bars represent SEM. **D.** Apoptosis in NIH 3T3 and hTert-BJ cells co-infected with MSCV or MSCV-Myc and MLS-shFLuc.1309, MLS-sh4E.389, or MLS-sh4E.610. Graph represents quantitation of flow cytometry analysis of $\%\ GFP^+/PI^+$ cells. n=2, Bars represent SEM.

Figure S3. Selective Inhibition of Protein Synthesis Upon eIF4E Suppression; Related to Figure 3. A. SDS-PAGE analysis of ^{35}S-labelled proteins from $B220^+$ cells isolated from mice of the specified genotype. **B.** Western blot analysis of eIF4E responsive targets in bone marrow-derived $B220^+$ lymphocytes from vehicle or DOX-treated mice of the indicated genotypes. **C.** Reversible suppression of eIF4E targets. Western blot analysis of whole cell lysates from *4E.389/rtTA/Eμ-Myc* $B220^+$ cells isolated from mice before (lanes 1, 4), during (lanes 2, 5), and after (lanes 3, 6) the indicated exposure to DOX. $B220^+$ cells were isolated from spleens (lanes

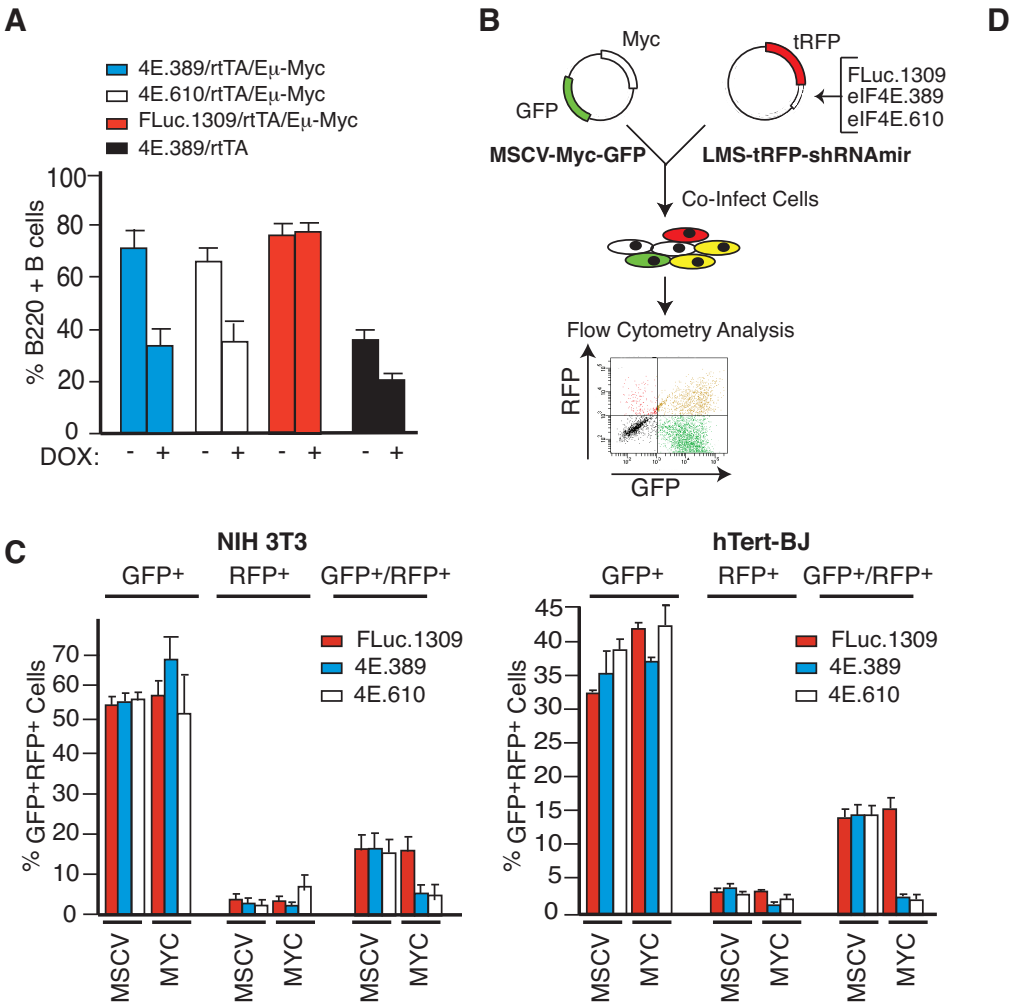
1-3) or bone marrow (lanes 4-6). **D.** Western blot showing that expression of the cap-independent p27Kip1 transcript is unaffected by suppression of eIF4E levels *in vivo* in $B220^{+}$ cells.

Figure S4. Suppression of eIF4E in the Intestines leads to a Degenerative Phenotype that is Readily and Completely Reversible; Related to Figure 4. **A.** Four wk old *4E.389/rtTA/Eμ-Myc* or F*Luc.1309/rtTA/Eμ-Myc* mice were treated with DOX (starting at Day 0) for 2 wks and then taken off DOX (at Day 14). Body weights were monitored every 2 days. Values represent the average of three independent mice/experiment. Error bars are SEM. **B.** Four wk old *4E.389/rtTA/Eμ-Myc* mice were treated with or without DOX for 2 wks, and then were taken off DOX for 1 wk. Sections of small (left panels) and large (right panels) intestine were subjected to hematoxylin and TUNEL staining. Representative results are shown. There is multifocal crypt depletion (bottom 1/3 – 2/3) and the epithelium lining the crypts is hyperplastic and immature. The dotted arrows denote the goblet cells and the solid arrows show apoptotic cells. Bars, represent 25 μM. **C.** Quantitation of apoptotic cells in intestines of vehicle and DOX-treated *4E.389/rtTA/Eμ-Myc* mice. Apoptotic cells were quantitated on an Aperio ScanScope using the software ImageScope from 6 different fields. Error bars are SEM.

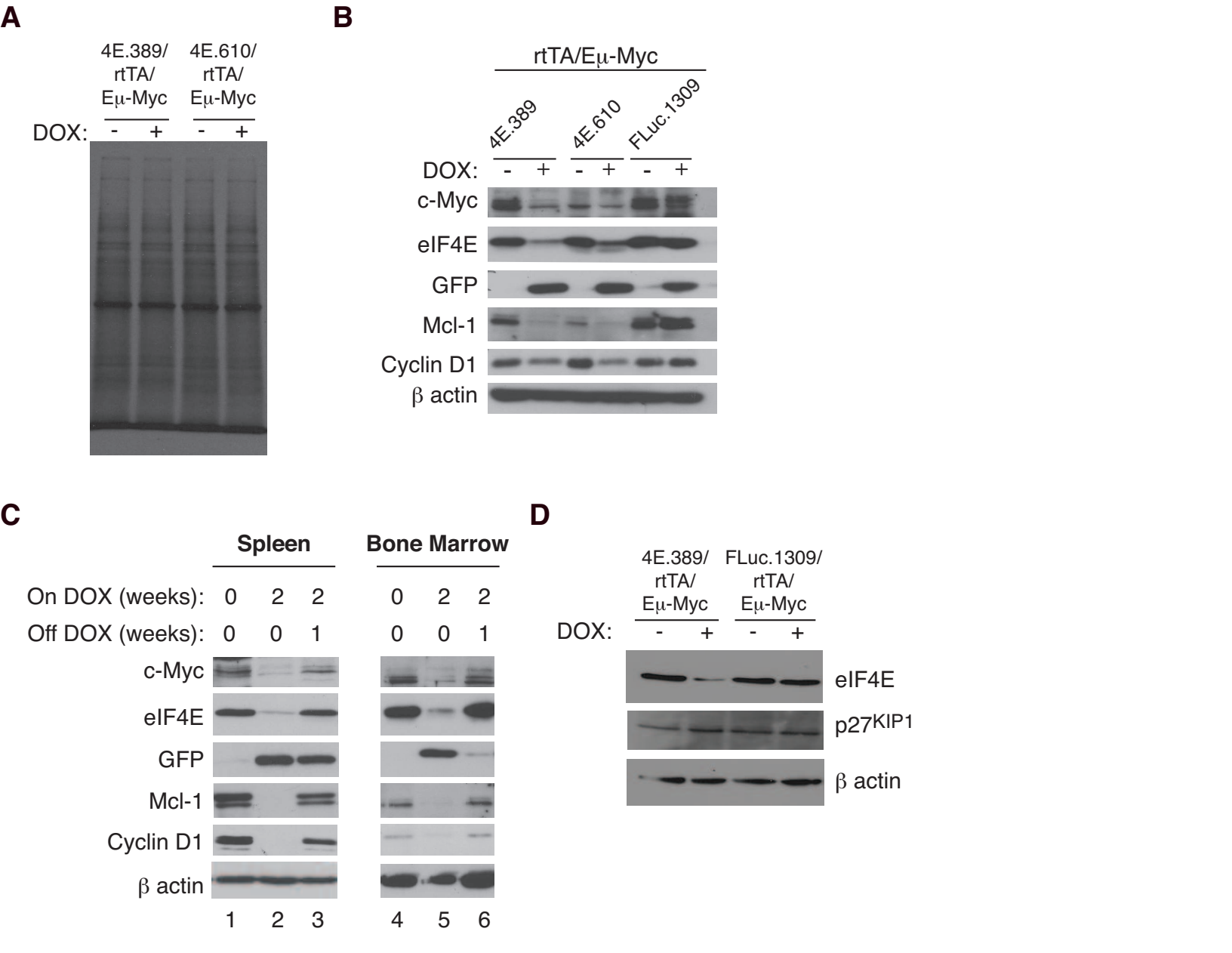
Supplemental Figure 1



Supplemental Figure 2



Supplemental Figure 3



Supplemental Figure 4