Supplementary Figure 1

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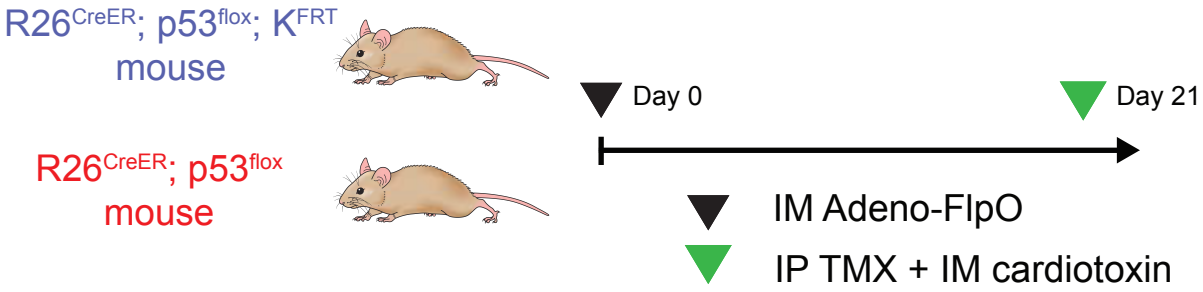

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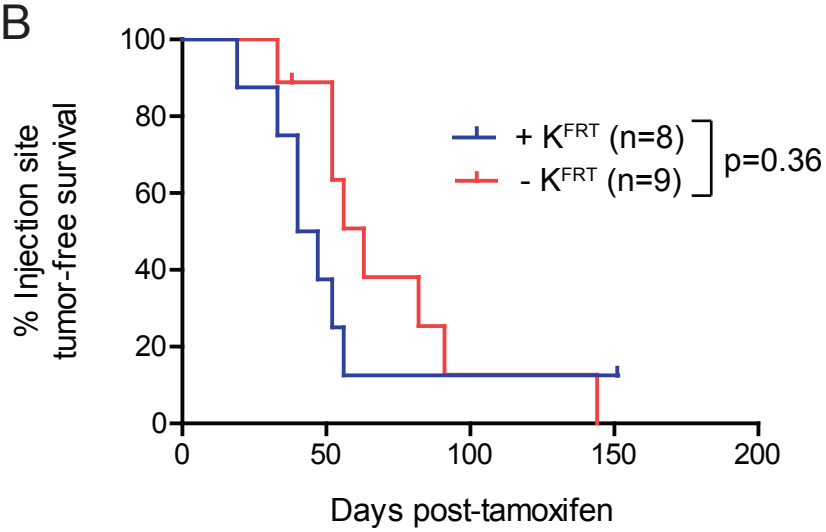
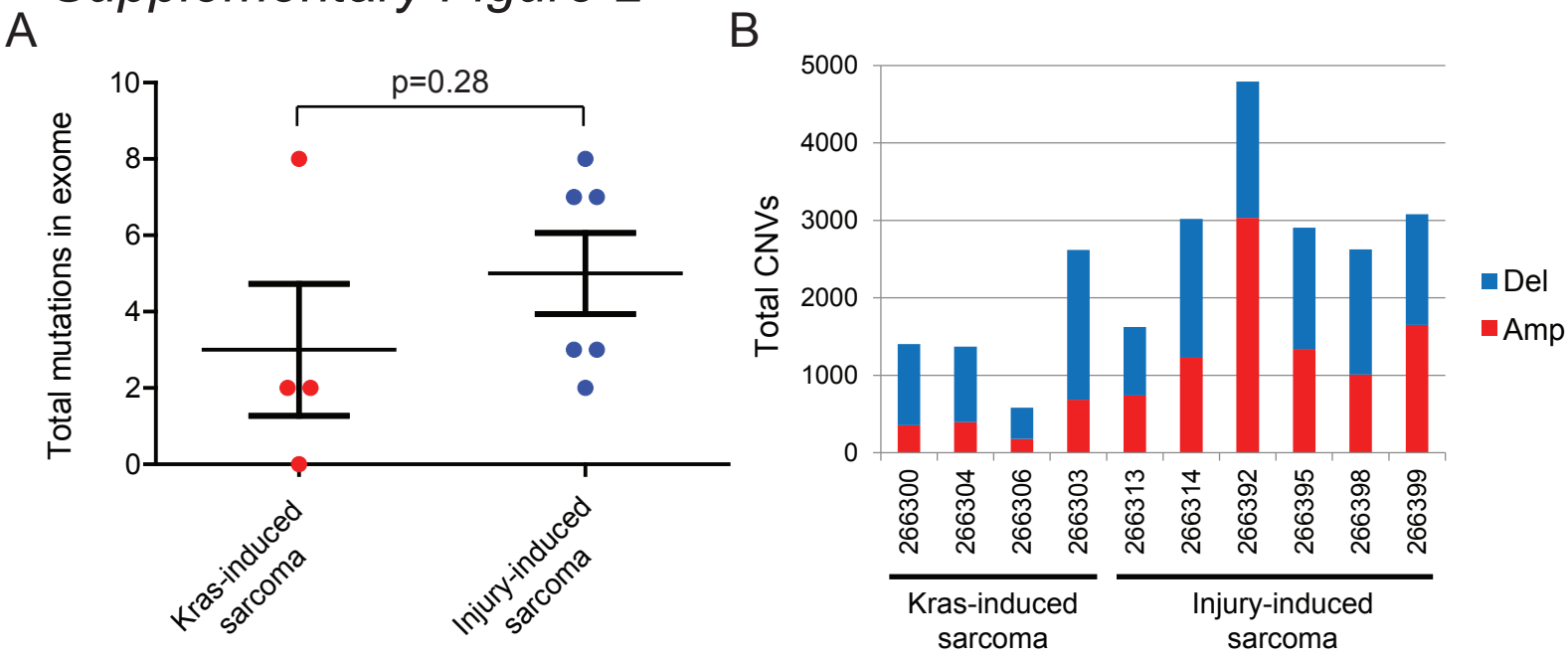
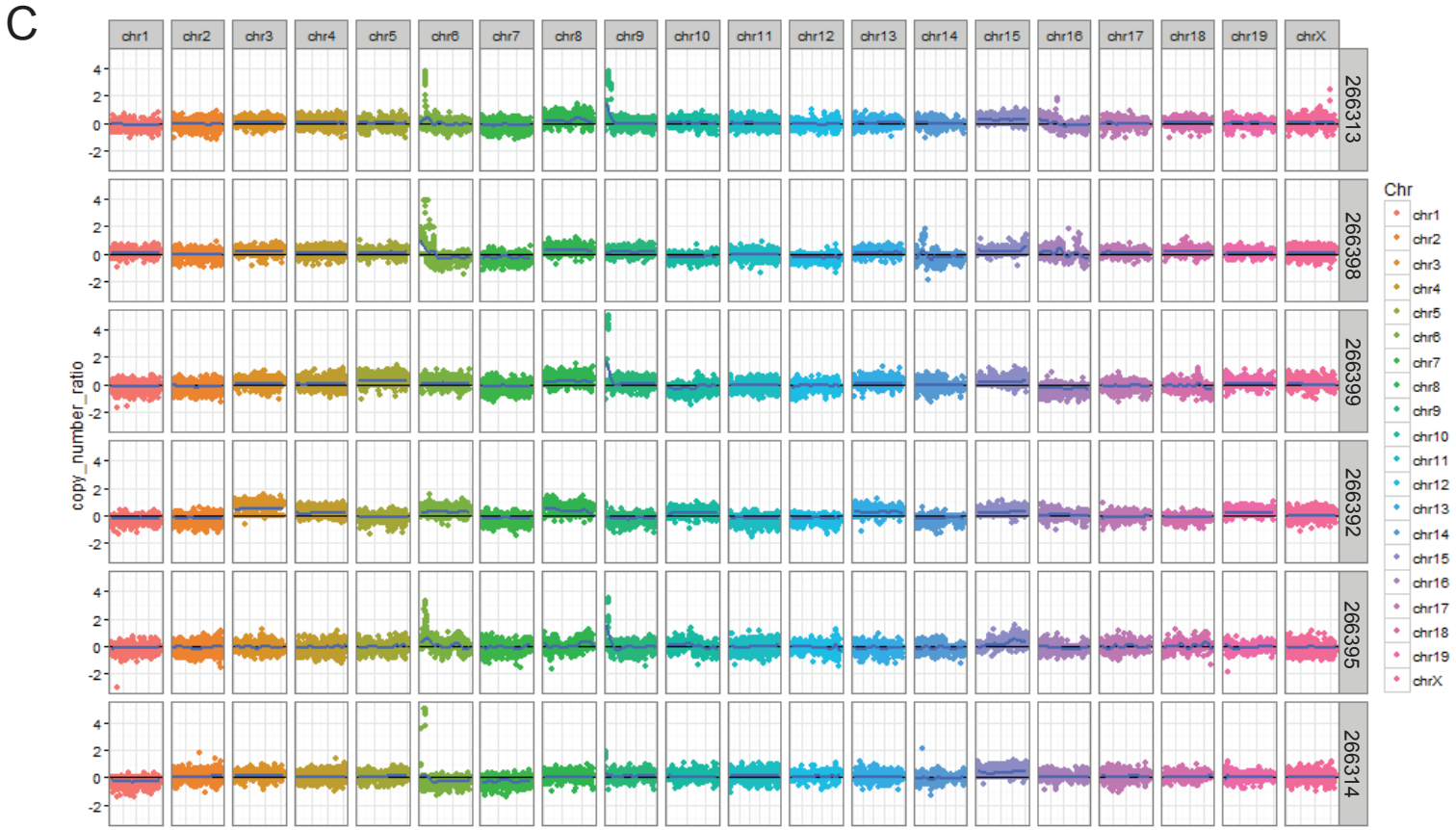
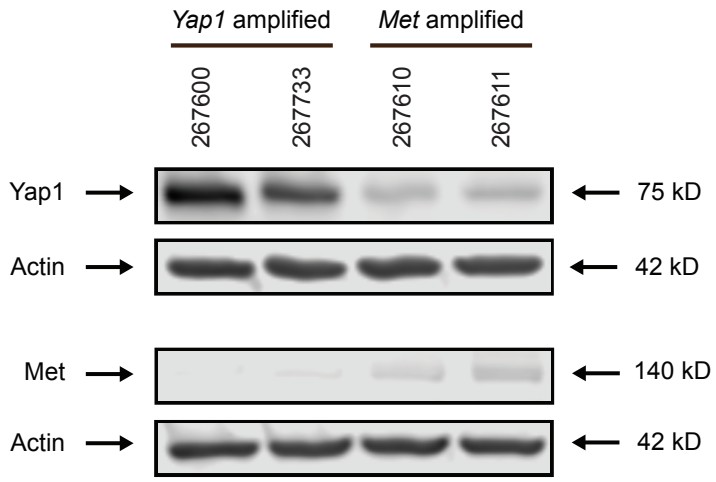


Supplementary Figure 2





Supplementary Figure 3



Supplementary Figure 4

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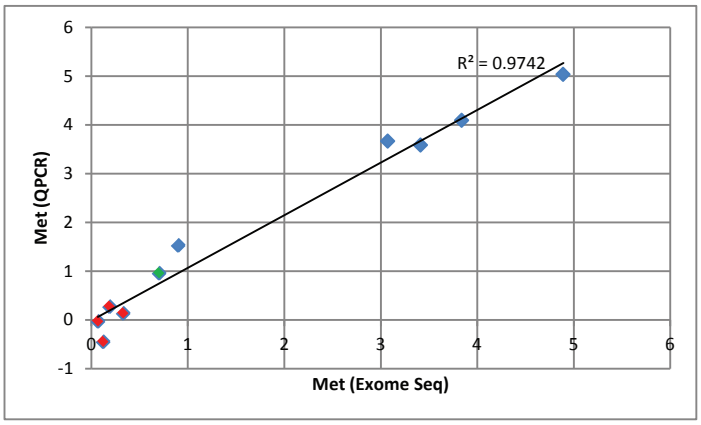

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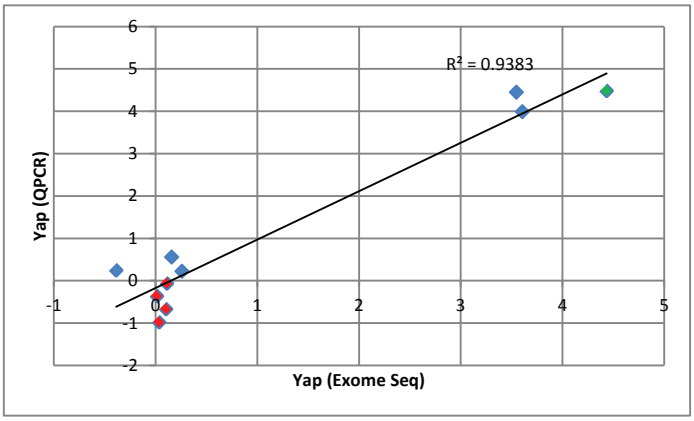

Supplementary Figure 5

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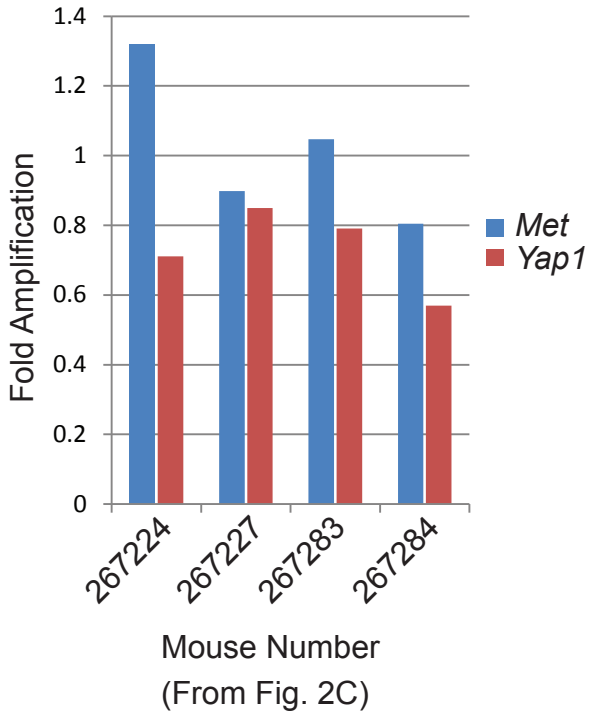

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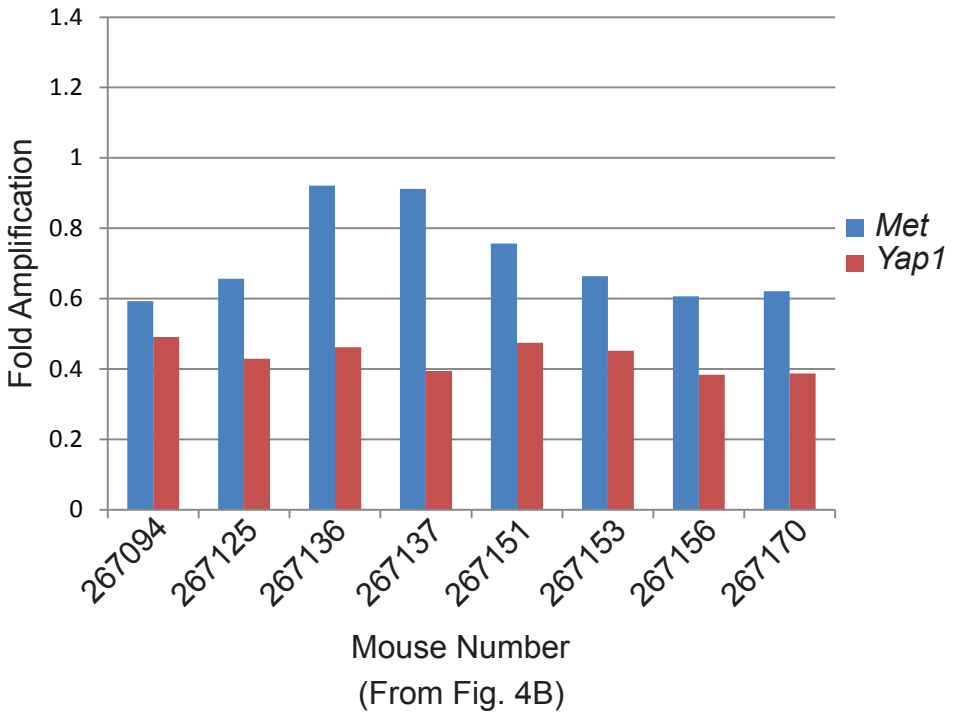

Supplementary Figure 6

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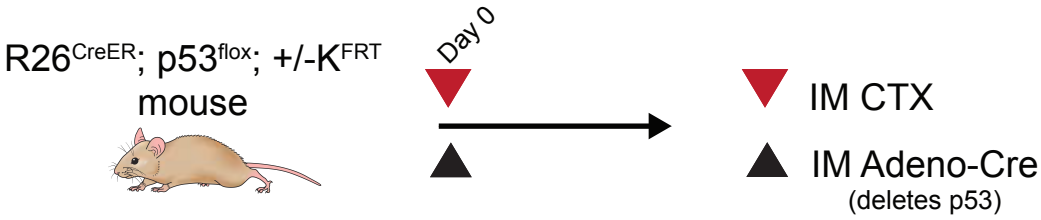

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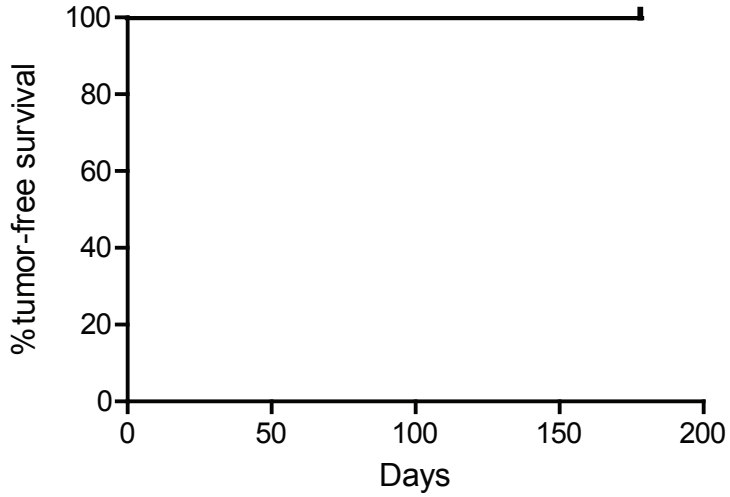

Supplementary Figure Legends:

Supplementary Figure 1. Kras activation is not required for sarcoma formation in the setting of systemic p53 deletion and concurrent injury. **A)** Schematic of experiment. $R26^{CreER}$; $p53^{flox}$ mice with or without K^{FRT} were treated in an identical fashion with IM adeno-FlpO on day 0. Only mice with K^{FRT} activated $Kras^{G12D}$ on day 0. All mice were then treated with IP tamoxifen and IM cardiotoxin on day 21. **B)** Kaplan-Meier survival plot reveals that mice developed sarcomas regardless of K^{FRT}, though the presence of K^{FRT} resulted in a non-statistically significant trend toward more rapid sarcoma formation (similar results to **Fig. 2**).

Supplementary Figure 2. Additional data from exome sequencing of Kras-induced and injury-induced sarcomas. **A)** No significant difference in the number of non-synonymous mutations in the 2 groups. The total number of mutations in each sarcoma was <10. **B)** The total number of genes with variation (CNVs) in each sarcoma is shown, with contribution of deletions (blue) and amplifications (red). **C)** Graphical representation of copy number variation across the mouse exome for the injury group.

Supplementary Figure 3. Protein expression of Met and Yap1 correlates with gene amplification. Cell lysates were prepared from primary sarcoma cell lines generated from $R26^{CreER}$; $p53^{flox}$; K^{FRT} mice following p53 deletion and muscle injury. Tumors from mice numbered 267600 and 267733 were found to have *Yap1* amplification, and tumors from mice numbered 267610 and 267611 were found to have *Met* amplification. A western blot was performed using anti-Yap1 and anti-Met antibodies, and an anti-actin antibody was used as a loading control.

Supplementary Figure 4. Validation of QPCR assays. **A)** Validation of QPCR assay for *Met*. Scatter plot of $\log_2$ copy number ratio of *Met* amplification from exome sequencing on X-axis

and relative copy number difference of *Met*:*Brca1* in tumor versus normal DNA via ΔΔCT method on Y-axis. **C)** Validation of QPCR assay for *Yap1*. Scatter plot of $\log_2$ copy number ratio of *Yap1* amplification from exome sequencing on X-axis and relative copy number difference of *Yap1*:*Brca1* in tumor vs normal DNA via ΔΔCT method on Y-axis. Red marks indicate DNA from Kras-induced sarcomas, blue marks indicate DNA from injury-induced sarcomas. The green mark represents DNA from an injury-induced sarcoma with *Yap1* amplification, but not *Met* amplification.

Supplementary Figure 5. *Met* and *Yap1* are not amplified in the setting of activated Kras. **A)** Sarcomas from **Fig. 2C** which had been generated by IM adeno-FlpO on day 0 (activate Kras) and IP tamoxifen (delete p53) and IM cardiotoxin on day 21 were shown to harbor recombined Kras. No evidence for *Met* or *Yap1* amplification was seen in those sarcomas. **B)** Sarcomas from **Fig. 4B** that were treated with IP tamoxifen (delete p53) on day 0 and IM adeno-FlpO (activate Kras) and IM cardiotoxin on day 21 were tested for *Met* and *Yap1* amplification. No evidence for amplification was seen, providing further evidence for mutual exclusivity of *Met/Yap1* amplification and Kras activation in $R26^{CreER}$; $p53^{flox}$; K^{FRT} mice.

Supplementary Figure 6. Focal recombination of p53 with concordant muscle injury fails to promote sarcoma formation. **A)** Schematic of experiment. $R26^{CreER}$; $p53^{flox}$; K^{FRT} and $R26^{CreER}$; $p53^{flox}$ littermates were treated with an intramuscular injection of adeno-Cre in the hindlimb to induce focal recombination (and loss) of p53. They were also injected with intramuscular cardiotoxin at the same site. **B)** Kaplan-Meier curve showing survival of 12 treated mice. No mice developed an injection site sarcoma in the 178 day observation period.