Supplemental Information

Supplemental Experimental Procedures

Liver Tissue Fractionations

Whole liver cell suspensions were centrifuged at 50 x g. The resulting hepatocyte pellet was washed. Next, the hepatocytes and contaminating miscellaneous cell types were diluted in 5 mL of 50% Percoll (GE Healthcare). The Percoll and cell suspension was then diluted with PBS to a final concentration of 30% and centrifuged at 50 x g for 20 min at 4 °C. A final wash was performed to remove residual Percoll, and cells were subsequently pelleted. The non-parenchymal cell suspension from the original 50 x g hepatocyte supernatant was centrifuged twice more at 50 x g to remove contaminating hepatocytes. The supernatant was then centrifuged at 450 x g to pellet all non-parenchymal cells. The pellet was washed once, and the supernatant was run over a 17.6% (4 mL) and 8.2% (4 mL) OptiPrep™ (Sigma) step gradient. The interface of the gradient (the non-parenchymal cells) was washed with PBS containing 0.5% BSA and 2 mM EDTA and pelleted at 450 x g. Cell concentration and viability were determined for all fractions of interest prior to cell pelleting.

Histological evaluation

Liver samples were fixed in 10% buffered formalin (Thermo Fisher Scientific) and embedded into paraffin wax. Multiple adjacent 4-mm sections were cut and mounted on glass slides. After deparaffinization, sections were rehydrated and stained. Hematotoxylin and eosin (H&E) staining was performed according to previously published procedures (Freida et al., 2009). For periodic acid solution staining (PAS), slides were incubated in PAS (Sigma) for 5 min and then washed with water three times. Next, slides were placed in Schiff reagent (Sigma) at 4 °C for 18 min and then washed in 0.55% potassium metabisulfite (Sigma) for 1 min prior to a 10 min wash in water. *Immunohistochemistry* staining, heat-induced epitope retrieval was performed in PT Module buffer (Thermo Fisher Scientific)) for 20 min on slides. Prior to blocking in either Rodent Block M (Biocare) or Background Buster (Innovex), slides were washed in TBS (Roche) three times for 2 min each. Slides were then incubated in primary antibody for 1 h at room temperature or overnight

at 4 °C. Antibodies used were anti-Ki-67 (DAKO) diluted 1:200 and anti-COX IV (Abcam) diluted 1:500. Slides were then rinsed with TBS three times for 2 min at each wash. Appropriate secondary antibody with HRP conjugation was added (Jackson Immunoresearch). Slides were then rinsed in three times with TBS for 2 min each rinse. DAB Chromagen (DAKO) was then applied and slides were incubated for 5 min. Slides were rinsed with distilled water and counterstained using a Leica autostainer. Apoptosis was detected using the ApopTag Plus Peroxidase *in situ* Apoptosis Detection Kit (Millipore) using the manufacturer's protocol. For Sirius Red staining, slides were immersed in 0.2% phosphomolybdic acid (Newcomer Supply) for 5 min and then incubated for 90 min at 4 °C with picro-siriusm red (Polysciences) before rinsing in 0.5% acetic acid twice for 2 to 4 min each wash. The slides were then dehydrated in ethanol alcohol 70%, 95%, and 100% for five minutes each, and lastly cleaned in xylene twice for 5 min.

List of primer probe set sequences

Target	**Forward Sequence (5' to 3')**	**Reverse Sequence (5' to 3')**	**Probe Sequence (5' to 3')**
RNase H1	CAAACCAGAGGGCCGAGAT	ACCAGCTTGCTGATGTTC TGA	FAM - CTGCAAGGCCATCATGCAAGCCA-TAMRA
Cre	GCGGTCTGGCAGTAAAAACTATC	GTGAAACAGCATTGCTG TCACTT	FAM-AAACATGCTTCATCGTCGGTCCGG-TAMRA
MTND1	CTGACCCATAGCCATAATATGATTT ATC	GATTCTCCTTCTGTCAGG TCGAA	FAM-CAACCCTAGCAGAAACAAACCGGG C-TAMRA
MTND2	AACAAACGGTCTTATCCTTAACATA ACA	TGGGATCCCTTGAGTTA CTTCTG	FAM-CCTATCCATAAAACTAGGCCTCGCC C CA-TAMRA
MTCO1	CGCCATCATATTCGTAGGAGTAAA	TCTGAGTAGCGTCGTGG TATTCC	FAM-CATTCTTCCCTCAACATTTCCTGGG CCT-TAMRA
MTCO2	CCGACTAAATCAAGCAACAGTAACA	AAATTTCAGAGCATTGG CCATAG	FAM-CAAACCGACCAGGGTT-mgbnfq
MTCO3	GAGACGTAATTCGTGAAGGAACCT	CCGAGACGATGAATAGA ATTATACCA	FAM-CCAAGGCCACCACACTCCTATTGTA CA AAA-TAMRA
MTATP8	GCCACAACTAGATACATCAACATGA TT	TTATGGTTGTTAGTGATT TTGGTGAAG	FAM-AAGTCTCATCACAAACATTCCCACT GG CA-TAMRA
MTCYTB	AGACAACTACATACCAGCTAATCCA CTAA	GAATGGCGTATGCAAAT AGGAAA	FAM-CACCCCACCCCATATTAAACCCGAA TG-TAMRA
OH(7S_1)	AATCTACCATCCTCCGTGAAACC	GGCCCGGAGCGAGAAG	FAM-ACCCGCCCACCAATGCCCC-TAMRA

CBS (7S_2)	CCGTCAAGGCATGAAAGGA	GGGTTTTGCGGACTAATGATTC	FAM-AGCACACAGTCTAGACGCACCTACGG TG-TAMRA
PTEN	GCCACAGGCTCCCAGACAT	TCCATCCTCTTGATATCTCCTTTTG	FAM-ACAGCCATCATCAAAGAGATCGTTAGCAGAA-TAMRA
TTR	CGTACTGGAAGACACTTGGCATT	GAGTCGTTGGCTGTGAAAACC	FAM-CCCGTTCCATGAATTCGCGGATG-TAMRA
α-Actinin	GCACCAACCCCTATACAACCA	GGCACTAGCTGCCGTACATG	FAM-CACGCCTCAGGAGATCAATGGCAA-TAMRA
Apo CIII	CACCGGCTTCTGGGATTCTA	CAACACAGAAGTCTCACGACTCAA	FAM-CCCTGAGGACCAACCAACTCCAGCT-TAMRA
Factor VII	AATGAGGAACAGTGCTCCTTTGA	TGTAAACAATCCAGAACTGCTTGGT	FAM-CCCGGGAGATCTTCAAGAGCCC-TAMRA
Neat1	TCTGGGAGCATCATTCTTTGC	CCTCTACCCCCATGAAAAAGG	FAM-ATGCATGAATGGCAGCAGGCA-TAMRA
Malat1	TGGGTTAGAGAAGGCGTGTACTG	TCAGCGGCAACTGGGAAA	FAM-CGTTGGCACGACACCTTCAGGGACT-TAMRA
SRB1	TGACAACGACACCGTGTCCT	ATGCGACTTGTCAGGCTGG	FAM-CGTGGAGAACCGCAGCCTCCATT-TAMRA

List of ASO sequences and chemistries

Target	Design	Sequence (5'-3')
PTEN ss-siRNA	5'-VinylP-ssRNA	$T_sU_sA_oU_sC_oU_sA_oU_sA_oA_sU_oG_sA_oU_sC_sA_sG_sG_sU_sA_sA$
TTR ASO	5-10-5 MOE gapmer	$T_sA_sC_s A_sA_s A_sT_sG_sG_sG_s A_sT_sG_sC_sT_sA_sC_sT_sG_sC$
α-Actinin ASO	5-10-5 MOE gapmer	$G_sC_sC_sA_sA_sT_s A_sT_sC_sA_sT_sA_sA_sC_sC_sC_s A_sA_sG_sC$
Apo CIII ASO	5-10-5 MOE gapmer	$C_sA_sG_sC_sT_sT_sT_sA_sT_sT_sA_sG_sG_sG_sA_sC_sA_sG_sC_sA$
Factor VII ASO	5-10-5 MOE gapmer	$G_sA_sC_sC_sC_sT_sG_sG_sT_sG_sT_sA_sC_sA_sC_sC_sC_sC_s A_s A$
Neat1 ASO	5-10-5 MOE gapmer	$A_sT_sT_sA_sG_sA_sT_sA_sC_sG_sG_sC_sA_sT_sC_sT_sA_sC_sC_sA$
Malat 1 ASO	5-10-5 MOE gapmer	$C_sG_sG_sT_sG_sC_sA_sA_sG_sG_sC_sT_sT_s A_sG_sG_sA_sA_sT_sT$
PTEN ASO	5-10-5 MOE gapmer	$C_sT_sG_sC_sT_sA_sG_sC_sC_sT_sC_sT_sG_sG_sA_sT_sT_sG_s A$
SRB1 ASO	2-10-2 cEt gapmer	$T_sC_sA_sG_sT_sC_sA_sT_sG_s A_sC_sT_sT_sC$

2'F, 2'OMe, s = PS, o= PO, 2'-O-MOE, 2'-O-cEt, *T* = 5'-(*E*)-VinylP-2'-O-MOE T

Supplemental Reference

Freida L. Carson, Christa Hladik. (2009) *Histotechnology: A Self-Instructional*

Figure S1, related to Figure 2 and 4. Histological evaluation of the livers from RNase H1 knockout mice. Liver tissue was harvested from (1, 2) control *RNase H1* floxed mice (flox + tamoxifen) and inducible *RNase H1* knockout mice (iKO + tamoxifen) 1 week post tamoxifen treatment and (3-8) control *RNase H1* floxed mice (flox) and constitutive *RNase H1* knockout mice (cKO) at weeks 6, 14 and 26 (3-8). Liver sections were stained with: (A) hematotoxylin and eosin (H&E) The arrow indicates apoptotic cell ; (B) periodic acid-Schiff (PAS) for glycogen; (C) Ki-67 antibody a, nuclear marker for proliferation; (D) COX IV antibody; (E) terminal deoxynucleotidyl transferase (TUNEL) assay; (F) collagen/connective tissue stain Sirius red. See also Figure 2 and 4.

Figure S1A. Related to Figure 2 and 4

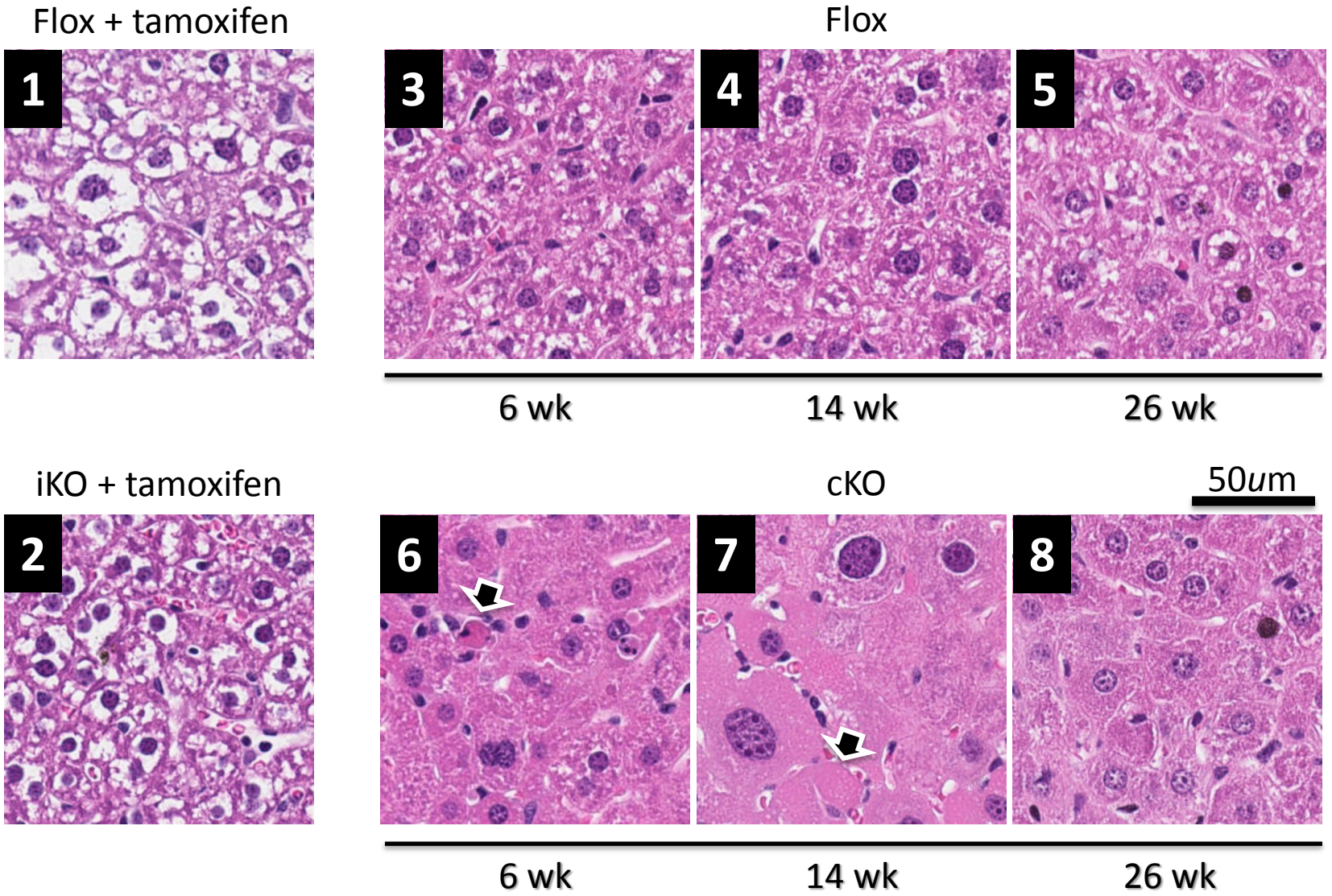

Figure S1B. Related to Figure 2 and 4

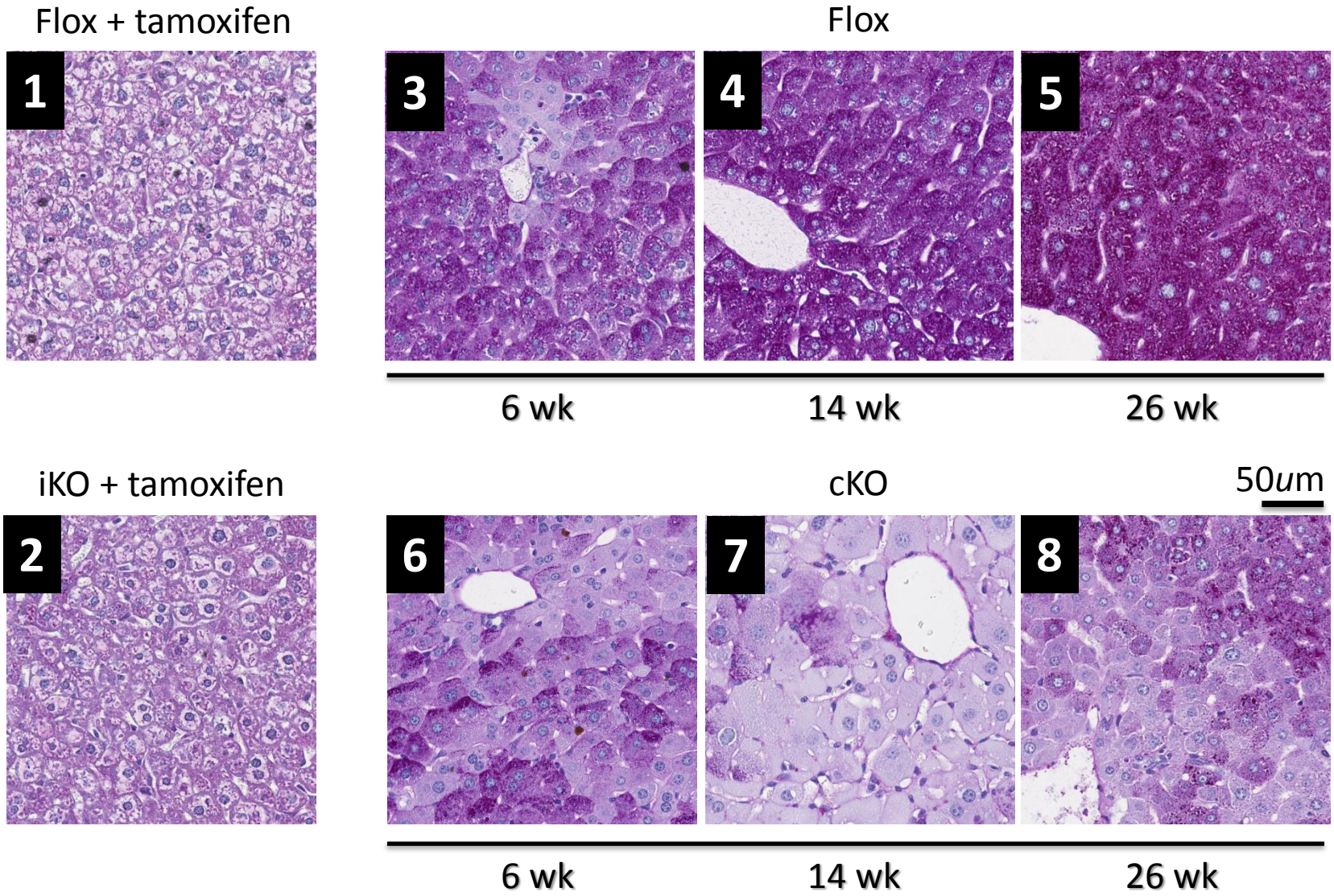

Figure S1C. Related to Figure 2 and 4

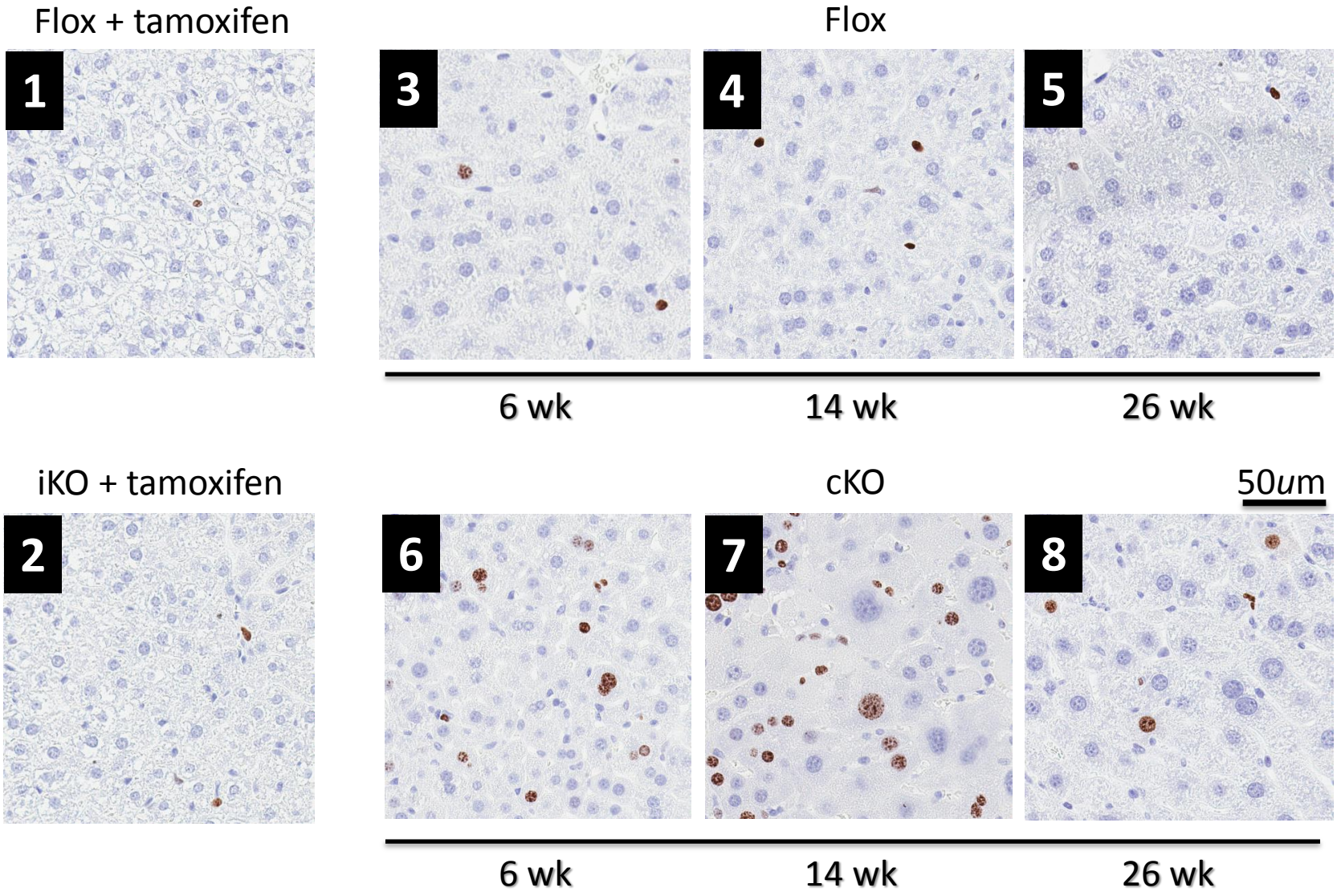

Figure S1D. Related to Figure 2 and 4

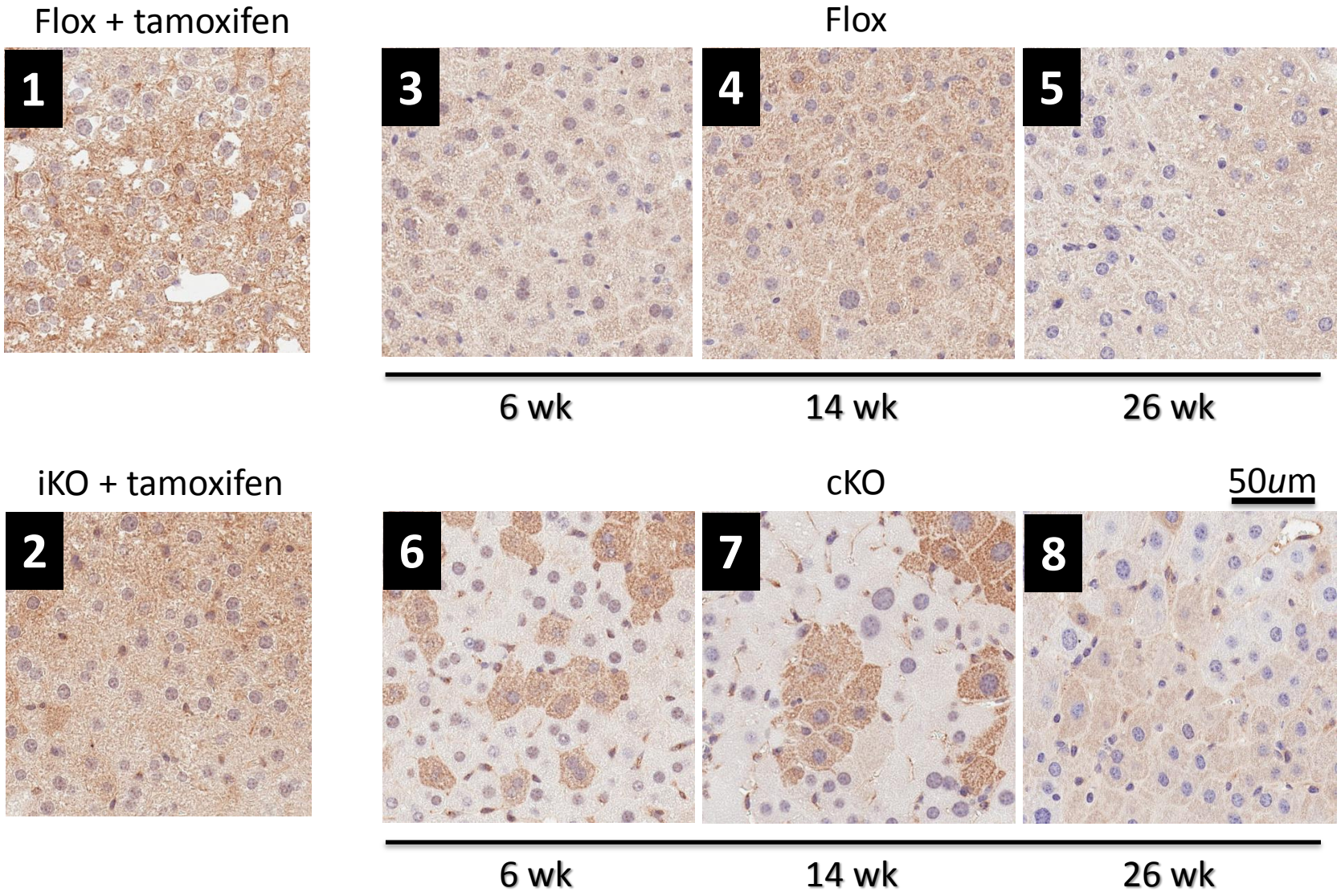

Figure S1E. Related to Figure 2 and 4

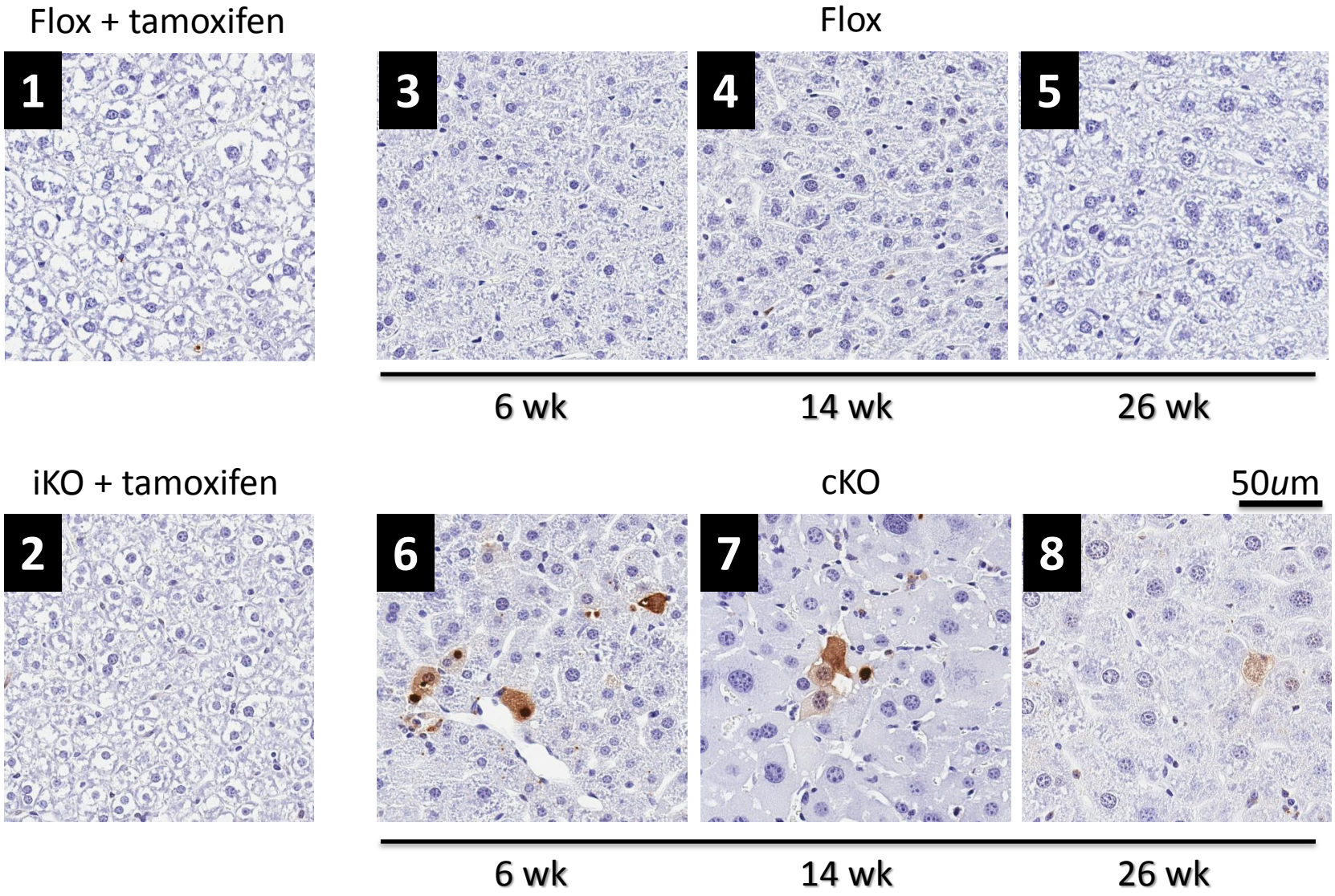

Figure S1F. Related to Figure 2 and 4