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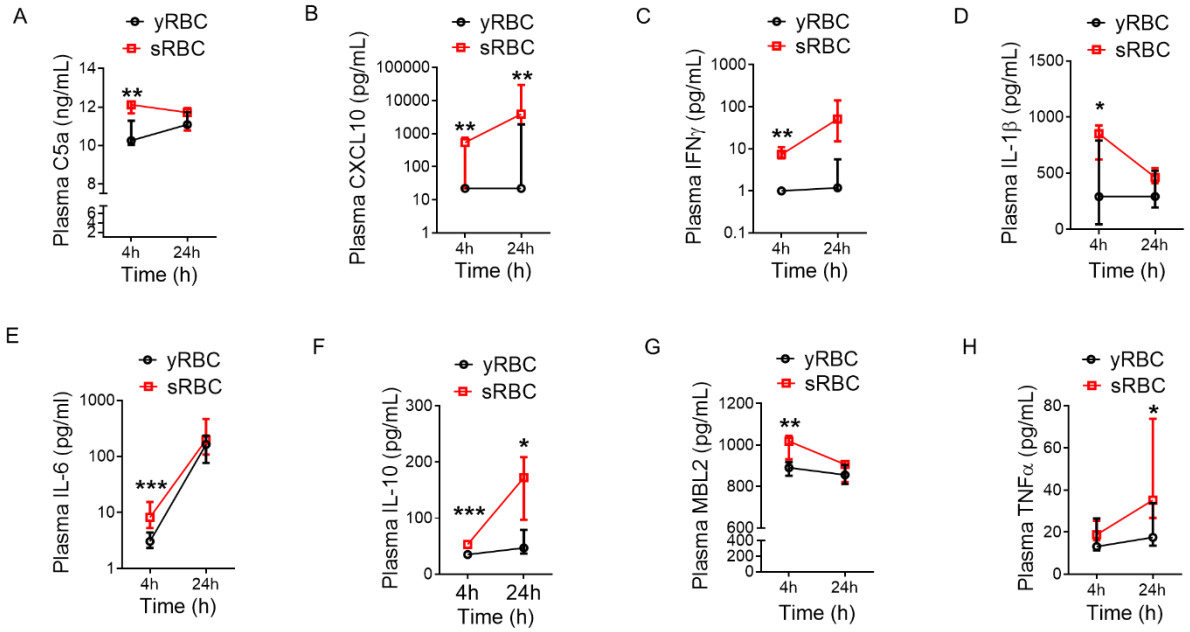

Figure S1: Increased systemic inflammatory response with sRBC delivery during *K. pneumoniae* extrapulmonary dissemination. *K. pneumoniae* was instilled intratracheally into C57BL/6 mice followed by challenge with either young (yRBC) or senescent RBC (sRBC). Mice were euthanized at pre-determined specified time points as indicated. Mouse plasma cytokines were measured by ELISA. (A) C5a, (B) CXCL10, (C) IFNγ, (D) IL-1β, (E) IL-6, (F) IL-10, (G) MBL2, and (H) TNF-α. Each point indicates median with error bars, n=4-8 mice/group. *p<0.05, **p<0.01, ***p<0.001 by Mann-Whitney U two-tailed test.

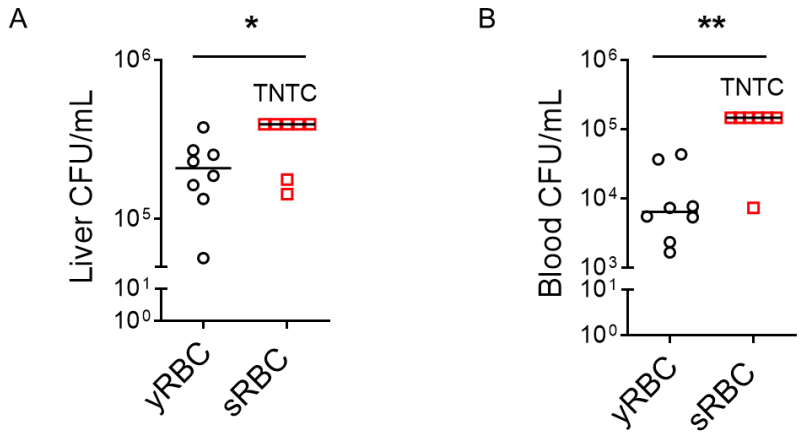

Figure S2: RBC washing prior to transfusion does not mitigate extrapulmonary bacterial proliferation. KP was instilled intratracheally into C57BL/6 mice and was followed by challenge with washed yRBC or sRBC. Bacterial burden was obtained from (A) liver tissue homogenates and (B) blood of mice 24 h post-KP instillation. n=7–8 mice per group. TNTC = Bacteria too numerous to count. *$p<0.05$, **$p<0.01$ by Mann-Whitney U two-tailed test.

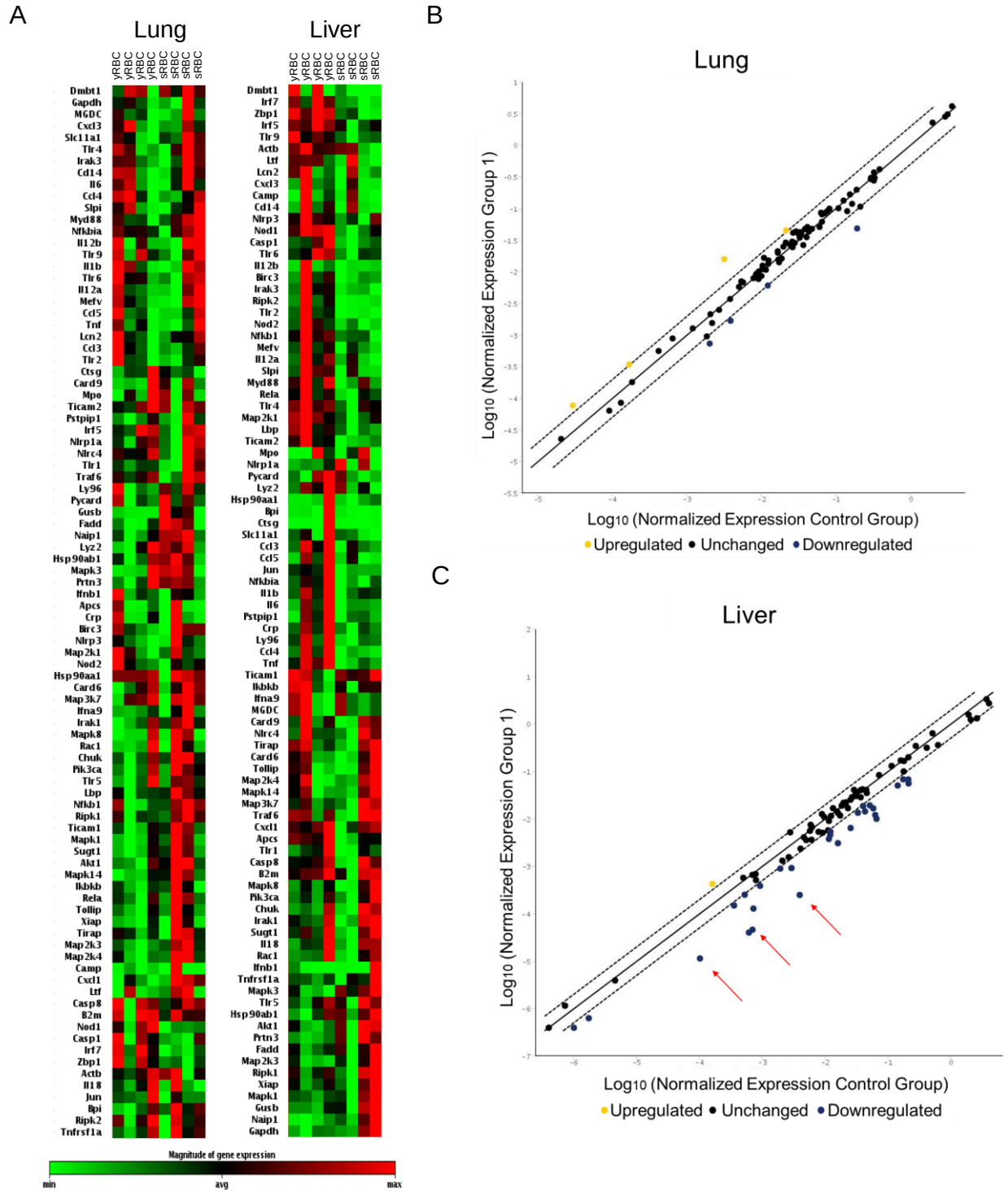

Figure S3: Differentially regulated genes in the lungs and livers of KP-infected mice challenged with yRBC or sRBC at 24 h. (A) Heat map depicting 87 genes examined by PCR-Array for alterations in mouse antibacterial response in lungs and livers of mice challenged with yRBC or sRBC 24 hours post-KP infection. Scatter plot of lung (B) and (C) liver depicting

differentially expressed genes with >2-fold change. Red = upregulated. Green = downregulated. n = 4 mice per group. Red arrows highlight marked downregulation of antibacterial gene expression in the liver following sRBC delivery.

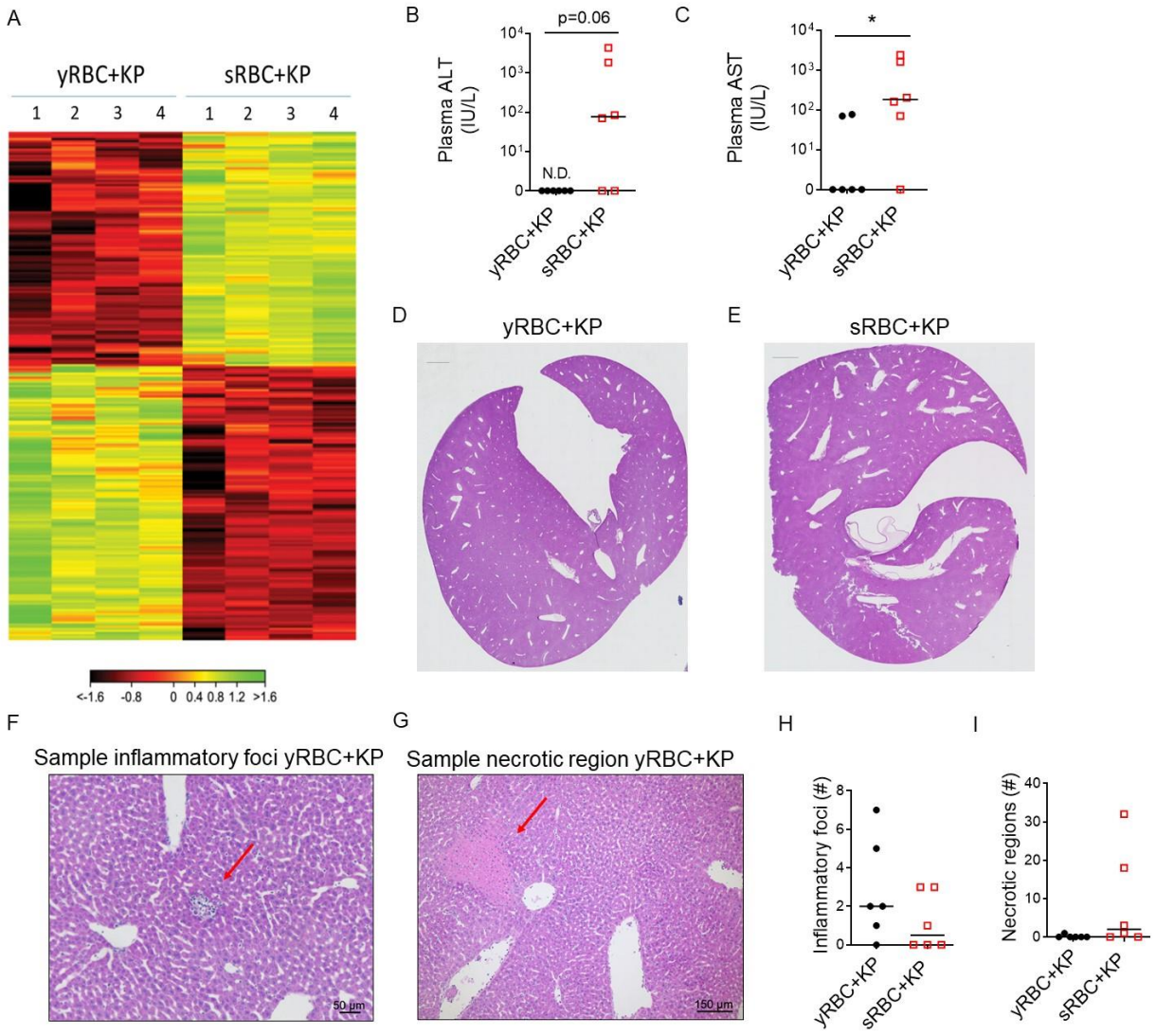

Figure S4: Mouse liver RNA-Seq, plasma transaminase concentrations, and liver histology following yRBC or sRBC delivery in the acute KP infection model. (A) Heat map depicting differentially expressed genes in the livers of mice challenged with either yRBC or sRBC 24 h post-KP infection. Threshold 1.5-fold change, FDR adjusted p-value ≤ 0.05. n=4 mice per group. Green = upregulated. Dark Red = downregulated. Alanine transaminase (ALT) (B) and Aspartate transaminase (AST) (C) were obtained in plasma of mice challenged with yRBC or sRBC 24 h post-KP infection. Line indicates median, n = 6 mice per group. *p<0.05 by Mann-Whitney U test. (D-E) Representative liver tissue section of mice challenged with yRBC or sRBC 24 h post-KP infection, n = 6 mice per group. Scale bar = 1 mm. (F) Sample inflammatory foci and (G) Sample necrotic regions in liver histology following yRBC delivery 24 h post-KP infection. (H, I) Number of inflammatory foci or necrotic regions per liver section with each data point depicting individual mouse. n = 6 mice per group.

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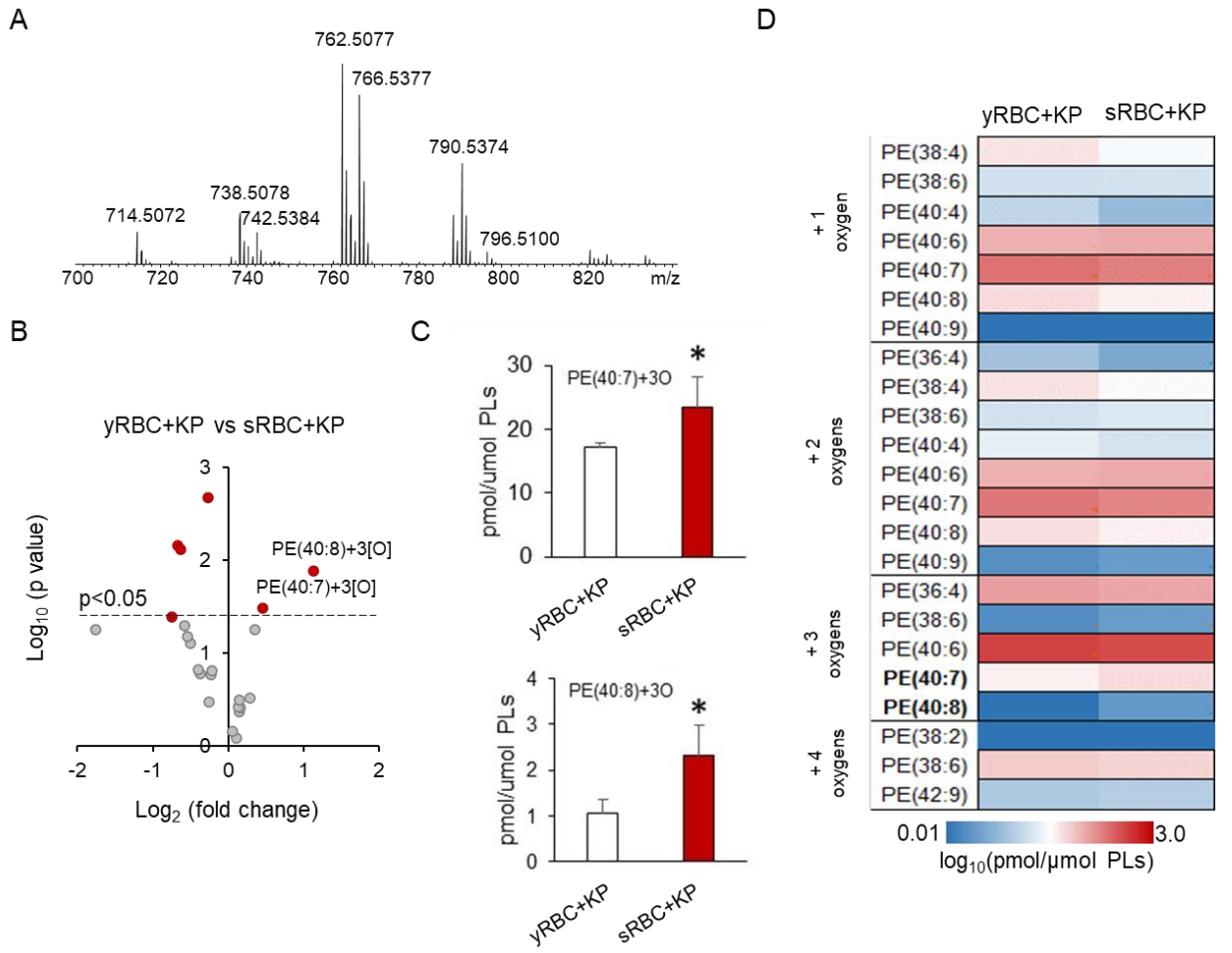

Figure S5: Assessment of oxygenated phosphatidylethanolamine (PE) species in mouse liver following sRBC delivery. (A) Typical mass spectrum of PE species from mouse liver. (B) Differences in the level of oxygenated PE (PEox) species in livers from KP-infected mice challenged with yRBC or sRBC. (C) Quantitative LC/MS assessment of PEox. n= 4 mice per group. (D) Heat map of PEox species.

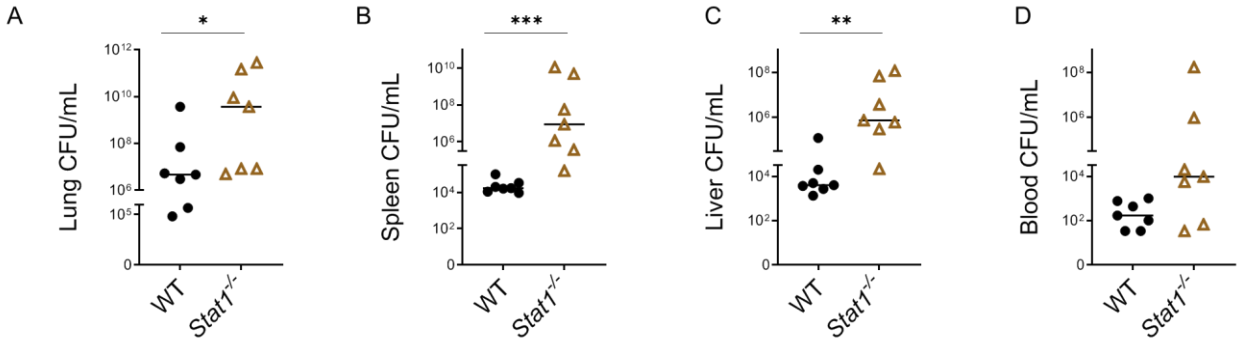

Figure S6: Mice deficient in STAT1 show increased extrapulmonary bacterial proliferation following *K. pneumoniae* intrapulmonary infection. (A) Lung, (B) Spleen, (C) Liver, and (D) Blood bacterial burden 48 h following intratracheal KP instillation in WT and *Stat1*$^{-/-}$ mice and reported as CFU/mL. (A-D) Each point indicates individual mice, n=7 mice per group. Line indicates median. *p<0.05, **p<0.01, ***p<0.001 by Mann-Whitney U two-tailed test.

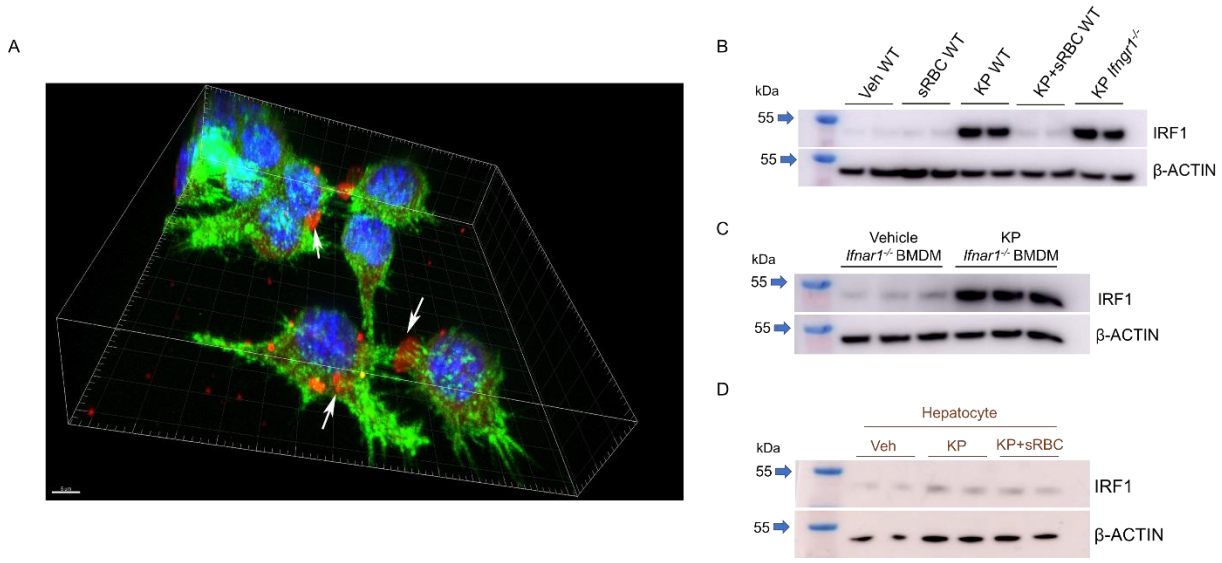

Figure S7: sRBC delivery impairs interferon expression in *K. pneumoniae*-infected macrophages independently of type I or II interferon receptor-mediated signaling. (A) Three-dimensional visualization of sRBC uptake in RAW 264.7 cells. Arrow indicates internalized CD235a-labeled sRBC (red), nuclei are stained with Hoechst (blue), and macrophages are labeled with F4/80 (green). Scale bar = 5 µm. (B-C) IRF1 immunoblots in bone marrow-derived macrophages (BMDM) obtained from *Ifngr1*$^{-/-}$, *Ifnar1*$^{-/-}$, and wild-type (WT) mice challenged with vehicle (PBS), sRBC, KP or KP + sRBC for 4 h. Blots are indicative of two independent experiments. (D) IRF1 immunoblots in primary hepatocytes obtained following collagenase perfusion of murine liver and challenged with vehicle, KP or KP + sRBC for 4 h. Blot is indicative of two independent experiments.

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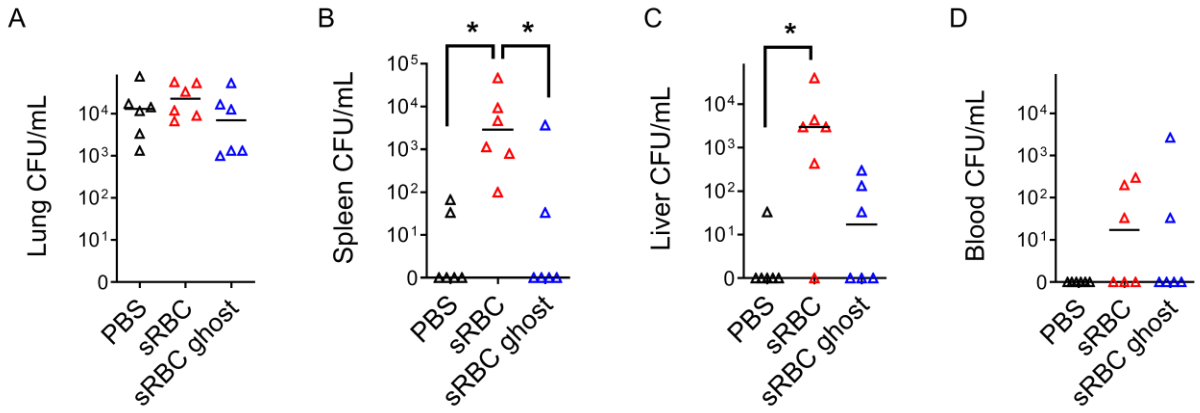

Figure S8: Depletion of hemoglobin from RBC limits *K. pneumoniae* extrapulmonary proliferation. *EntB ybtS* KP mutant was instilled intratracheally into C57BL/6 mice (10^3 CFU inoculum) and followed by challenge with PBS vehicle, sRBC or sRBC ghost. Mice were euthanized and tissue harvested 24 h post-infection. Bacterial burden was estimated in (A) lung, (B) spleen, (C) liver homogenates, and blood as CFU per milliliter. Each data point indicates individual mice, n = 6 mice per group. Lines indicate median. *p <0.05 by Kruskal-Wallis test with Dunn's multiple comparisons.

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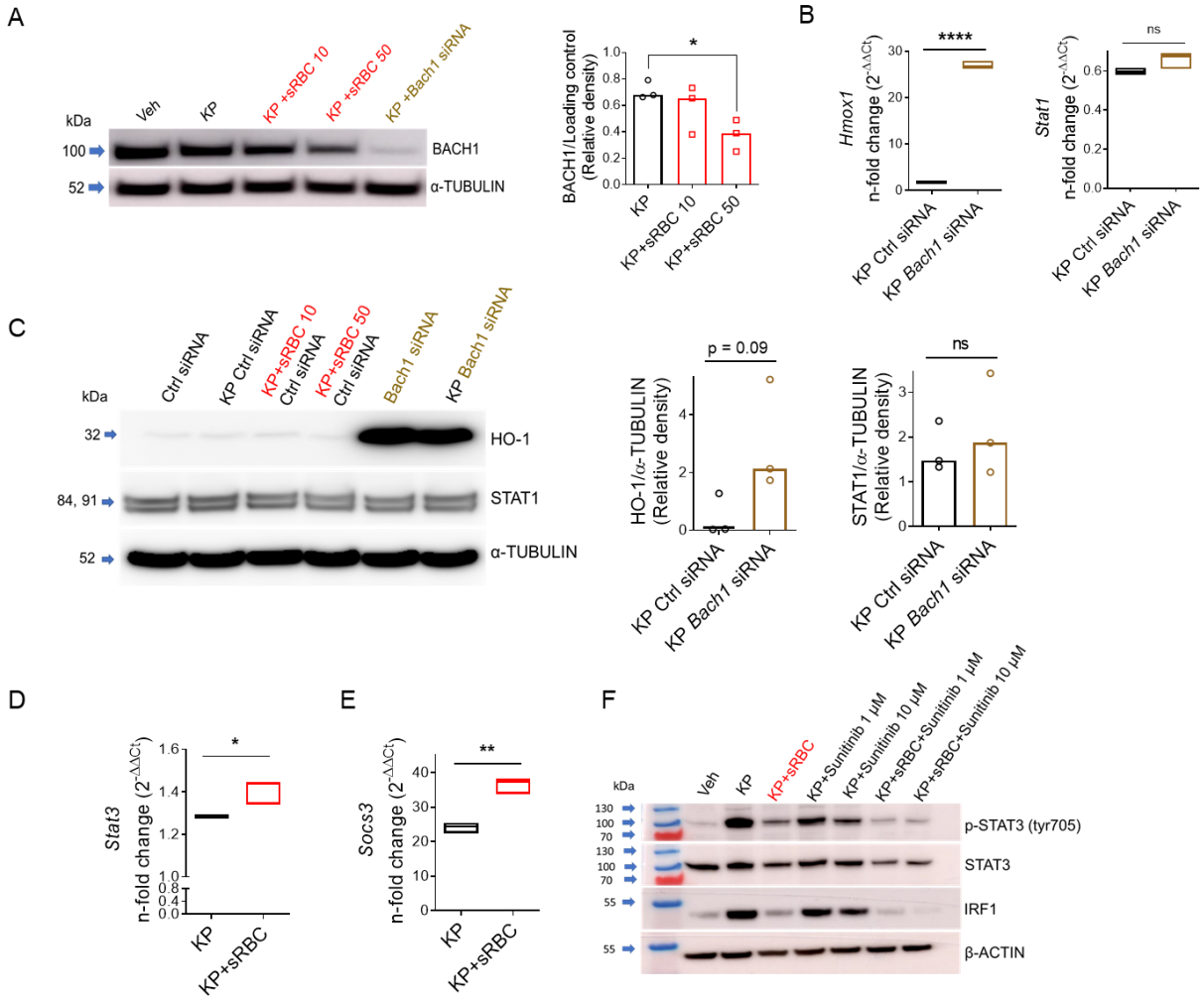

Figure S9: sRBC-mediated STAT1 suppression during *K. pneumoniae* infection is neither dependent on BACH1 degradation nor STAT3 activation. (A) BACH1 immunoblot in RAW cells challenged with vehicle (PBS), KP or KP + sRBC (50:1) for 4 h. Blot is indicative of three independent experiments. *Left*, immunoblot. *Right*, relative density of three independent experiments. *p<0.05 by one-way ANOVA with Tukey's multiple comparisons test. (B) *Hmox1* and *Stat1* expression in RAW cells transfected with scrambled siRNA (control siRNA) or *Bach1* siRNA and subsequently challenged with KP for 4 h. n = 3 technical replicates per group, ****p<0.0001 by two-tailed t test. (C) HO-1, STAT1 immunoblot in RAW cells transfected with control siRNA or *Bach1* siRNA and challenged with KP or KP + sRBC for 4 h. Blot is indicative of three independent experiments. *Left*, immunoblot. *Right*, relative density of three independent experiments. p=0.09 by two-tailed t test (D) *Stat3* and (E) *Socs3* gene expression in RAW cells challenged with *K. pneumoniae* (KP) or KP + sRBC for 2 h. Gene expression was evaluated by qPCR analysis. (D-E) Fold change relative to vehicle (PBS)-treated macrophages. Floating bar plots indicate median and 25-75%, n=3 technical replicates per group. *p<0.05, **p<0.01 by two-tailed t test. (F) p-STAT3, STAT3 and IRF1 in RAW macrophages challenged with vehicle (PBS), KP, KP + sRBC or KP + indicated concentrations of sunitinib for 4 h.

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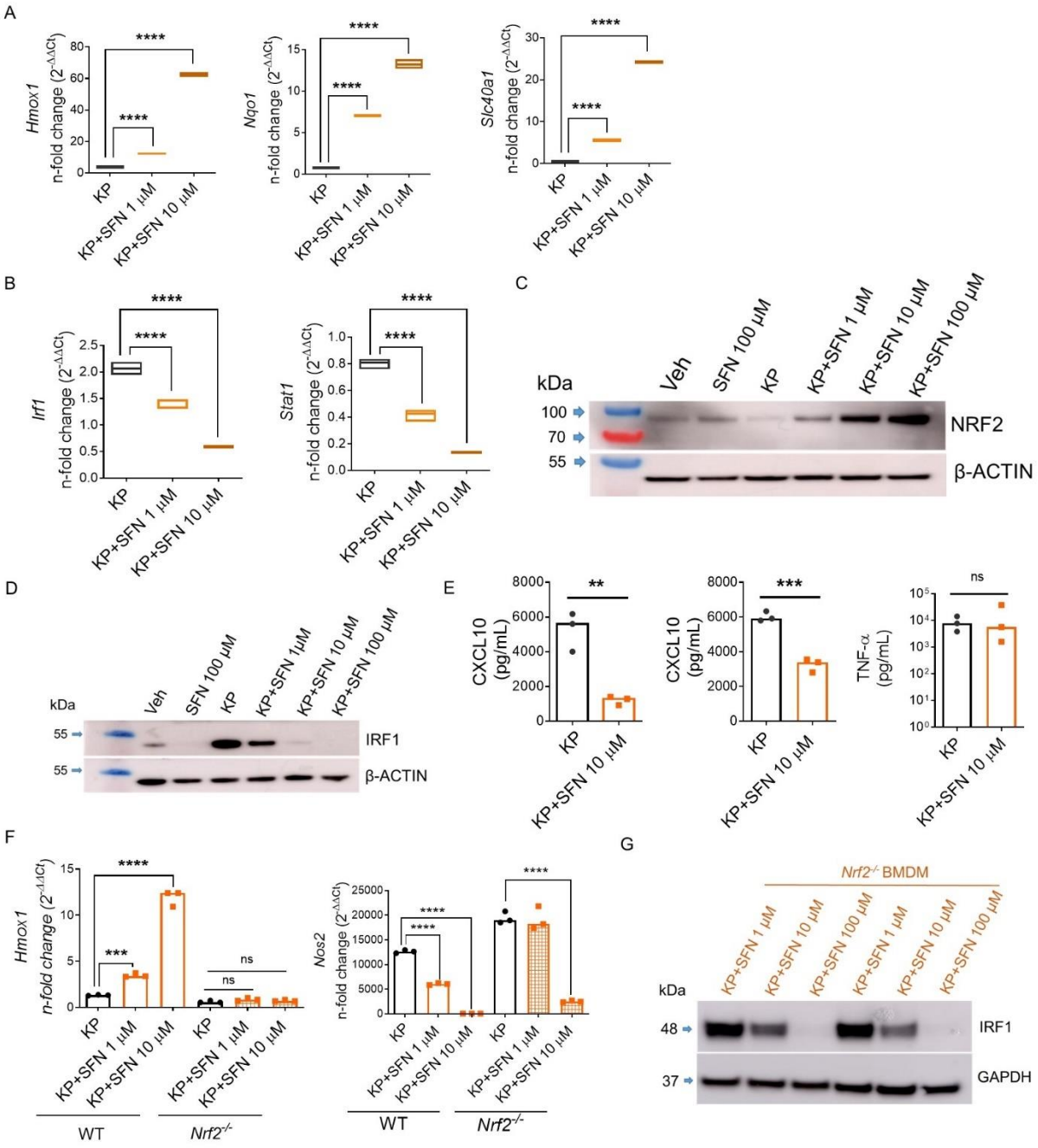


Figure S10: Sulforaphane phenocopies the effect of heightened RBC disposal in macrophages during *K. pneumoniae* infection even in the absence of NRF2. (A) NRF2 target genes *Hmox1, Nqo1, Slc40a1* expression, (B) *Irf1* and *Stat1* gene expression in RAW cells incubated with indicated concentrations of sulforaphane (SFN) for 1 h. Following pre-incubation, cells were challenged with vehicle (PBS) or *Klebsiella pneumoniae* (KP, MOI 10:1) for 4 h. Gene expression was evaluated by qPCR analysis. Fold change relative to vehicle (0.07% ethanol)-treated RAW cells. Floating bar plots indicate median and 25-75%, n=3 technical replicates per group. **** $p<0.0001$ by two-tailed t test. (C) NRF2 and (D) IRF1 immunoblots in RAW cells challenged with vehicle (PBS), KP, or KP + SFN for 4 h. (E) CCL5, CXCL10, and TNF-α were

measured in cell culture supernatant by ELISA 4 h post-infection. n=3 technical replicates per group. **p<0.01, ****p<0.0001 by two-tailed t test. (F) *Hmox1* and *Nos2* in *Nrf2*$^{+/+}$ and *Nrf2*$^{-/-}$ BMDMs challenged with KP or KP + SFN for 4 h. n=3 technical replicates per group, ***p<0.001 ****p<0.0001 by one-way ANOVA with Tukey's multiple comparisons test. Fold change relative to vehicle (0.07% ethanol)-treated BMDMs. (G) IRF1 immunoblot in *Nrf2*$^{-/-}$ BMDMs challenged with KP + increasing concentrations of SFN for 4 h.

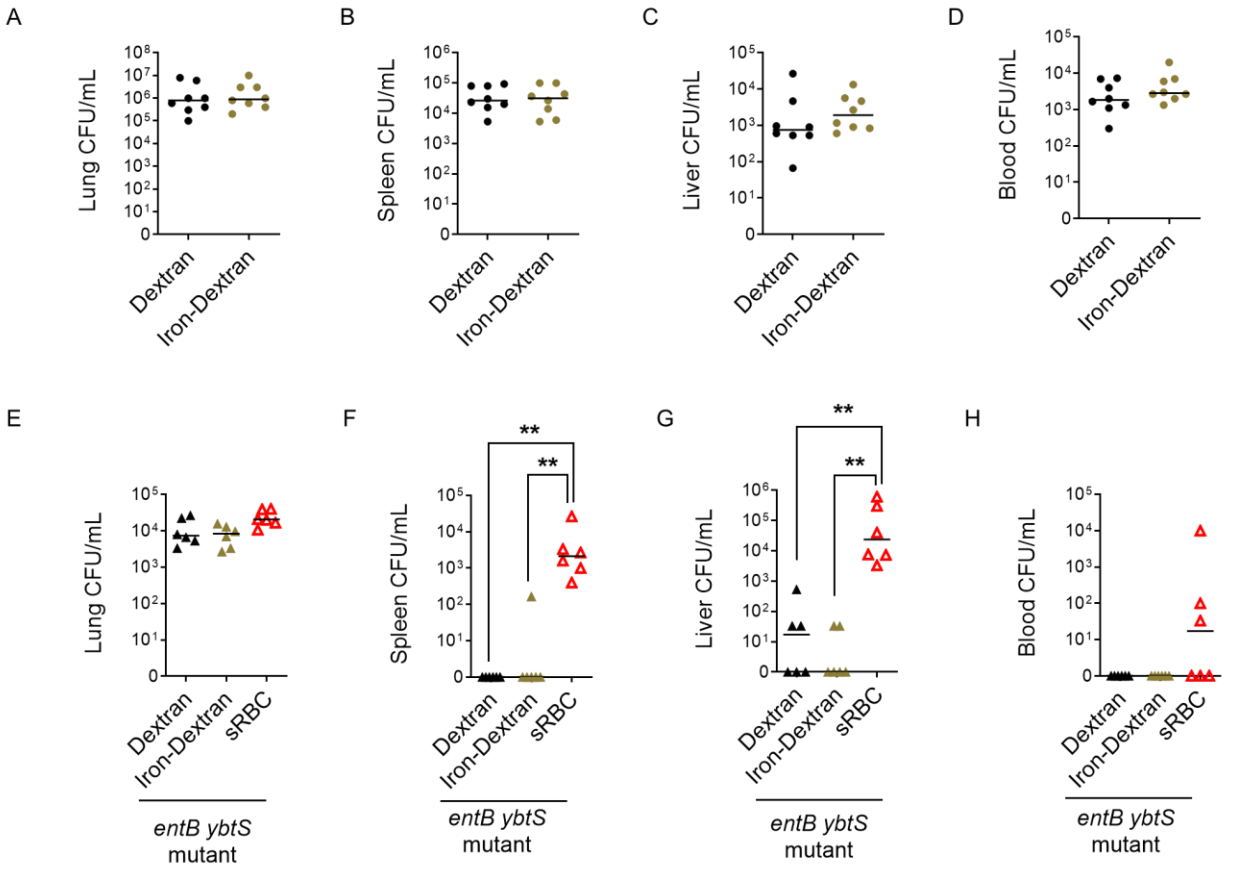
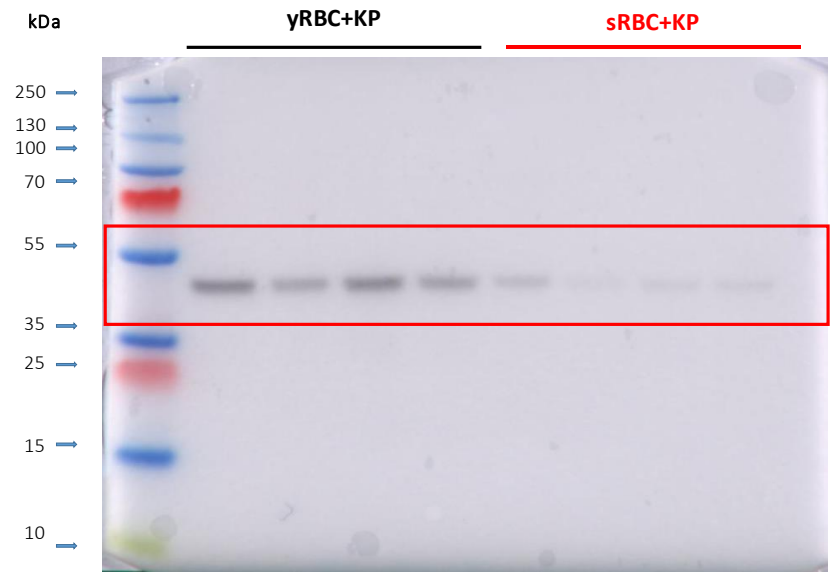


Figure S11: Iron dextran delivery does not promote *K. pneumoniae* extrapulmonary proliferation. (A–D) KP was instilled intratracheally into C57BL/6 mice and followed by transfusion of dextran or iron dextran (total 200 µg iron). Bacterial burden is shown as CFU/mL in (A) lung, (B) spleen, (C) liver homogenates, and (D) blood at 24 hours. Each point indicates individual mice, n=8 per group, line indicates the median, no statistical significance by Mann-Whitney U two-tailed test. (E-H) *EntB ybtS* KP mutant lacking siderophore production was instilled intratracheally into C57BL/6 mice and followed by transfusion of dextran or iron dextran (total 200 µg iron) or sRBC. Bacterial burden is shown as CFU/mL in (E) lung, (F) spleen, (G) liver homogenates, and (H) blood at 24 hours. Each point indicates individual mice. Line indicates median. n=6 per group, *p<0.05, **p<0.01, by Kruskal-Wallis test with Dunn's multiple comparisons.



IRF-1 (D5E4) XP® Rabbit mAb #8478

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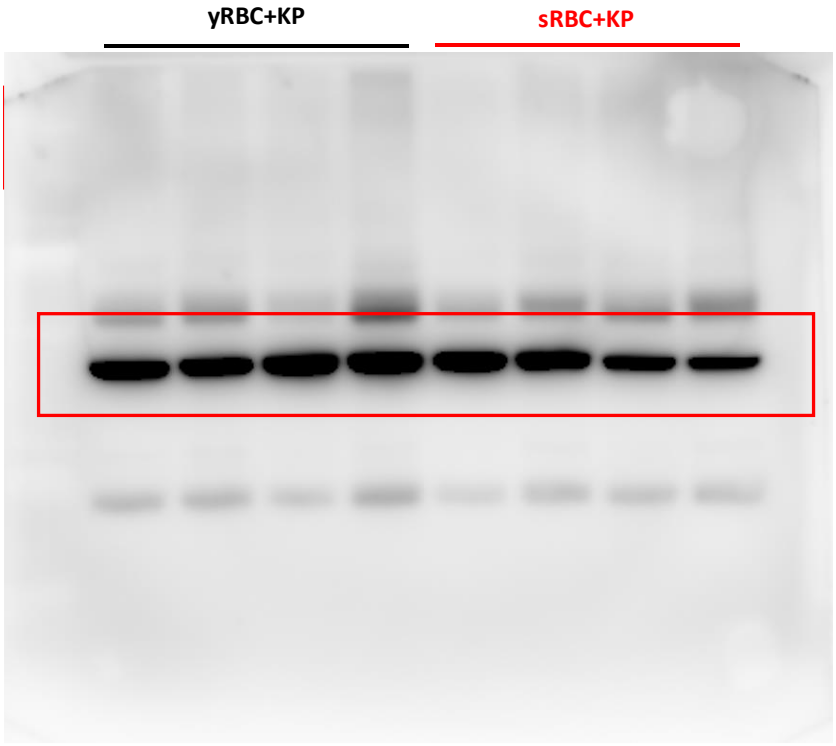

β-ACTIN Mouse mAb

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Figure 3C: Full unedited blots. Red rectangle indicates depicted image.

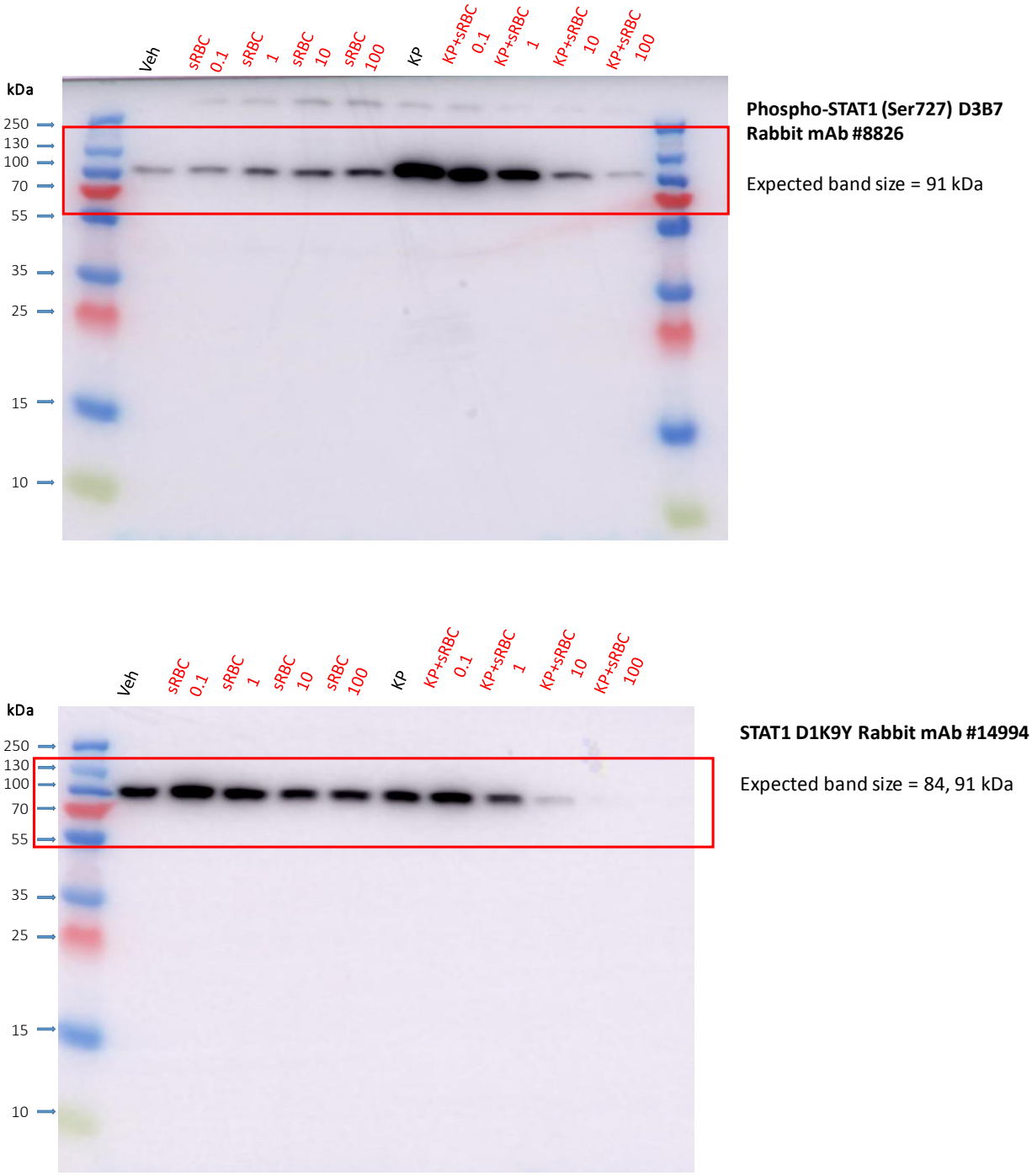


Figure 4G: Full unedited blots. Red rectangle indicates depicted image.

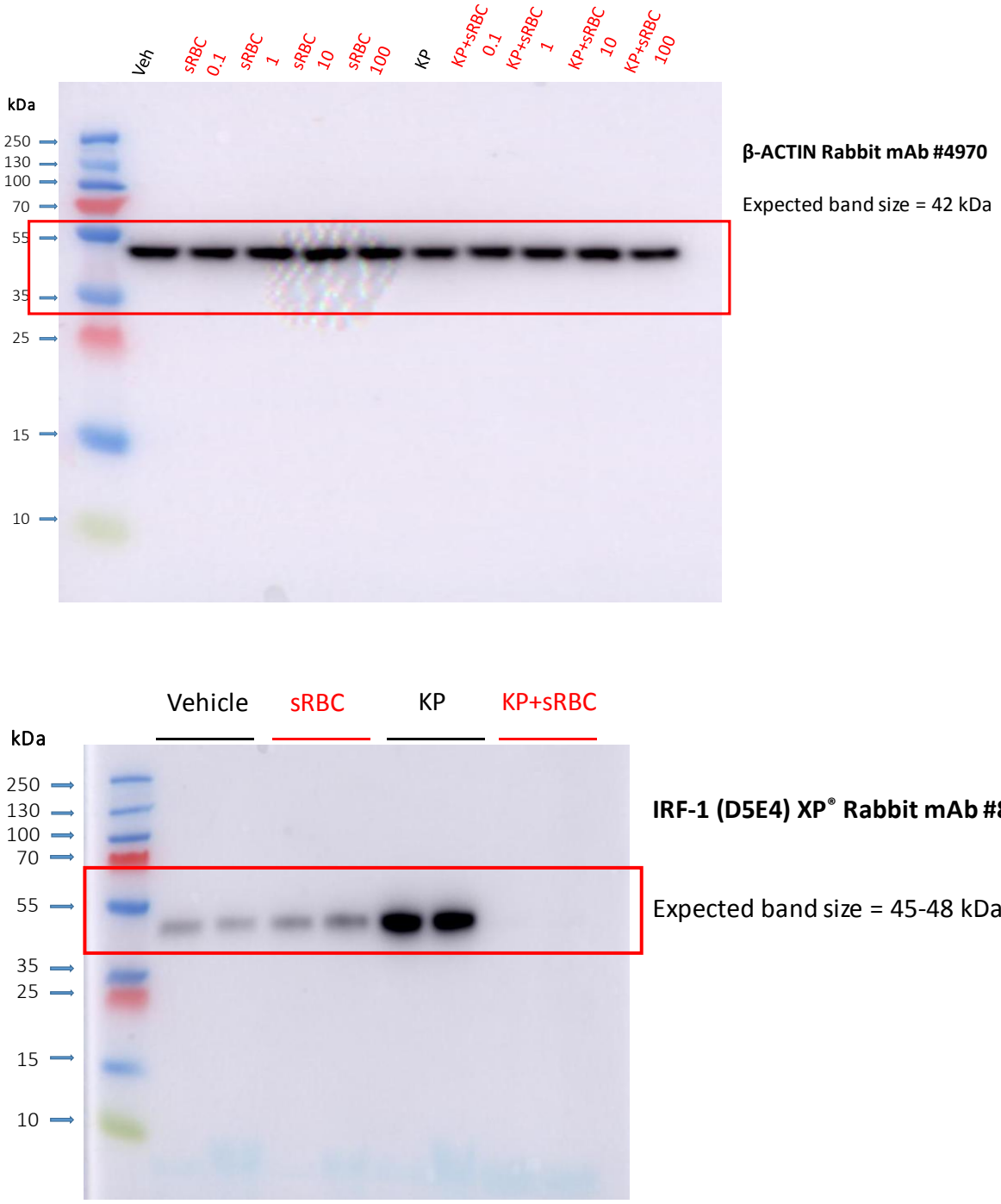
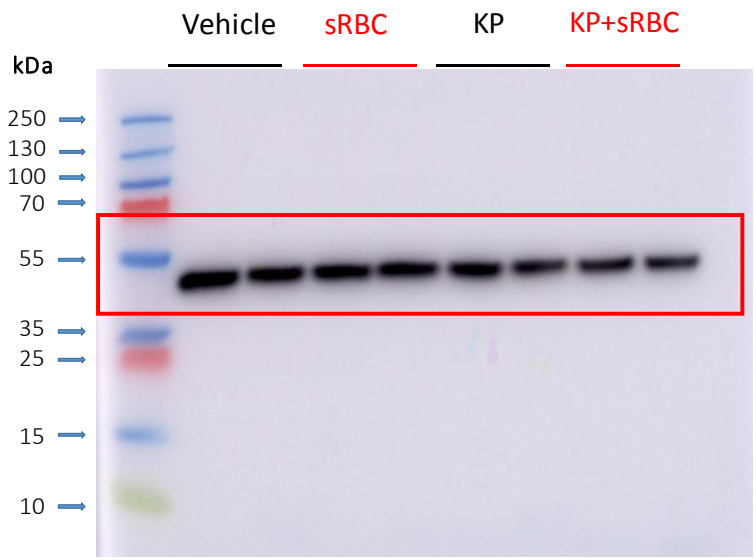


Figure 4G: Full unedited blots. Red rectangle indicates depicted image.



β-ACTIN Rabbit mAb

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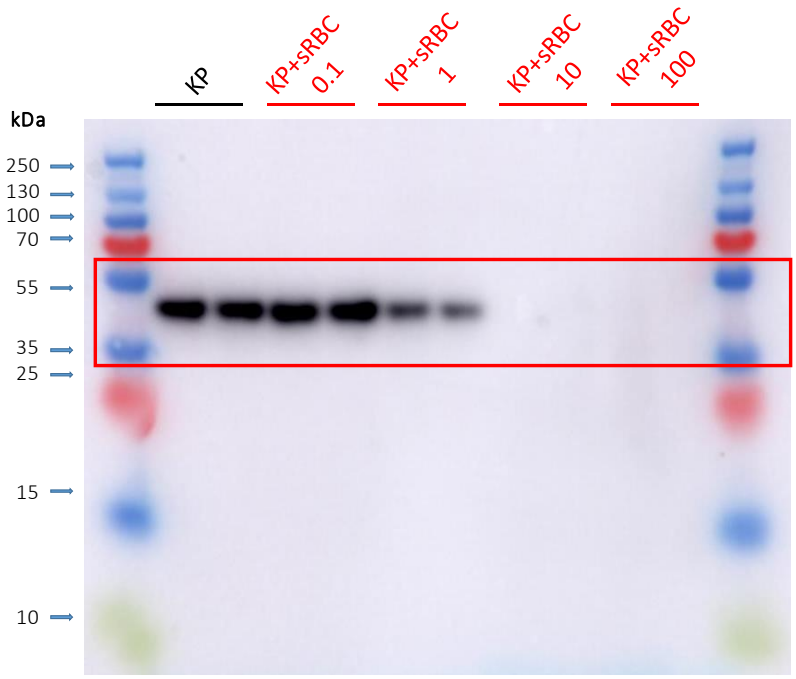

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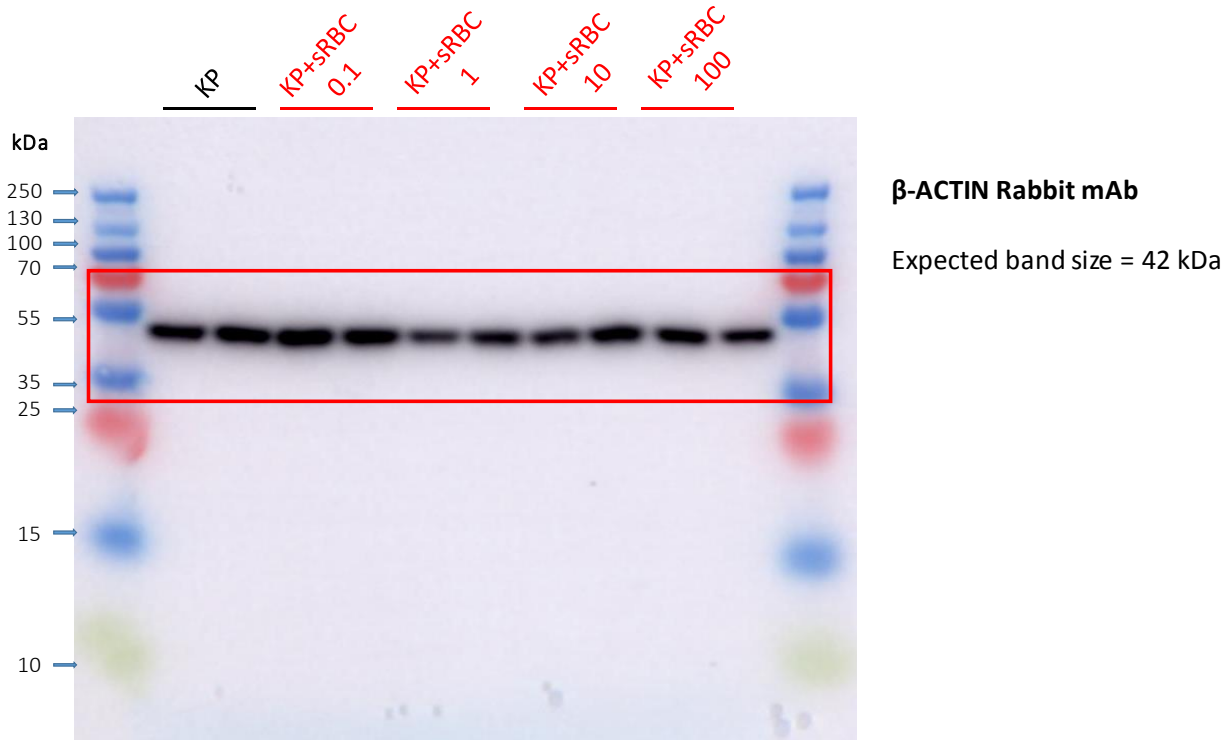
Expected band size = 45-48 kDa

Figure 4G: Full unedited blots. Red rectangle indicates depicted image.



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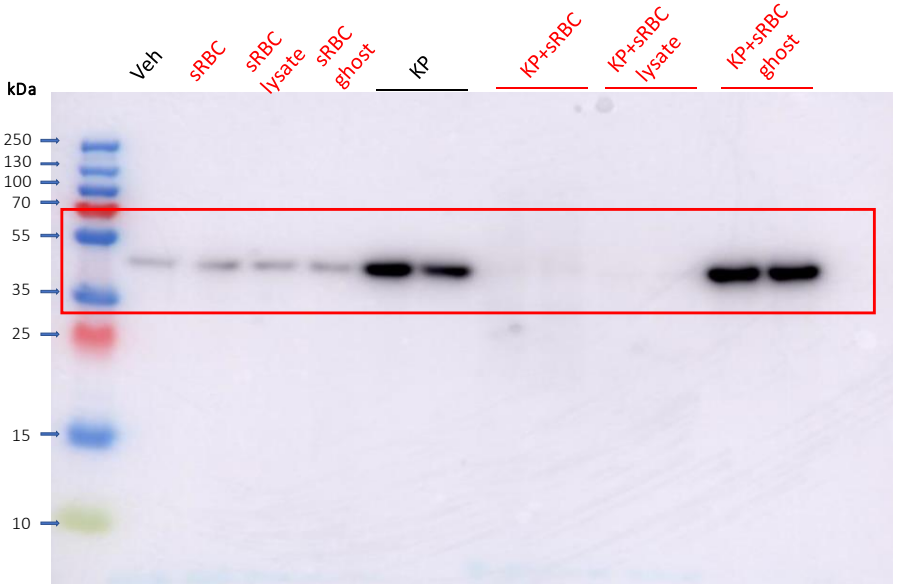

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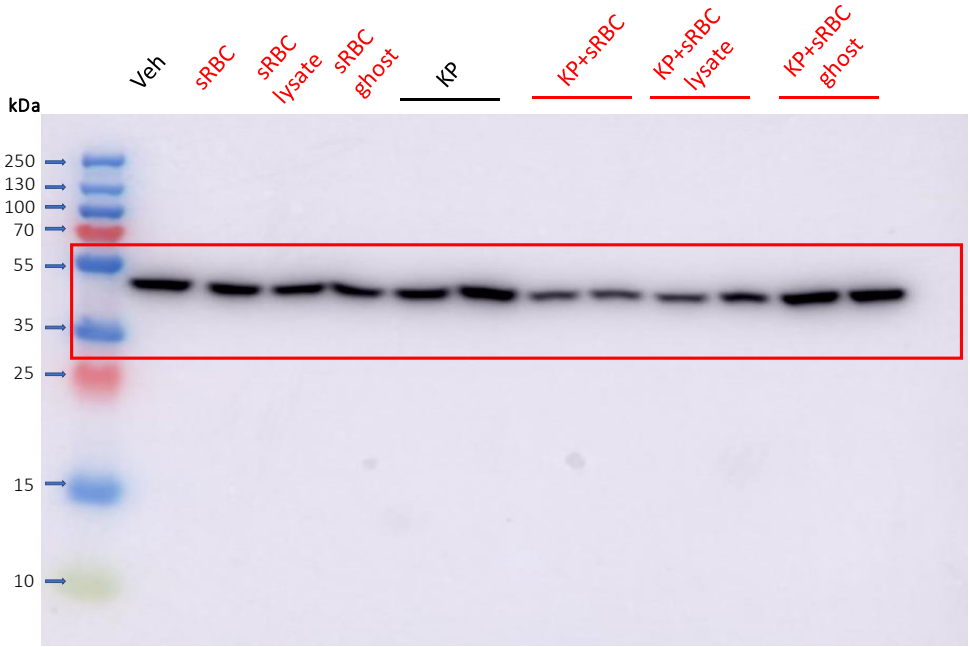
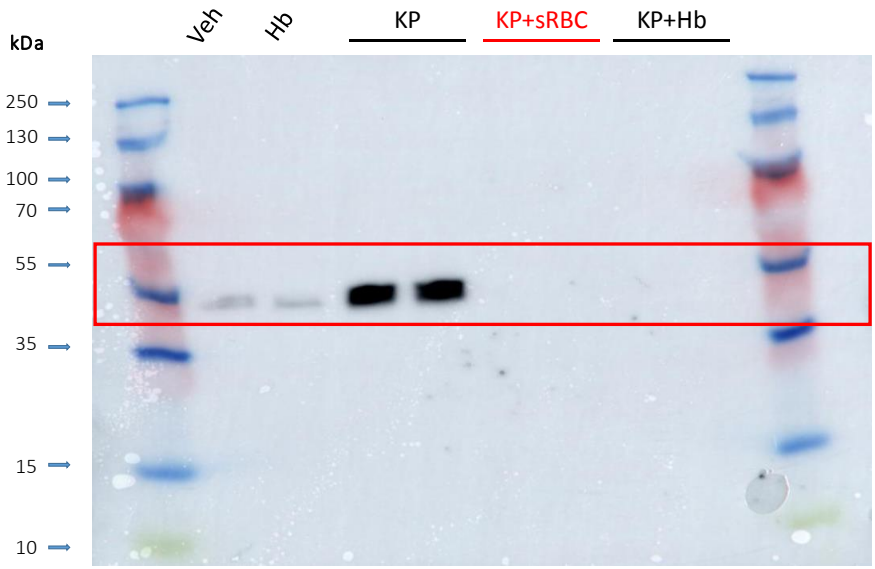


β-ACTIN Rabbit mAb

Expected band size = 42 kDa

Figure 5A: Full unedited blots. Red rectangle indicates depicted image.



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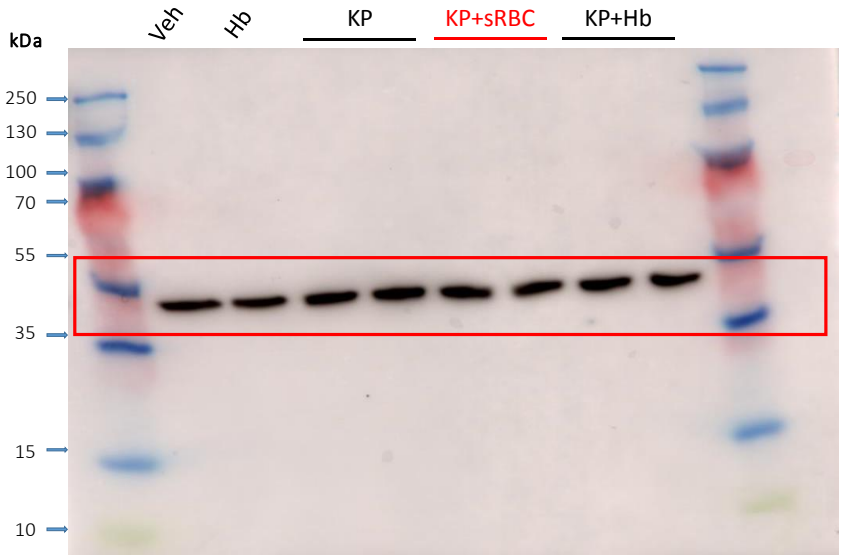

β-ACTIN Rabbit mAb

Expected band size = 42 kDa

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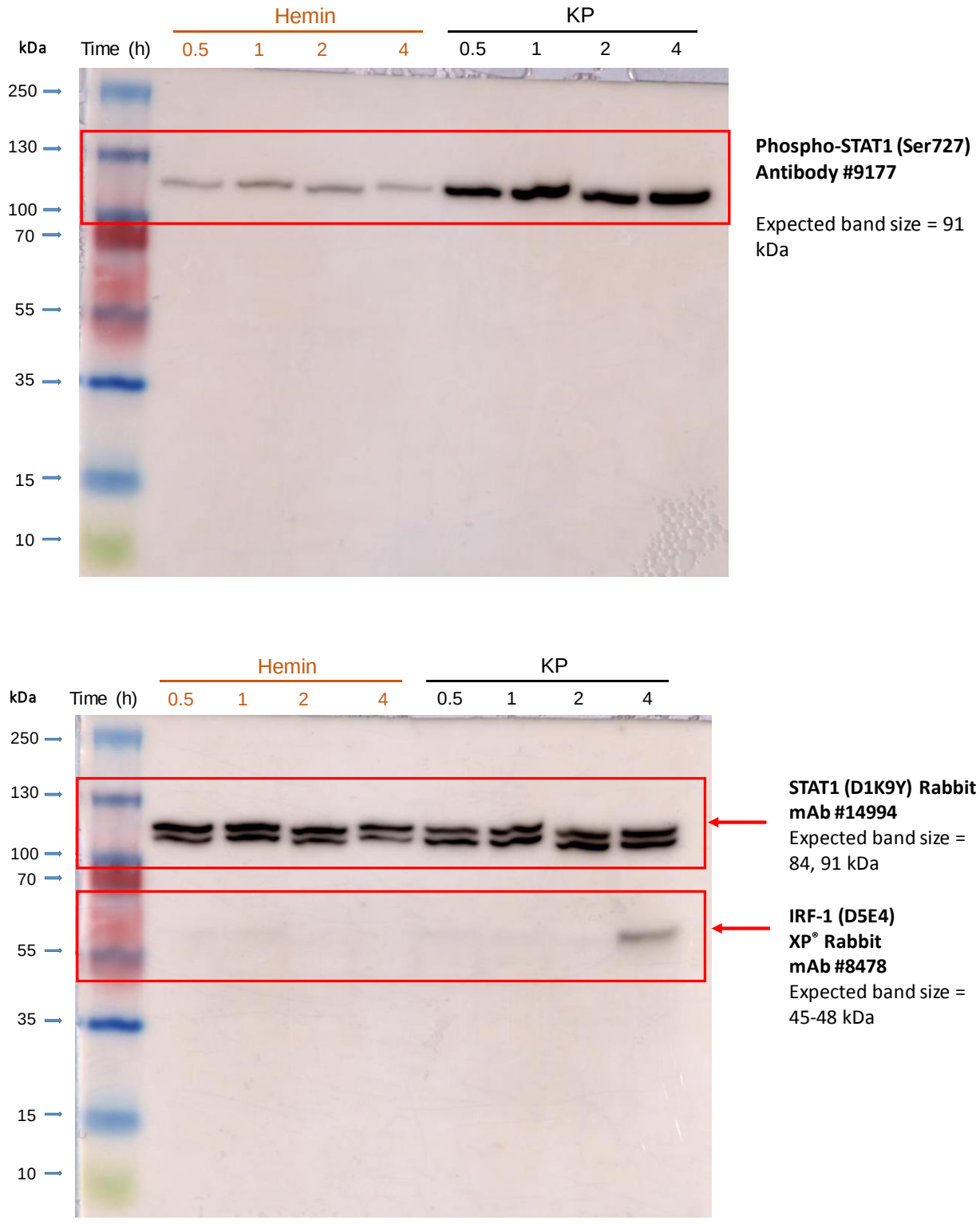
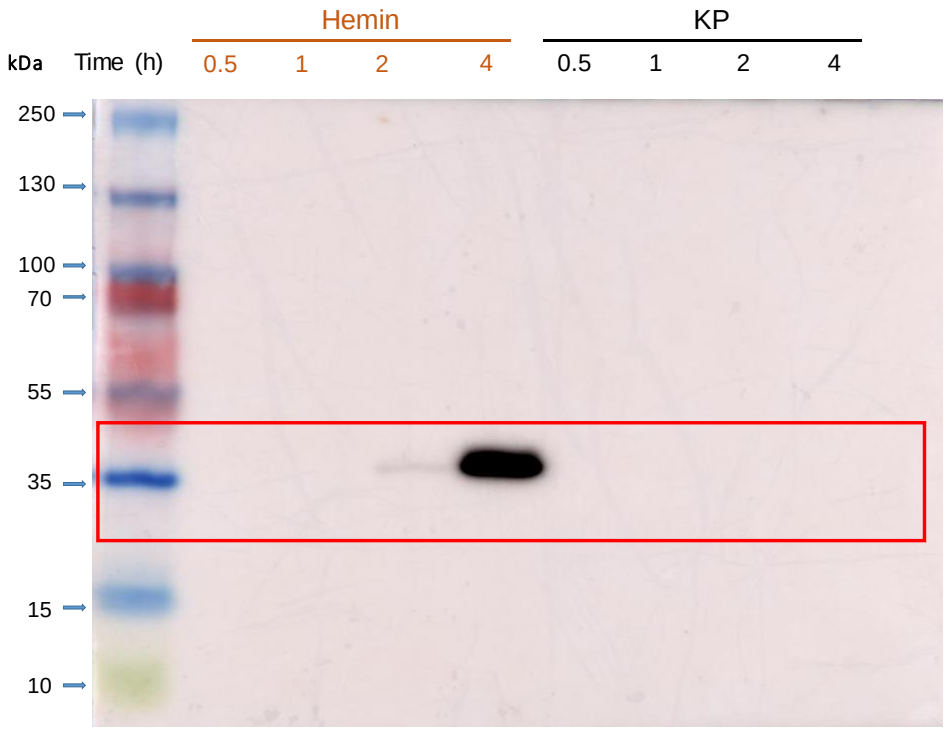


Figure 5C: Full unedited blots. Red rectangle indicates depicted image.



HO-1 Antibody (F-4): sc-390991

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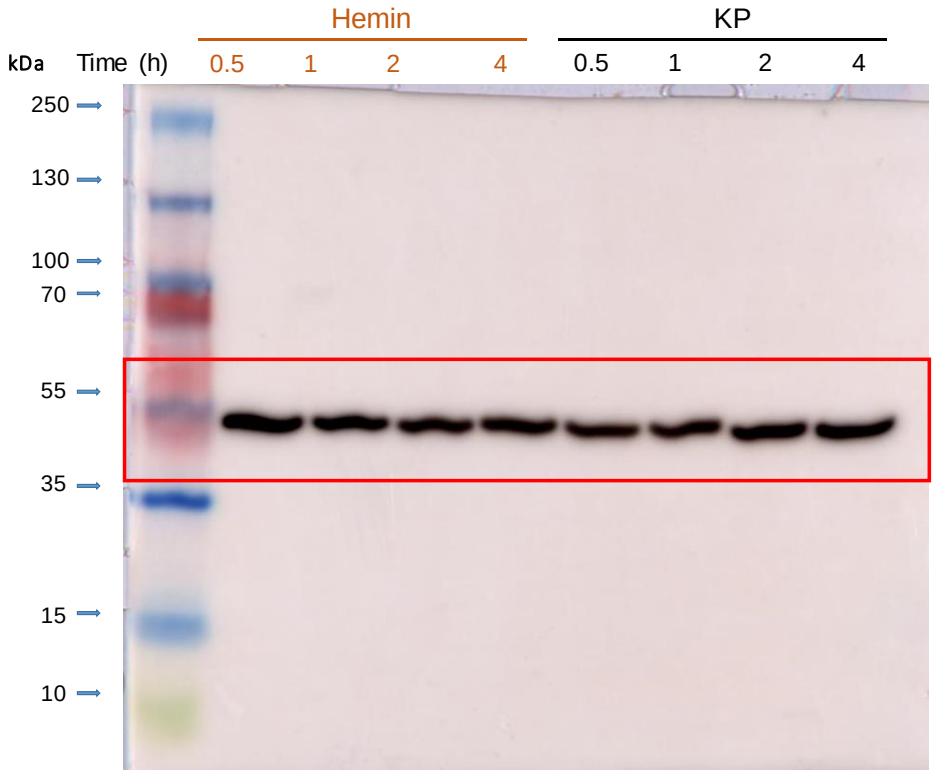
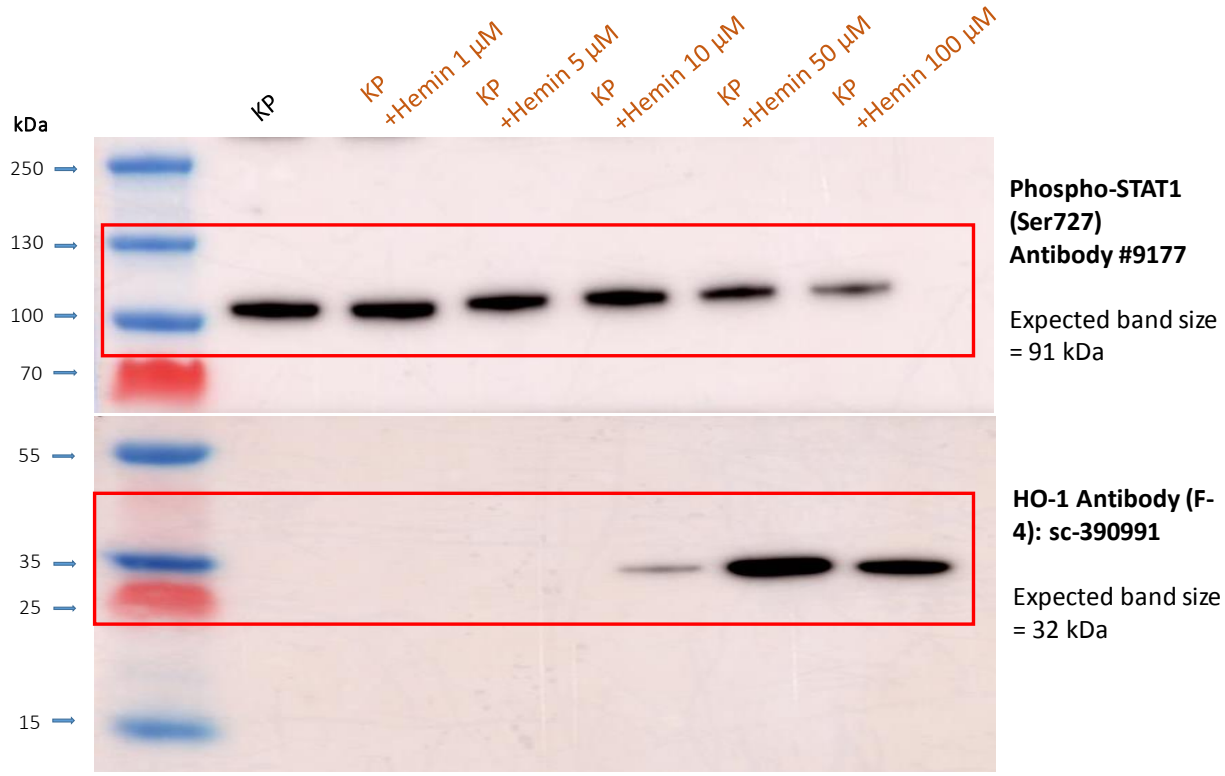


β-ACTIN Rabbit mAb

Expected band size = 42 kDa

Figure 5C: Full unedited blots. Red rectangle indicates depicted image.



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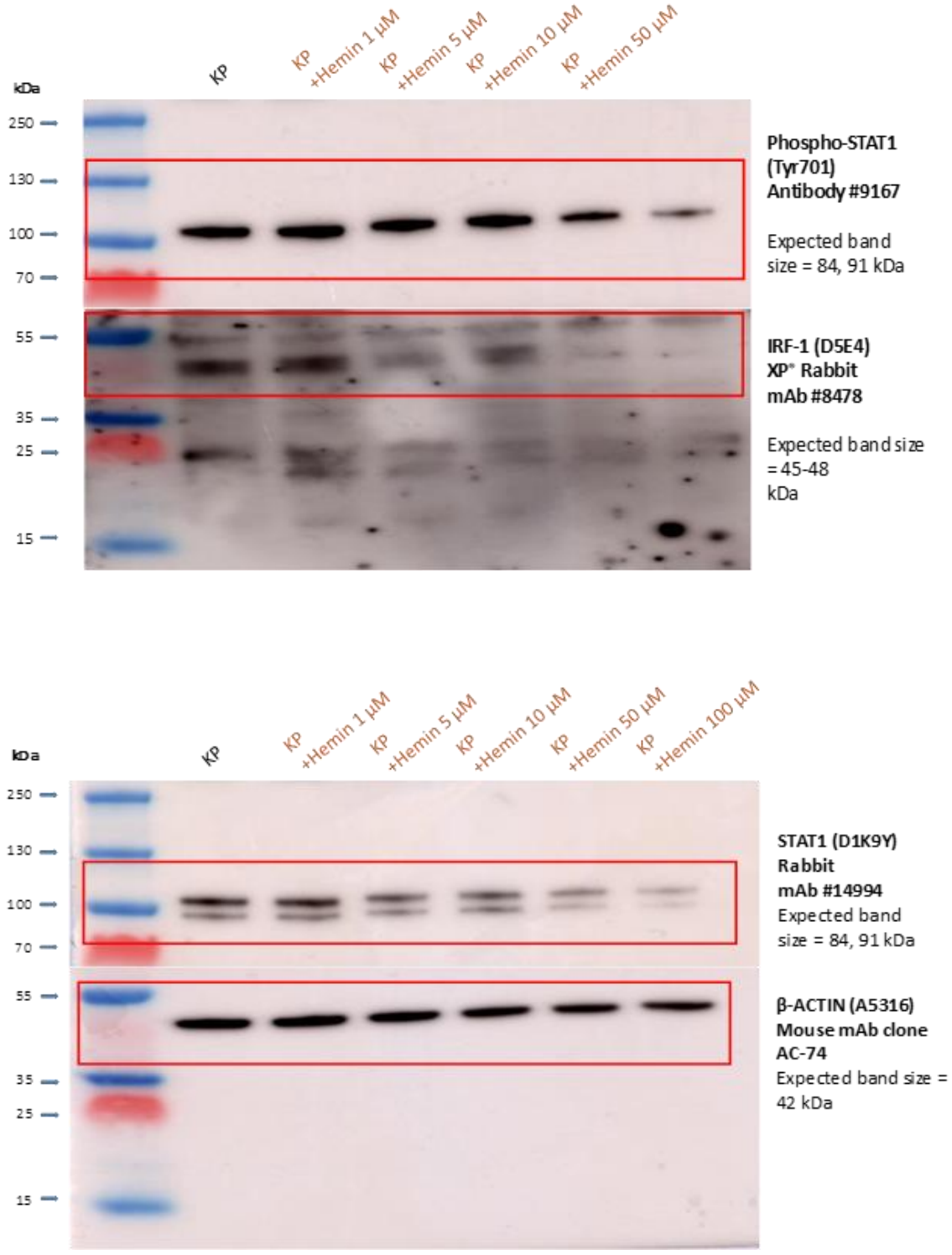

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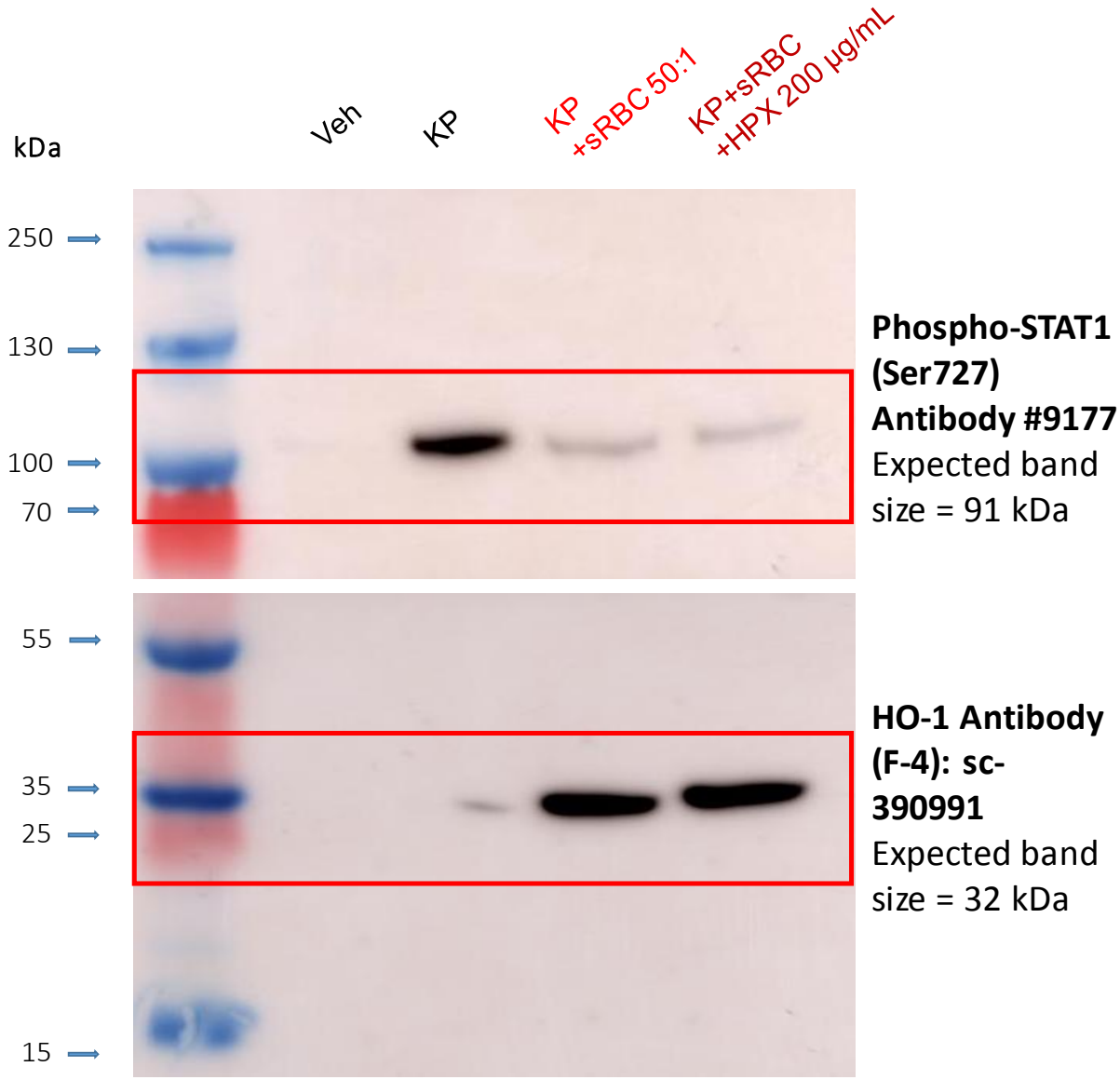

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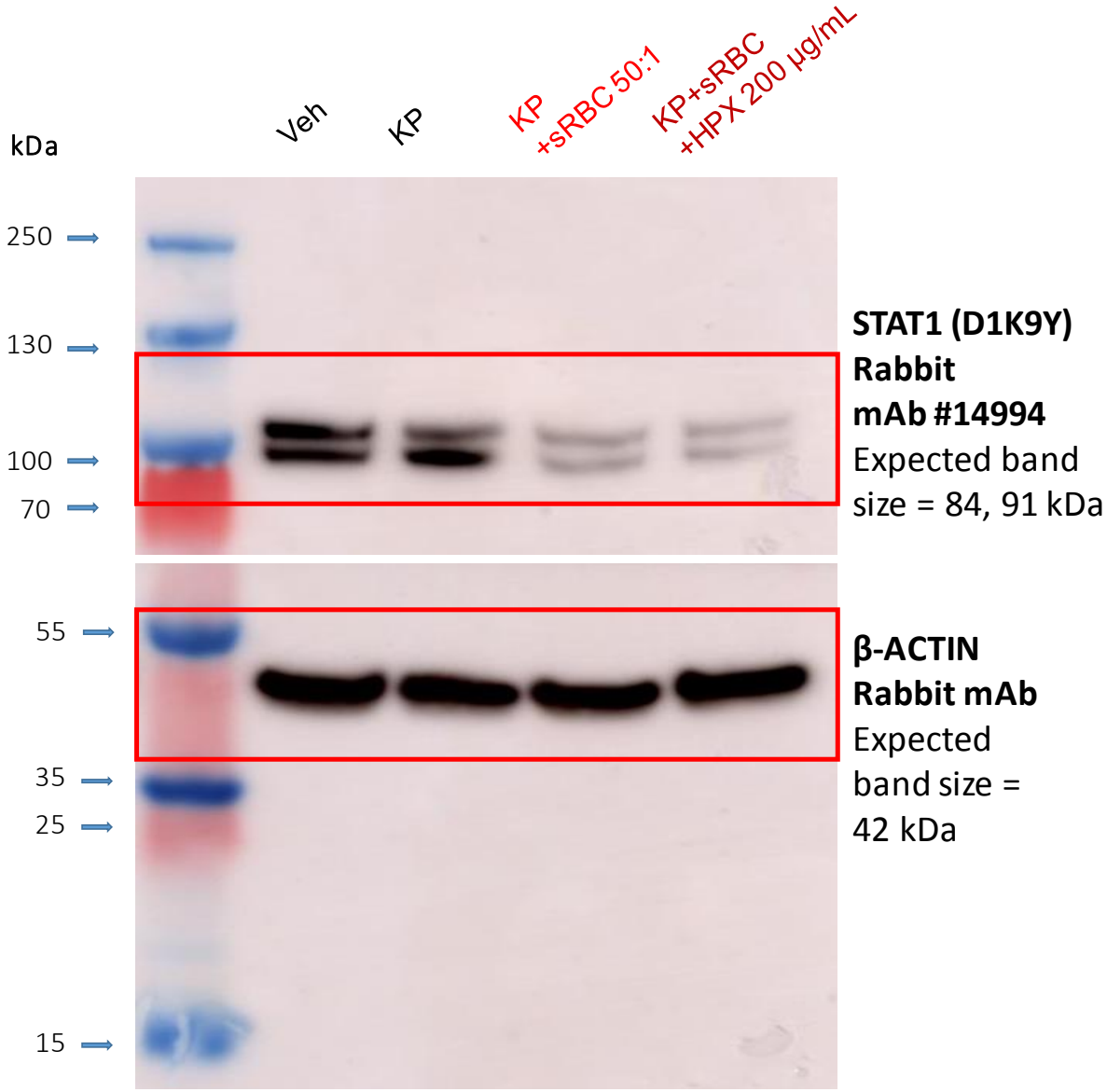

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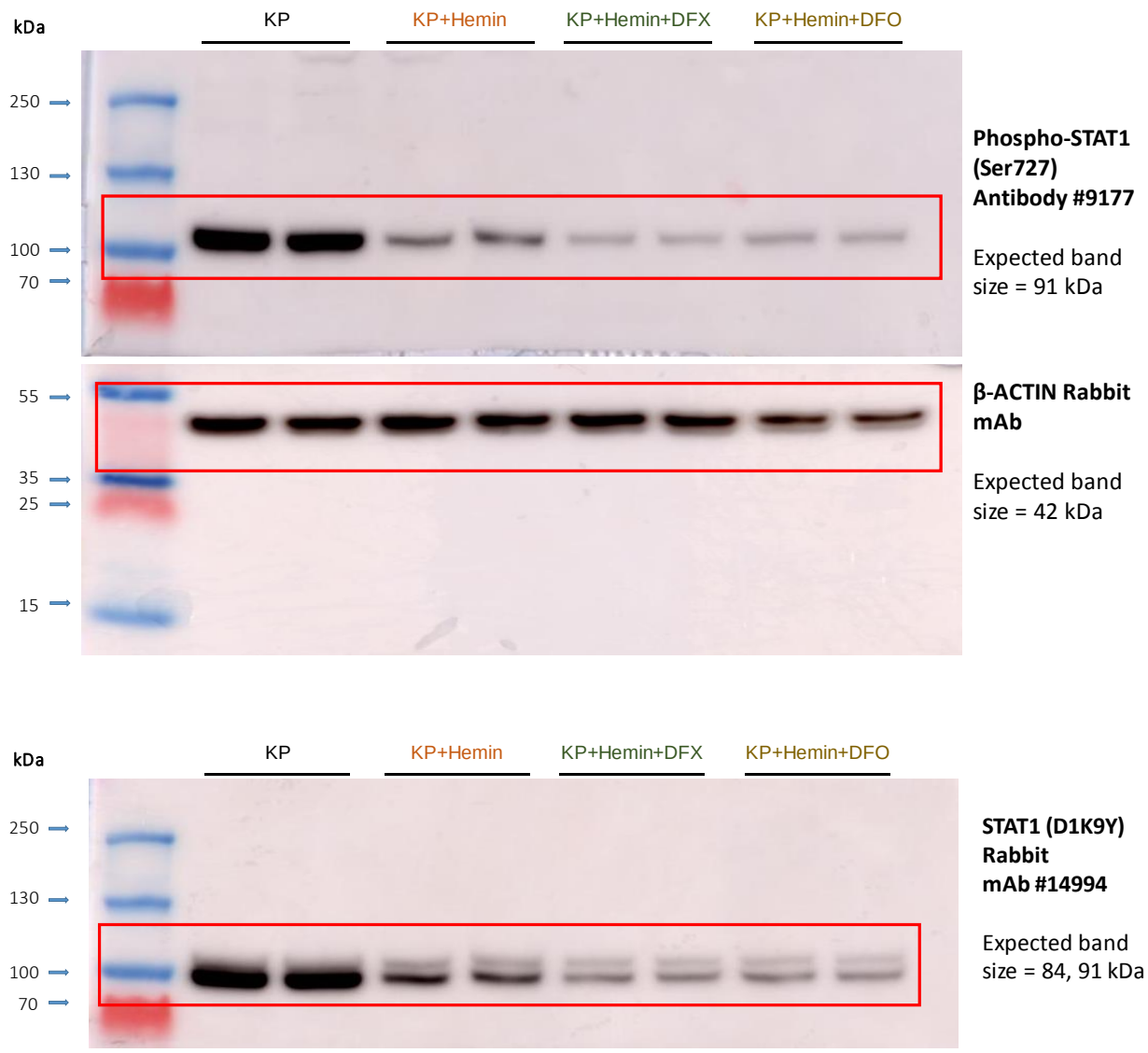


Figure 7A: Full unedited blots. Red rectangle indicates depicted image.

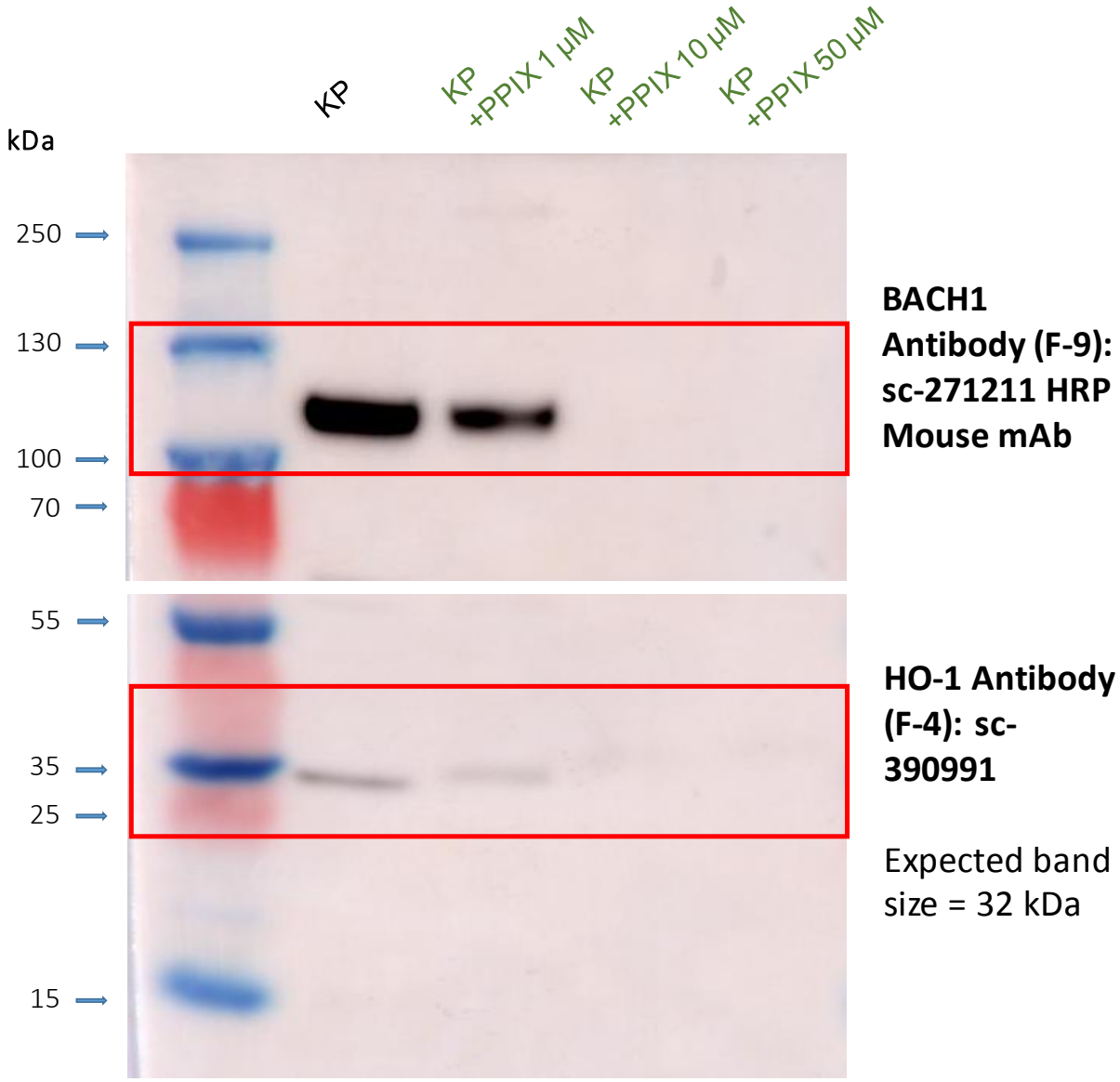
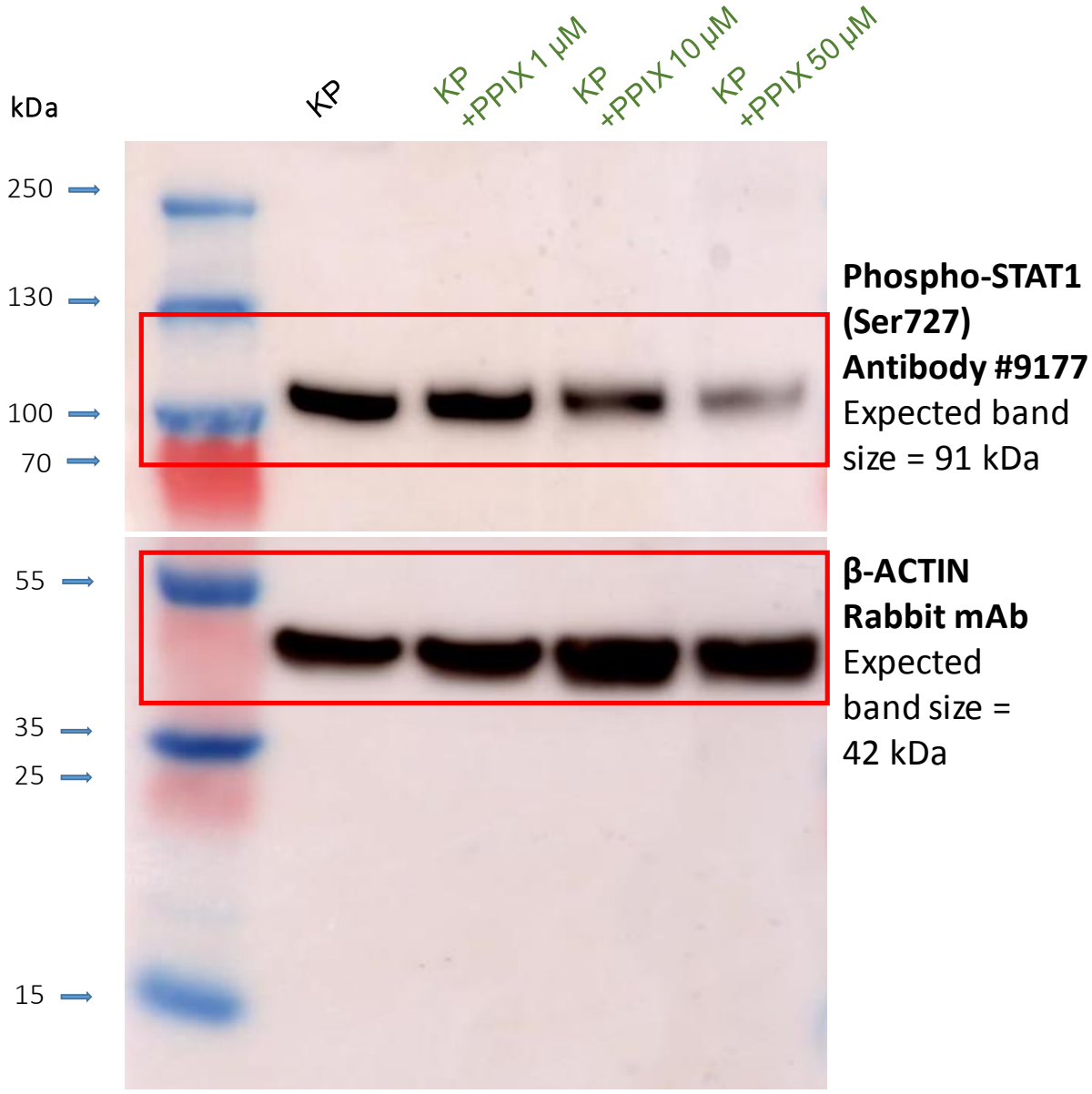


Figure 7G: Full unedited blots. Red rectangle indicates depicted image.



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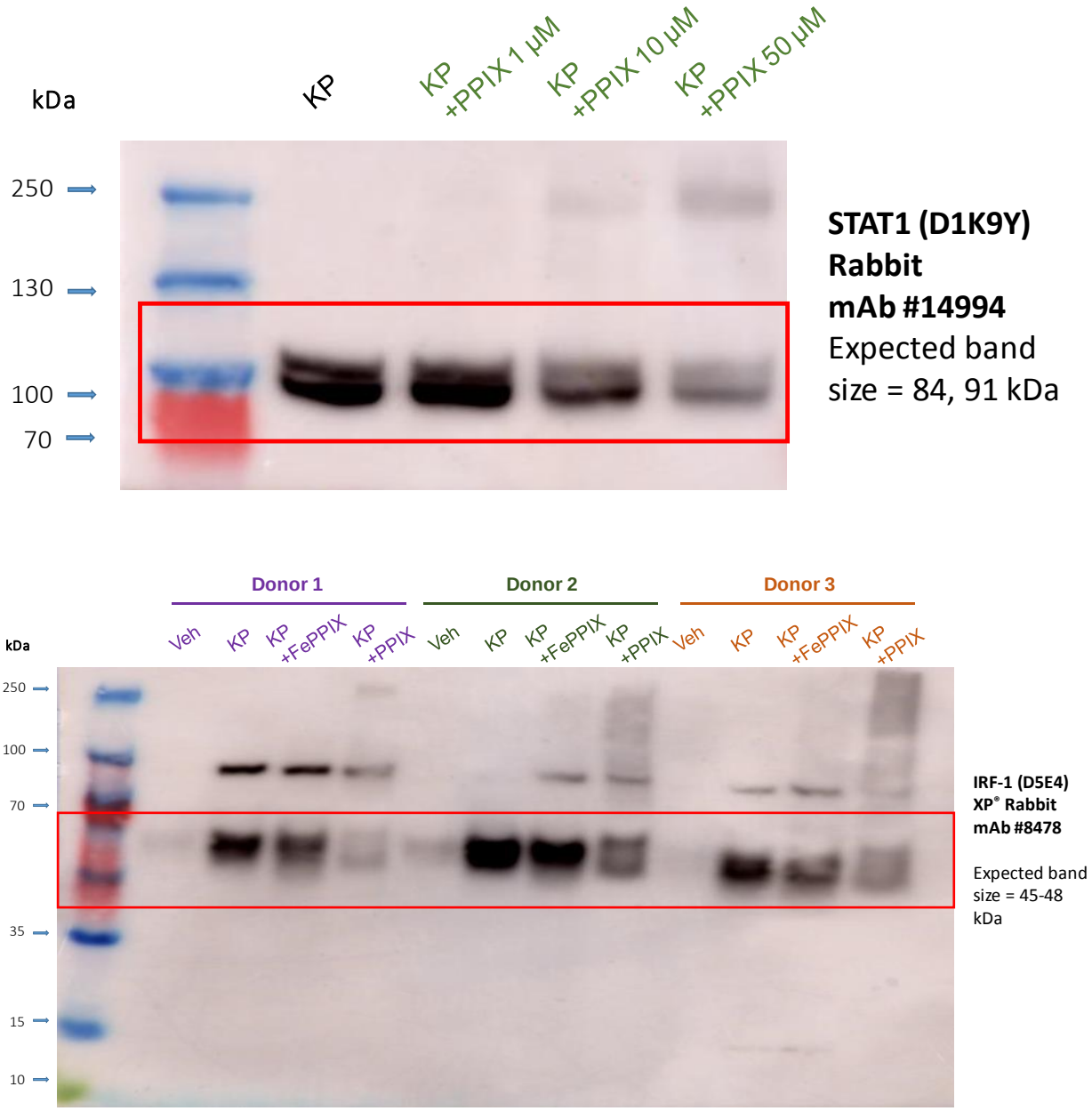
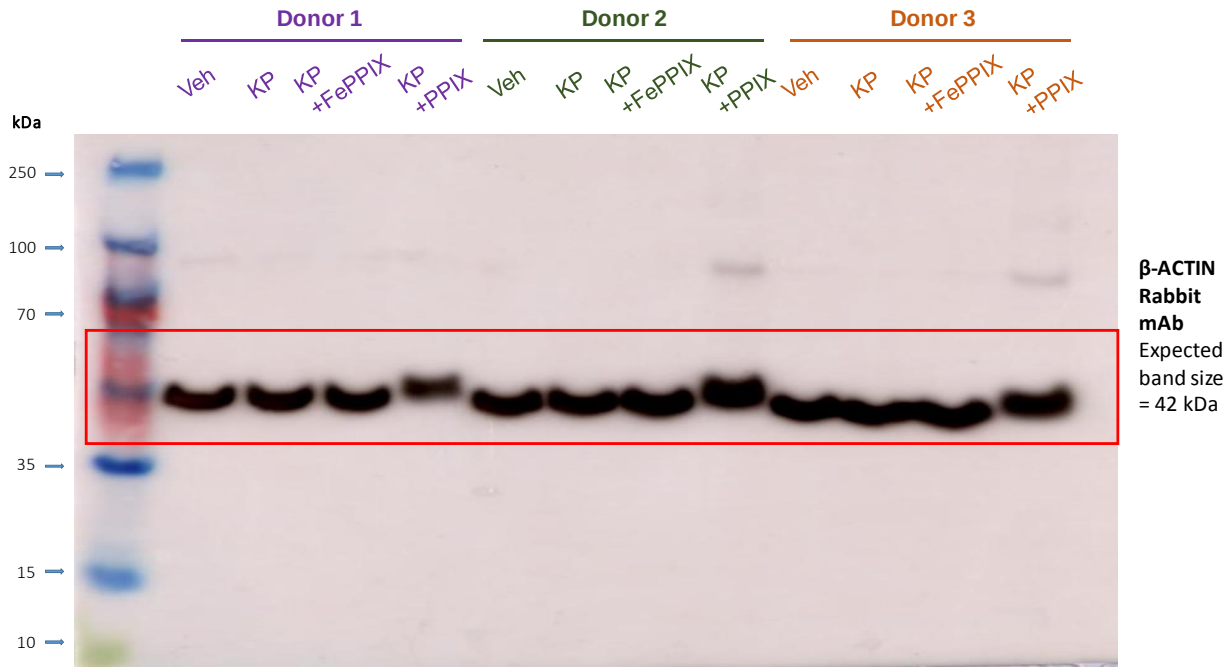


Figure 7H: Full unedited blots. Red rectangle indicates depicted image.



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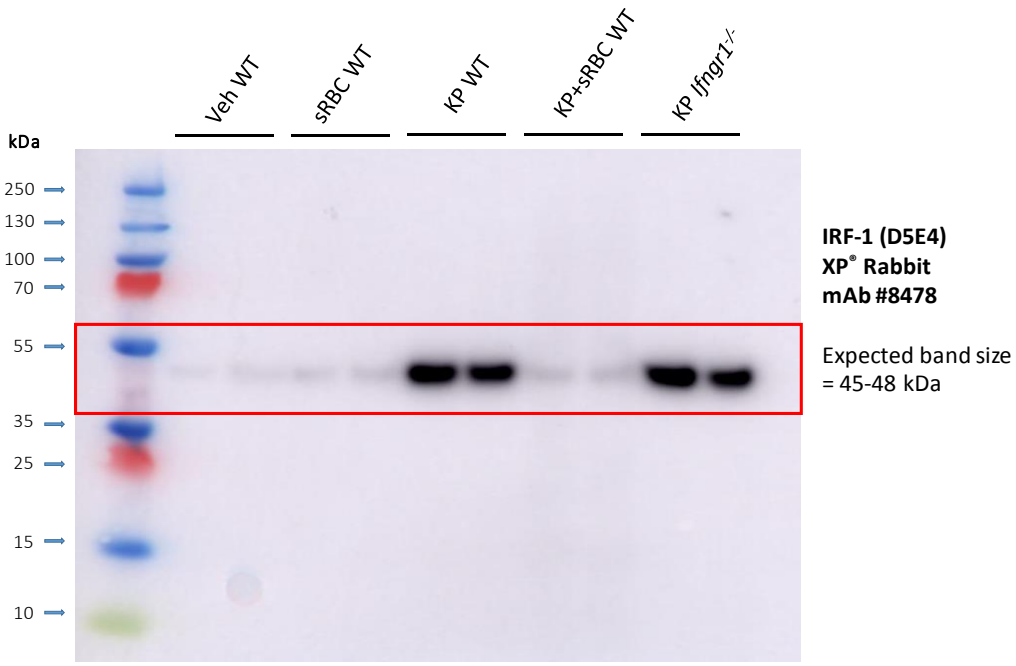
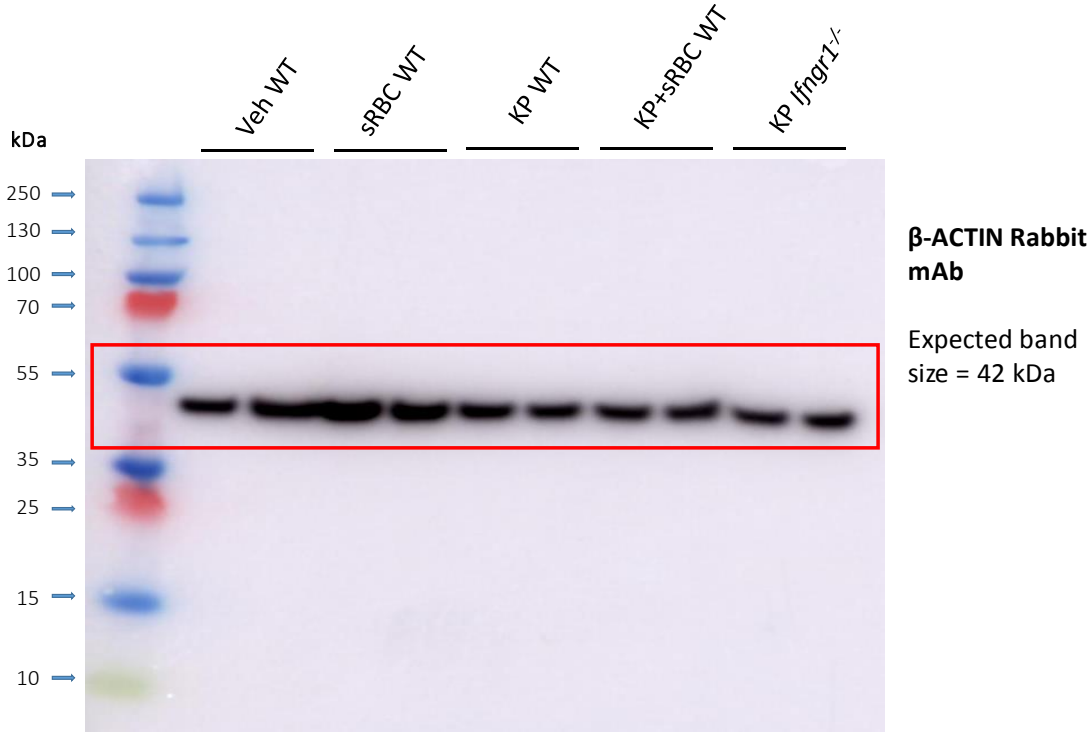
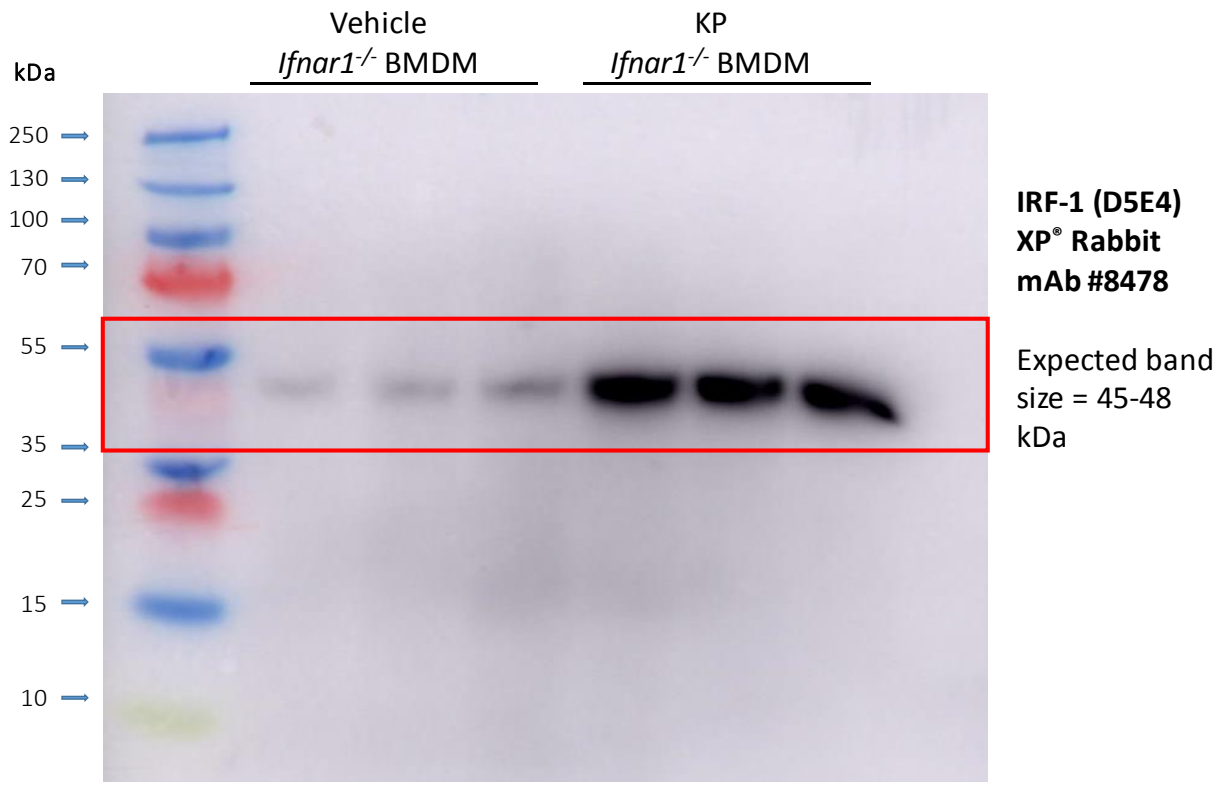
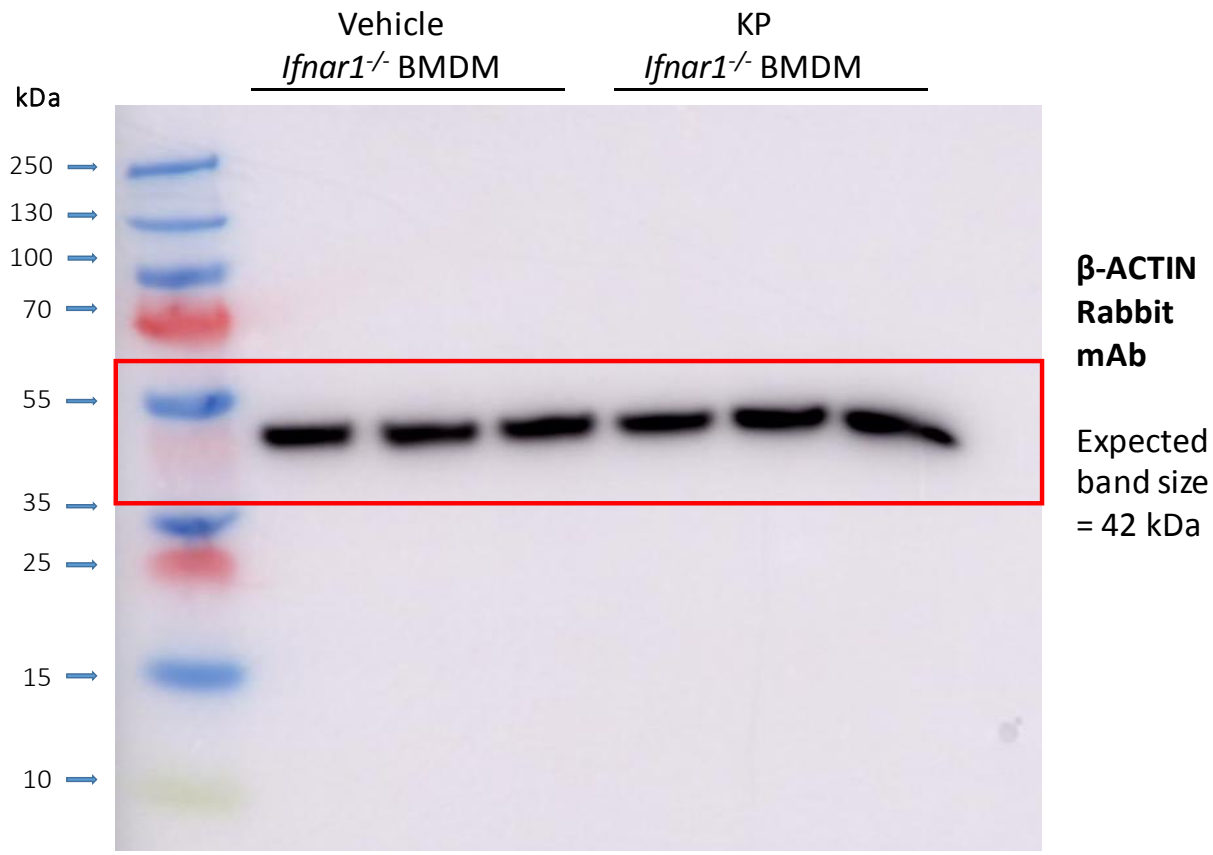




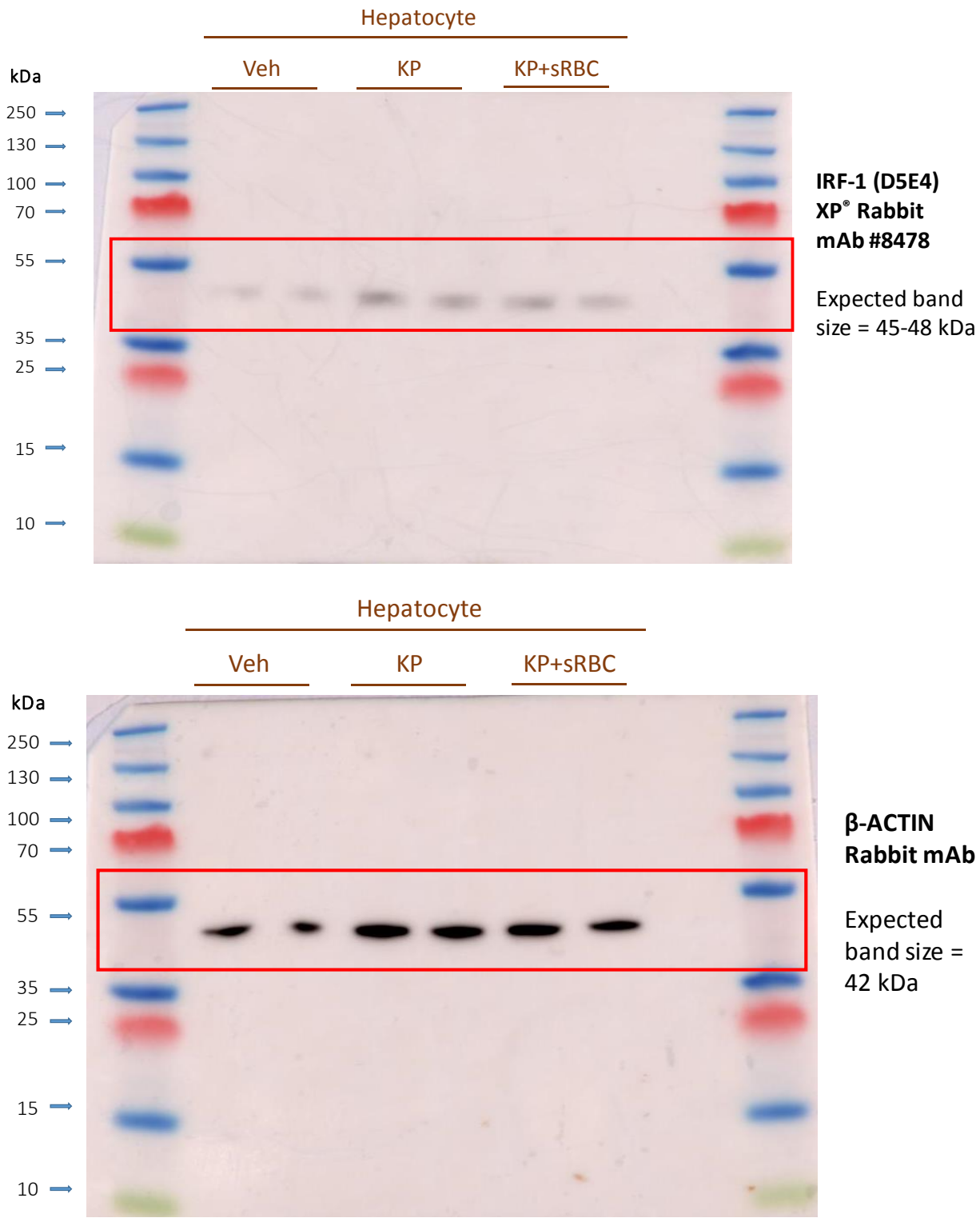
Supplemental Figure S7B: Full unedited blots. Red rectangle indicates depicted image.



Supplemental Figure S7C: Full unedited blots. Red rectangle indicates depicted image.

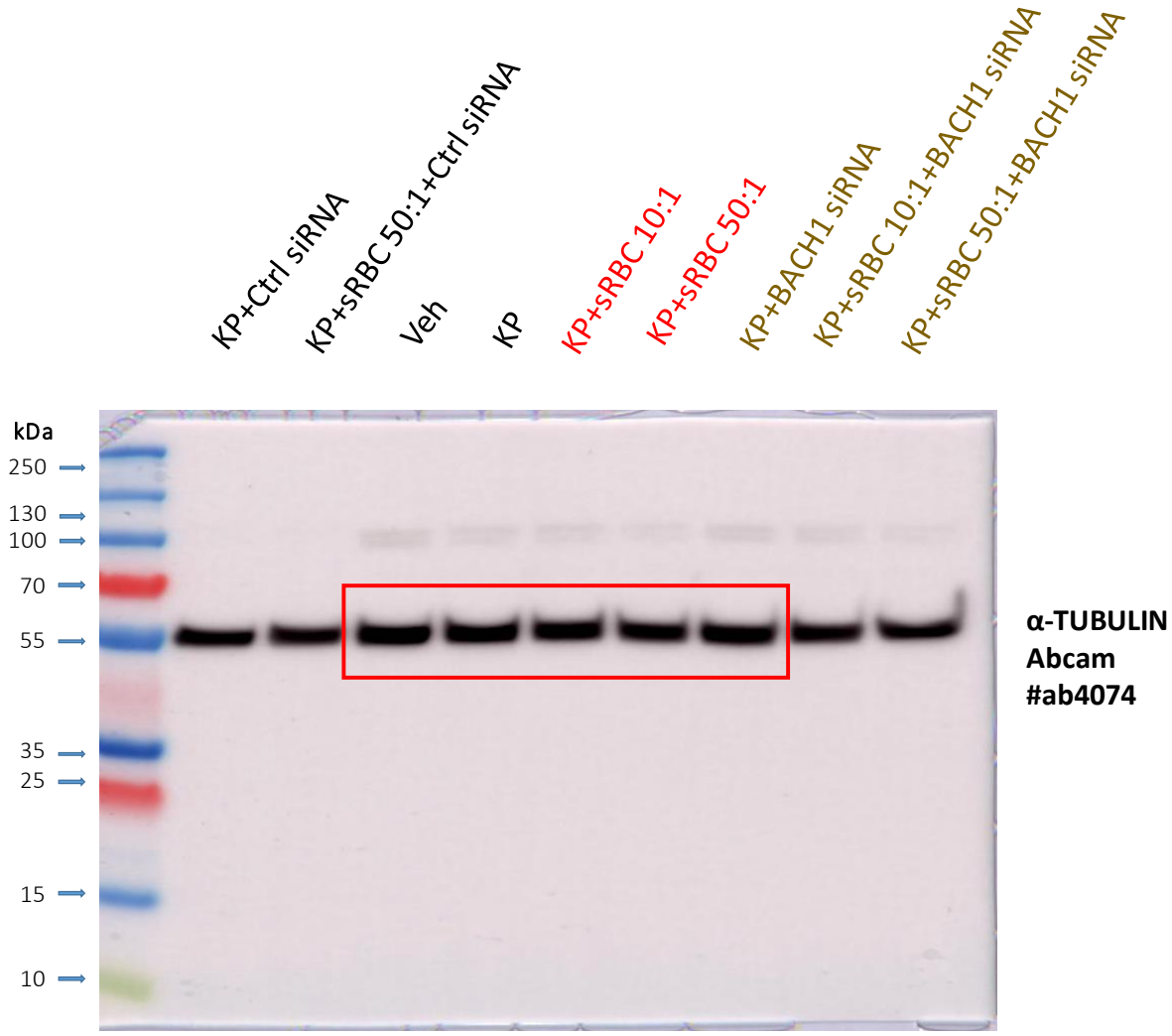


Supplemental Figure S7C: Full unedited blots. Red rectangle indicates depicted image.

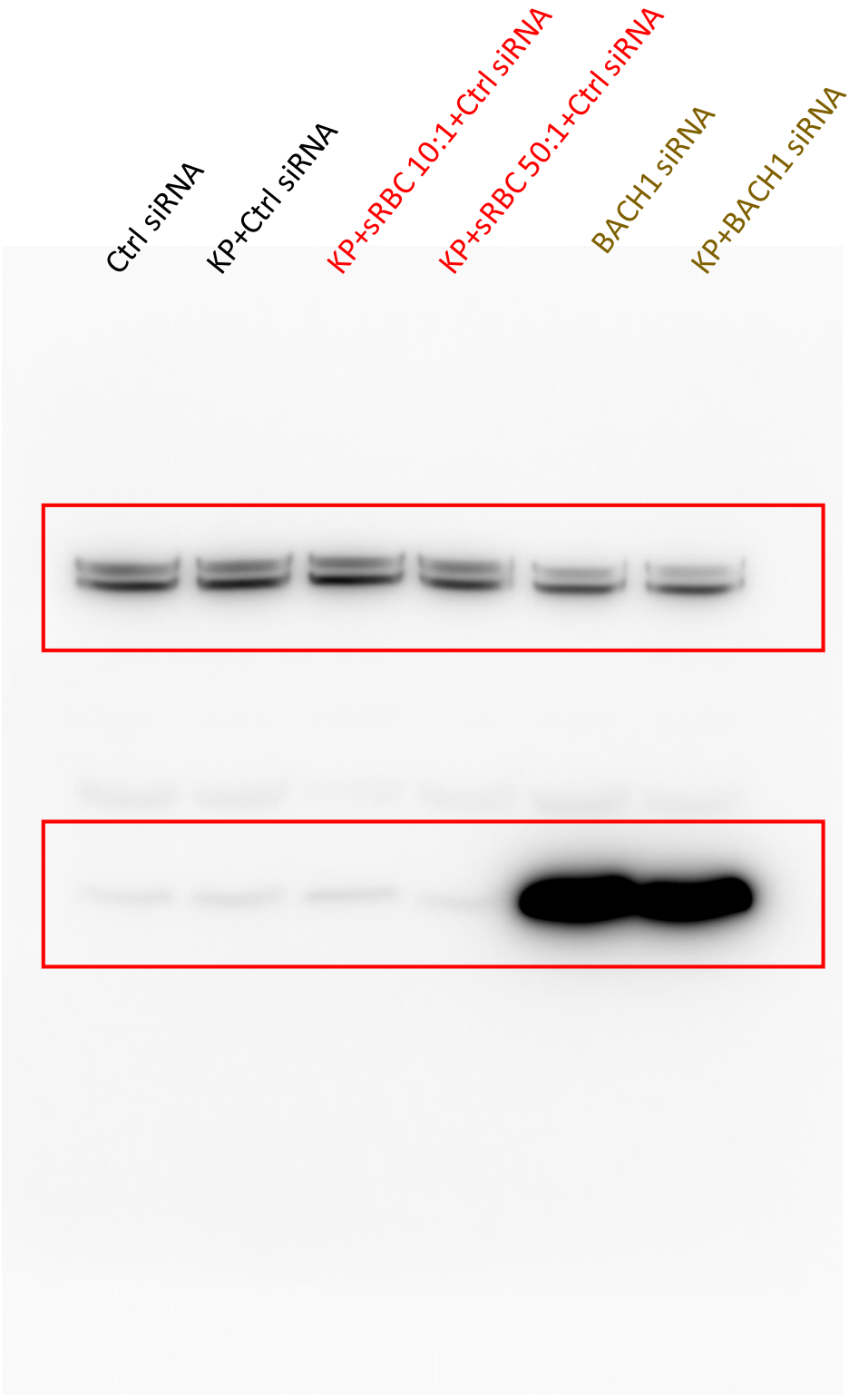


Supplemental Figure S7D: Full unedited blots. Red rectangle indicates depicted image.

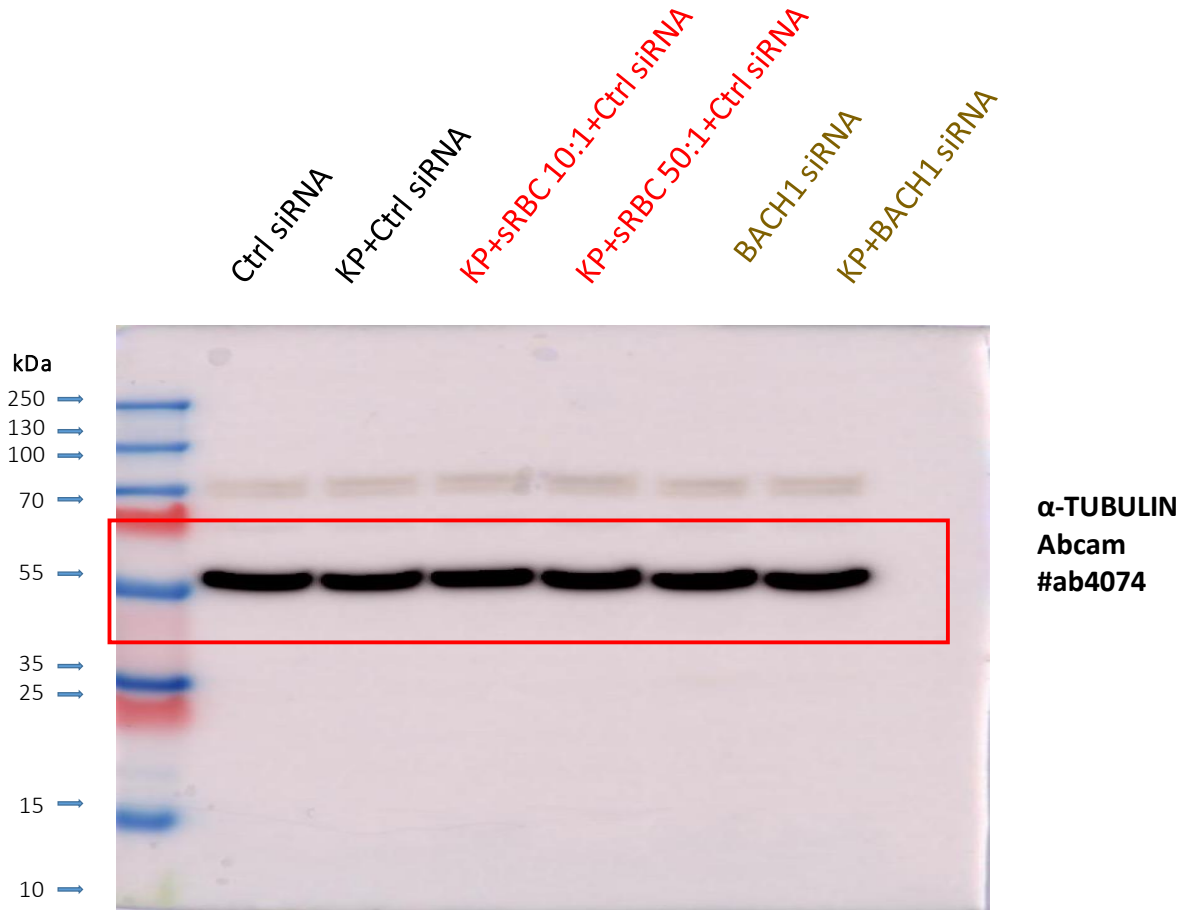
Supplemental Figure S9A: Full unedited blots. Red rectangle indicates depicted image.



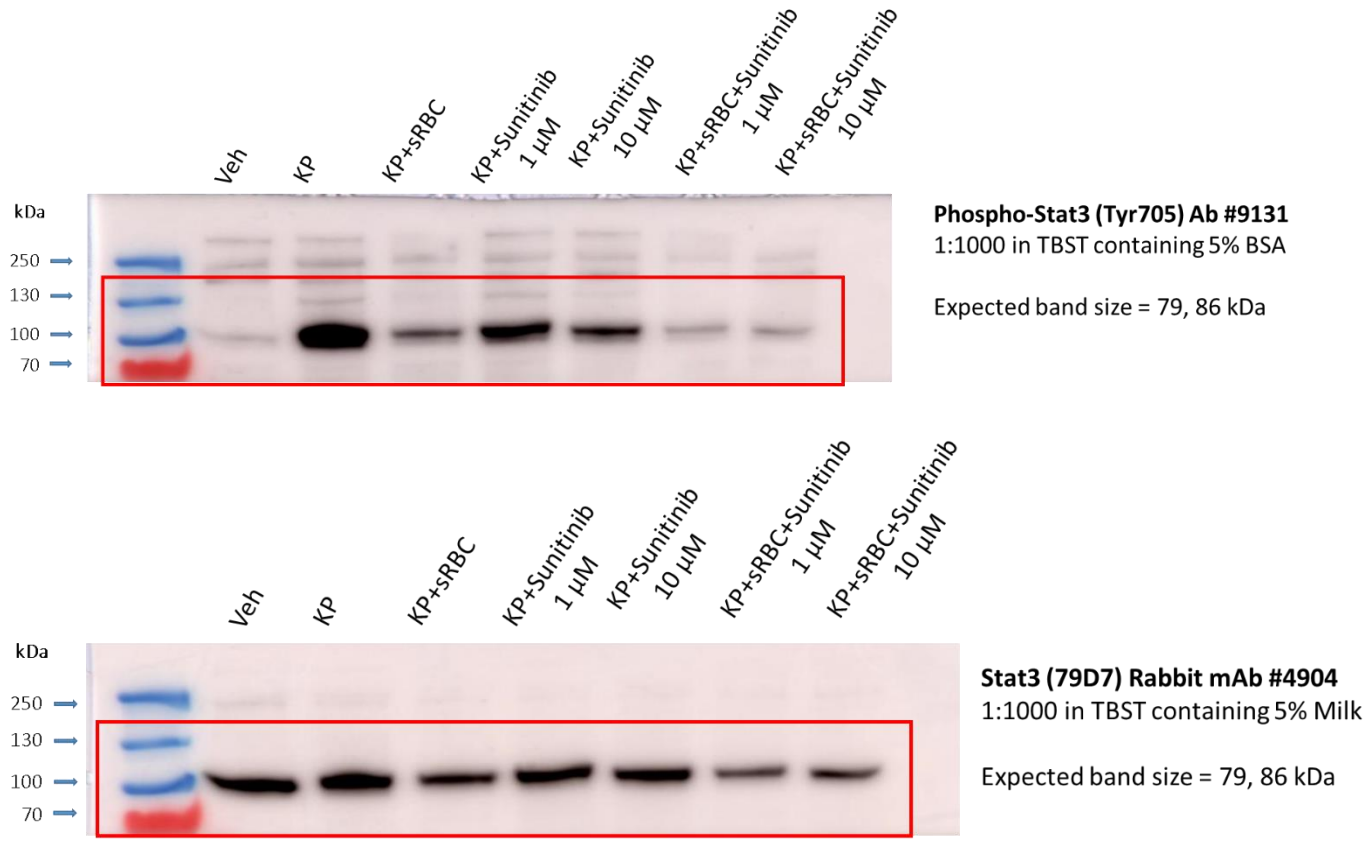
Supplemental Figure S9A: Full unedited blots. Red rectangle indicates depicted image.



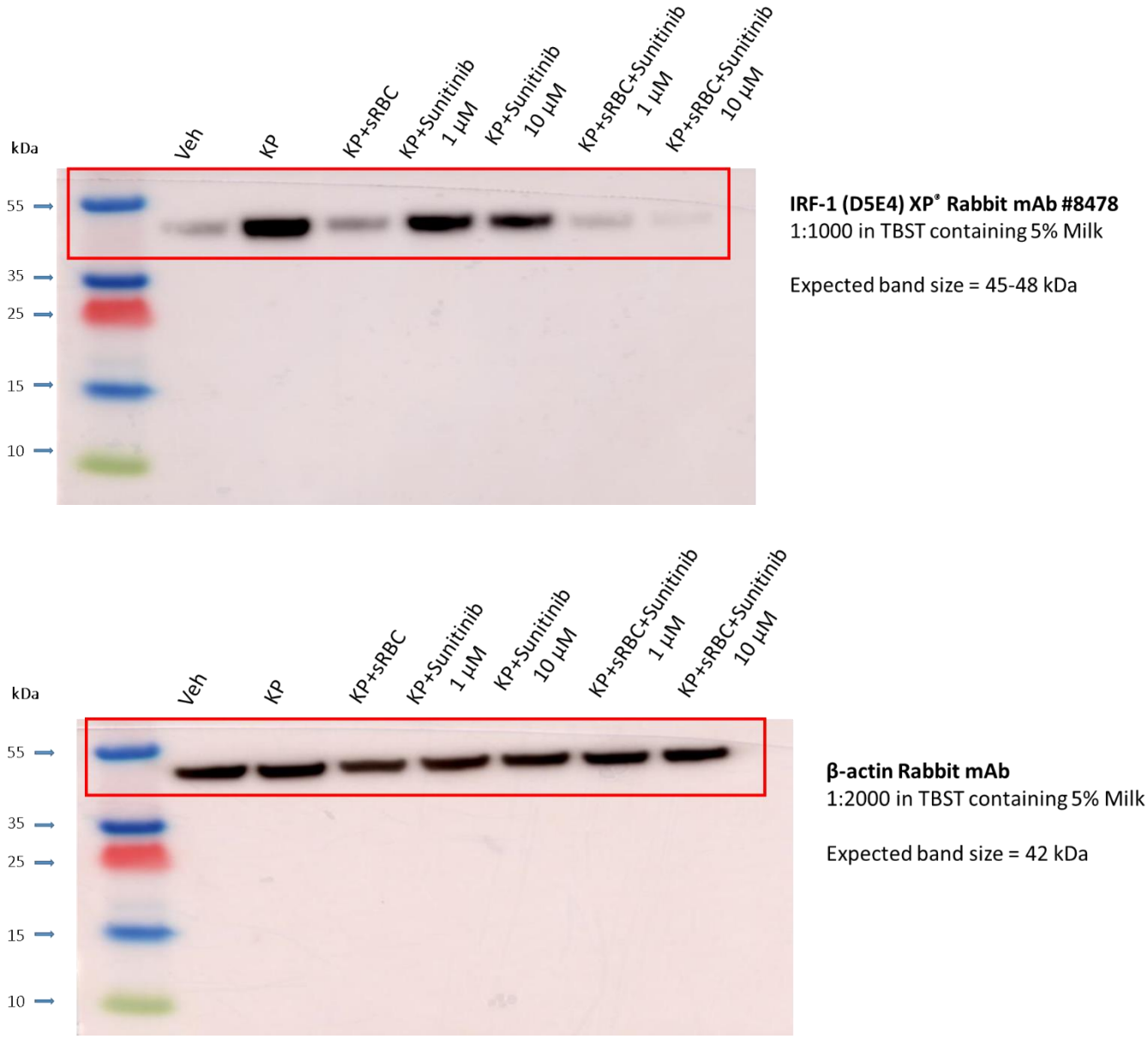
Supplemental Figure S9C: Full unedited blots. Red rectangle indicates depicted image.



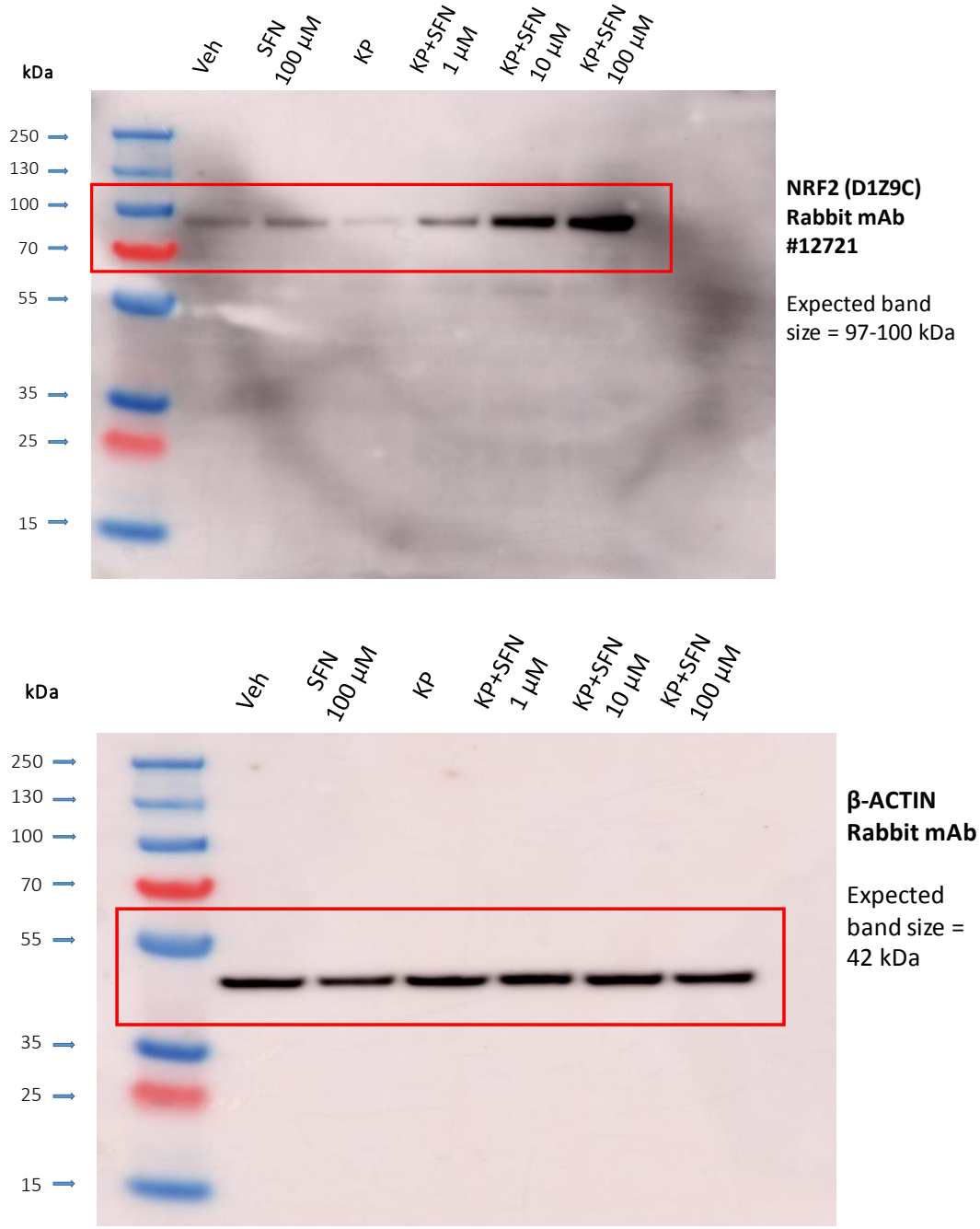
Supplemental Figure S9C: Full unedited blots. Red rectangle indicates depicted image.



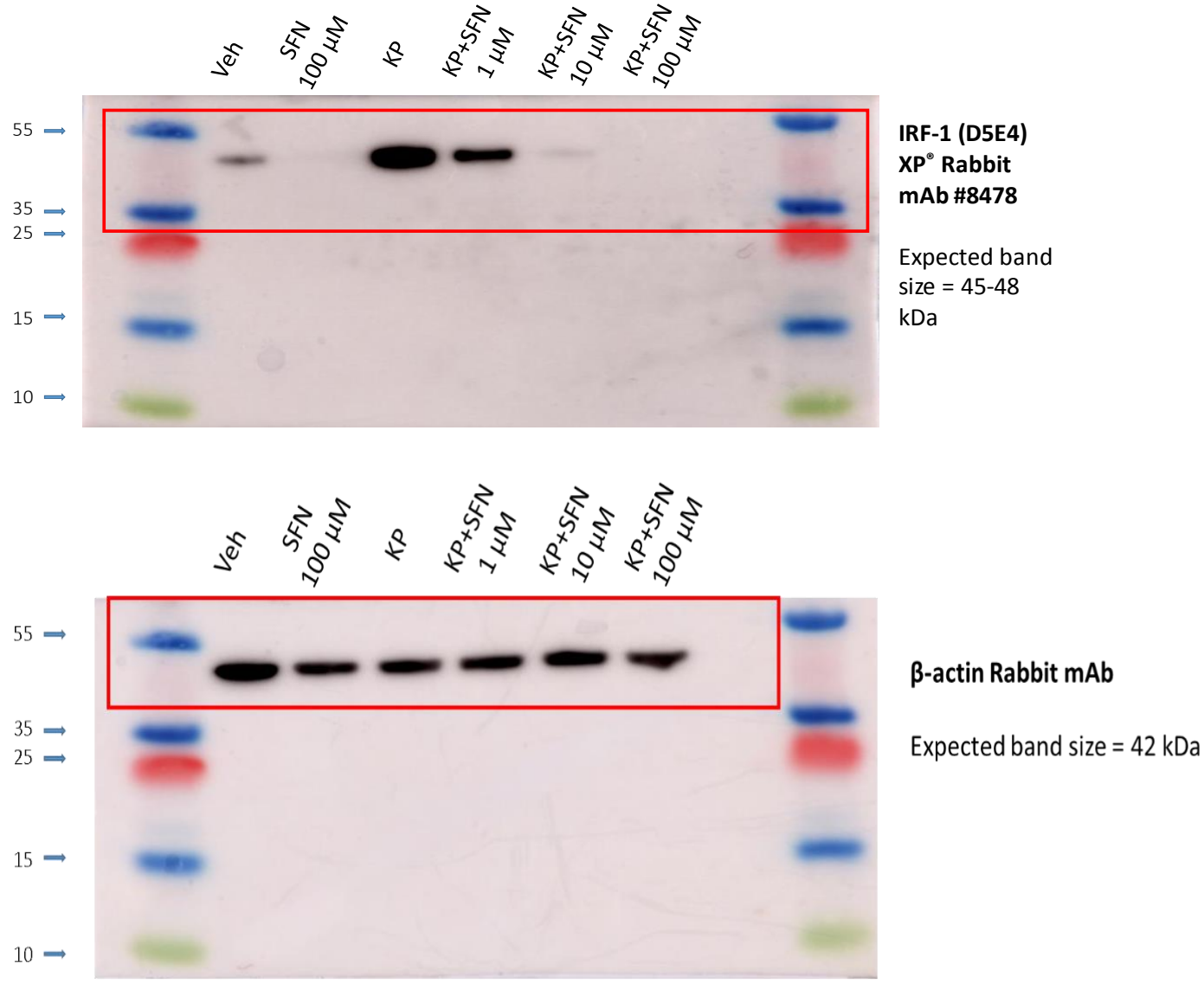
Supplemental Figure S9F: Full unedited blots. Red rectangle indicates depicted image.



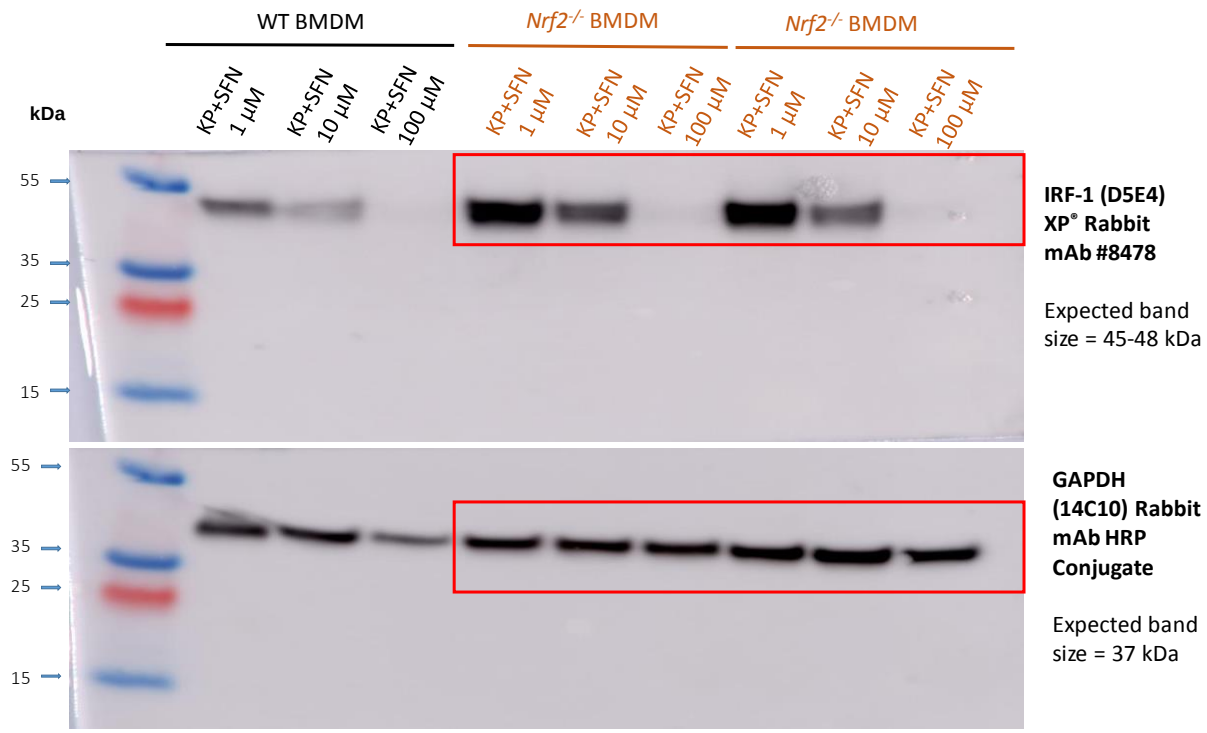
Supplemental Figure S9F: Full unedited blots. Red rectangle indicates depicted image.



Supplemental Figure S10C: Full unedited blots. Red rectangle indicates depicted image.



Supplemental Figure S10D: Full unedited blots. Red rectangle indicates depicted image.



Supplemental Figure S10G: Full unedited blots. Red rectangle indicates depicted image.