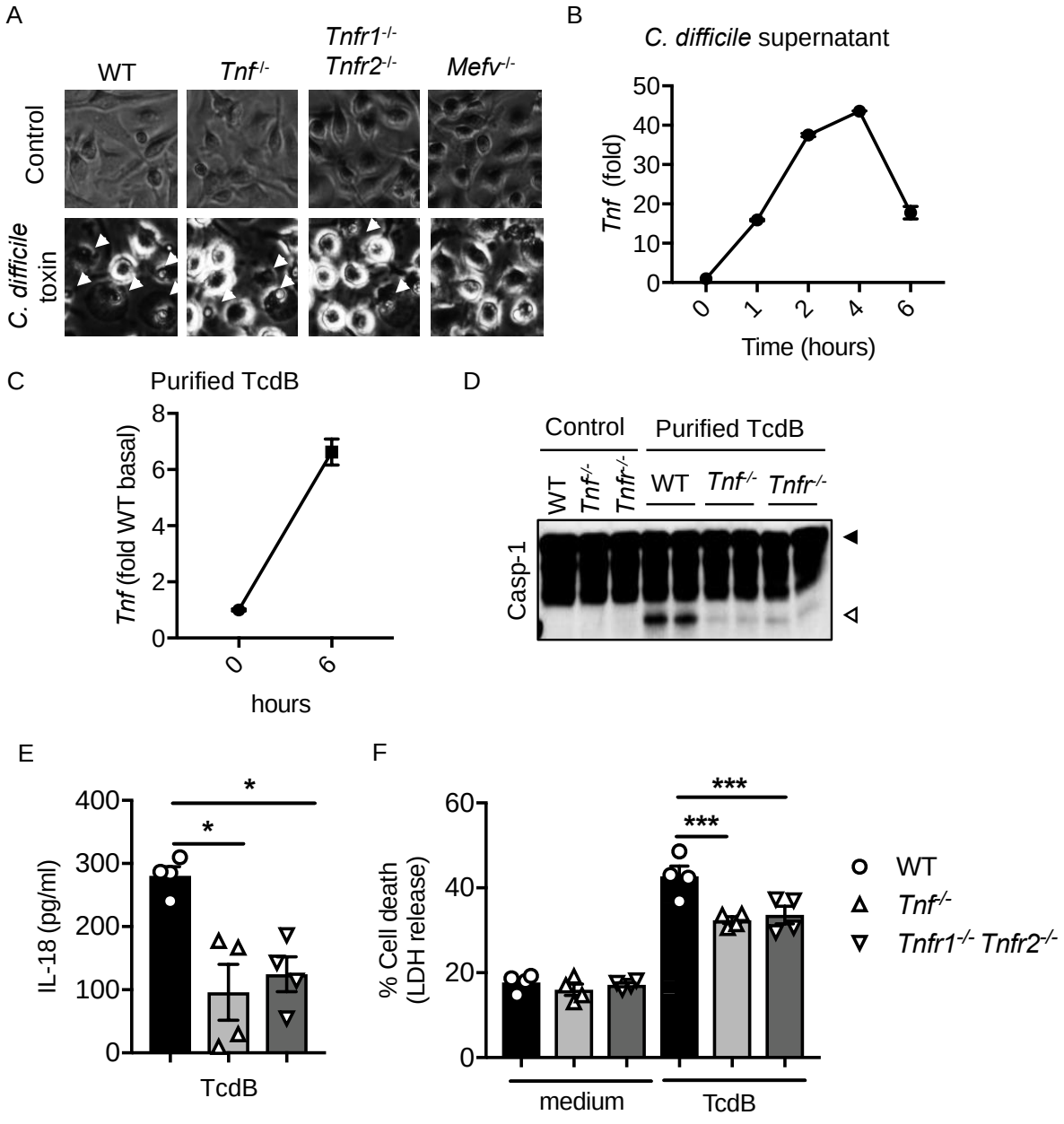
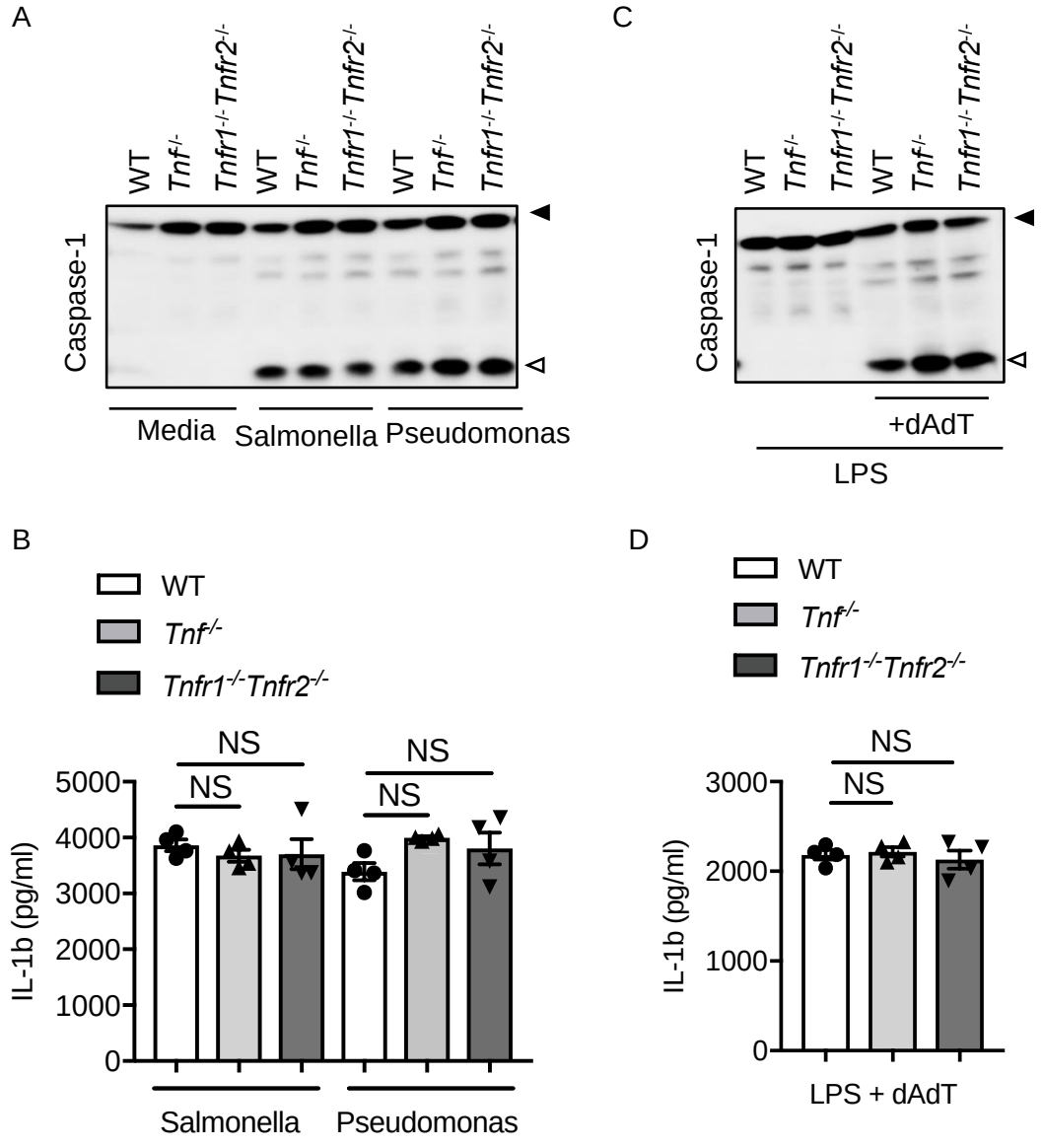
SUPPLEMENTARY INFORMATION



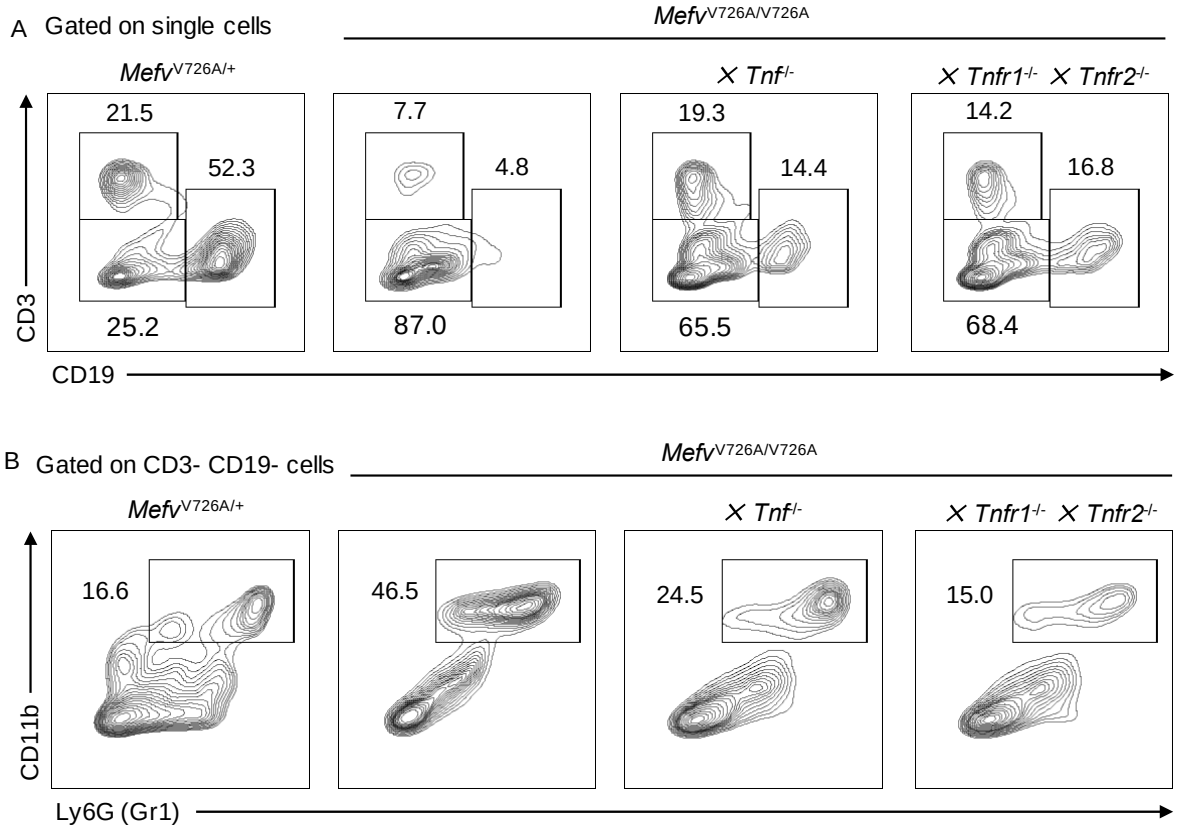
Supplementary Figure 1: TNF-TNFR promotes purified toxin induced Pyrin inflammasome activation. (A) Representative images marking pyroptotic cell death (white arrowheads) in BMDMs in response to control (to *C. difficile* toxin-negative) and *C. difficile* toxin stimuli. *Tnf* induction in response to (B) *C. difficile* toxin (in house) and (C) purified toxin (TcdB) stimuli. (D) Caspase-1 processing, (E) IL-18 and (F) LDH release in BMDMs

following stimulation with purified TcdB. (B, C, E, F) Data is presented as mean ± SEM and representative of atleast three independent repeats. (E, F) * P<0.5, and ***P<0.001 compared to WT by using (E) Student's t-test, (F) one-way ANOVA followed by Fischer's LSD post-test.

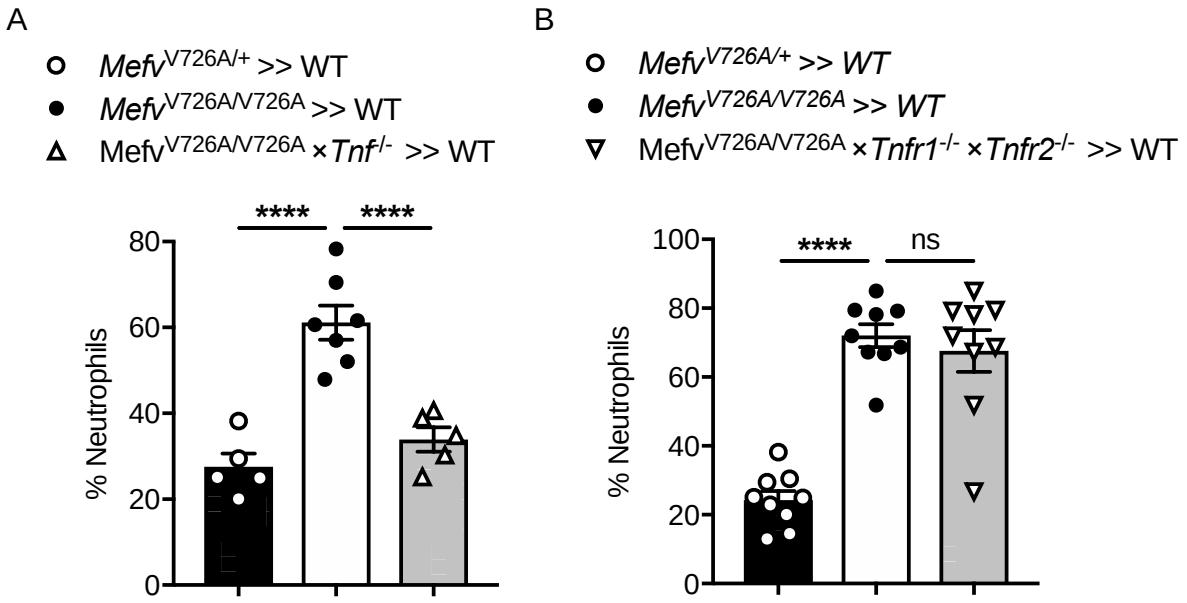


Supplementary Figure 2: TNF signaling does not affect NLRC4 and AIM2 inflammasome activation. (A) Caspase-1 processing and (B) IL-1β release in response to

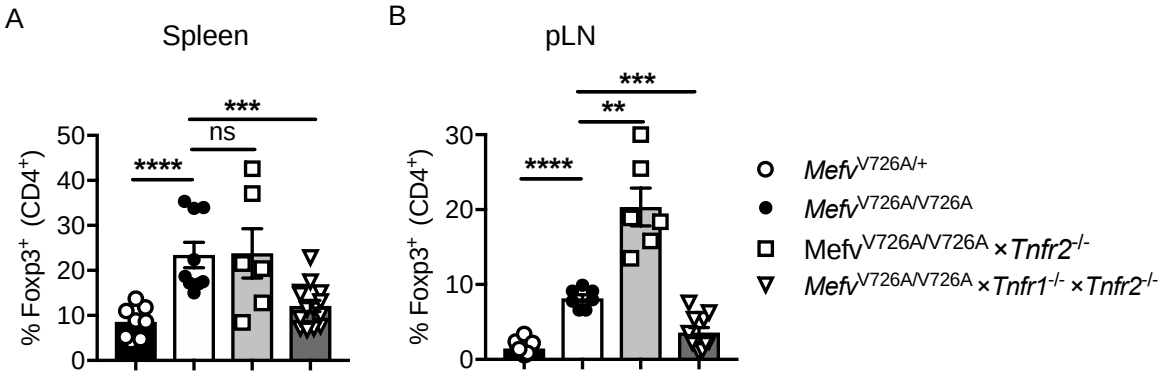
NLRC4 triggers, Salmonella (MOI 1) and Pseudomonas (MOI 1) for six hours. (C) Caspase-1 processing and (D) IL-1β release in response AIM2 activation- LPS primed cells transfected with dAdT (2.5μg/ml) for four hours. (B, D) Data is presented as mean ± SEM and is representative of atleast two independent repeats and (B, D) NS refers to not significant using Student's t-test.



Supplementary Figure 3: Splenic composition in *Mefv*$^{V726A/V726A}$ mice is modulated by TNF signaling. Representative flow plots demonstrating the proportion of (A) T cells (CD3), B cells (CD19+), and (B) neutrophils (CD11b+Ly6G+CD3-CD19-) in spleens of indicated mice.

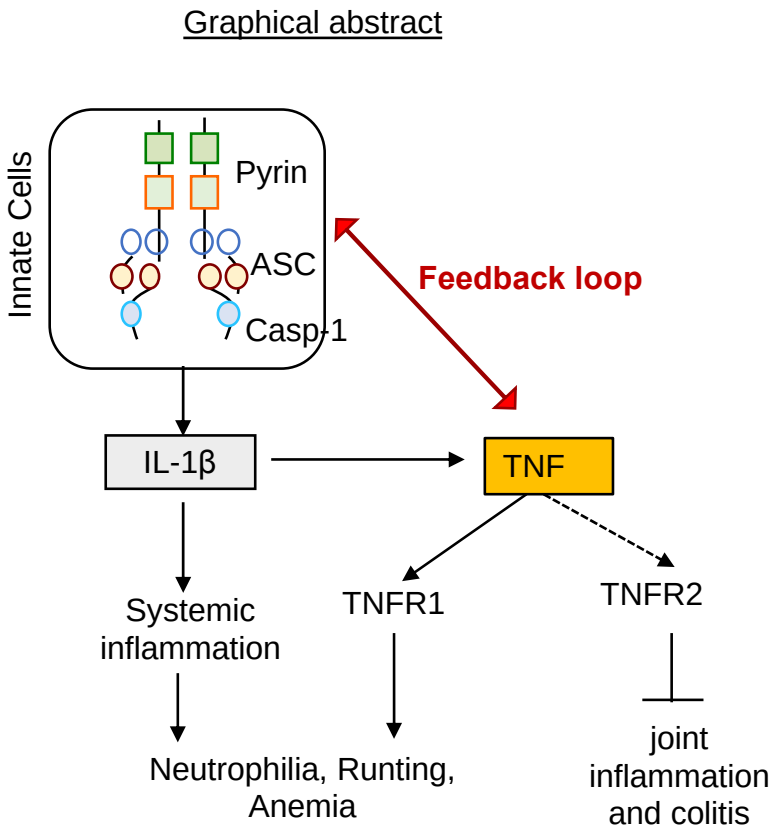


Supplementary Figure 4: TNF production by hematopoietic cells promotes neutrophilia in *Mefv*$^{V726A/V726A}$ mice. Proportion of neutrophils in blood of WT mice irradiated and reconstituted with bone marrow cells from various *Mefv* strains. The terminology for the groups is described as donor>>recipient. Data is presented as mean ± SEM and includes N=5-10 mice/experimental group. ****P<0.0001 and ns- not significant compared to *Mefv*$^{V726A/V726A}$ >> WT group using Student's t-test.



Supplementary Figure 5: Treg induction in *Mefv*$^{V726A/V726A}$ mice is not dependent on TNFR signaling. Proportion of CD4+ T cells that express Foxp3 in (A) spleen and (B)

popliteal lymph nodes (pLN). Data is presented as mean ± SEM and includes N=6-12 per genotype. * P<0.5, **P<0.01, ****P<0.0001 and ns- not significant compared to *Mefv*$^{V726A/V726A}$ by using one-way ANOVA followed by Fisher's LSD post-test.



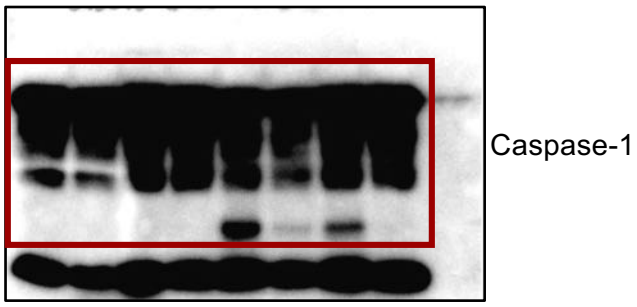
Supplementary Figure 6: Graphical abstract

Pyrin activation is promoted by the TNF-TNFR axis in both canonical stimuli and constitutive activation observed in FMF-KI cells. In the FMF mouse model, pyrin inflammasome activation leads to IL-1β production which is the dominant factor in FMF pathology. Inflammasome-mediated IL-1β promotes TNF production that signals through TNFR1 to promote neutrophilia, runting and anemia. Thus, TNF signaling forms a feedback loop for exacerbation of systemic inflammation in FMF model. On the other hand, TNFR2 signaling is specifically

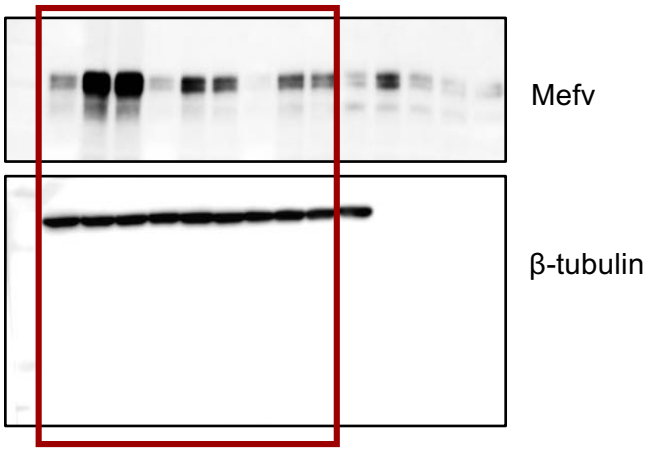
required to inhibit development of colon and joint inflammation.

UNCROPPED BLOTS: lanes that correspond to those shown in the cropped images within the manuscript are marked by a red box.

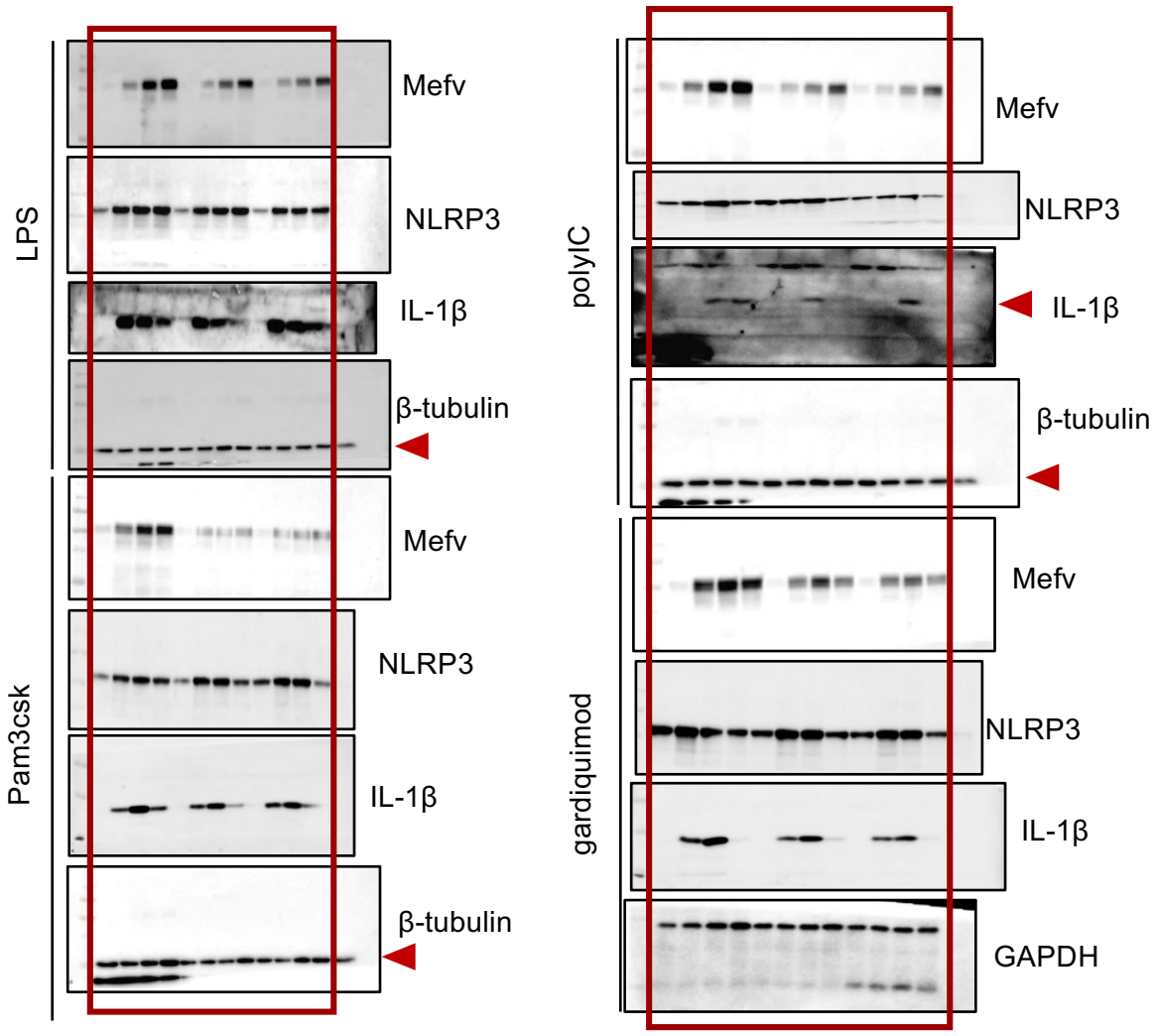
Full unedited gel for Fig 1A



Full unedited gel for Fig 1D



Full unedited gel for Fig 1E



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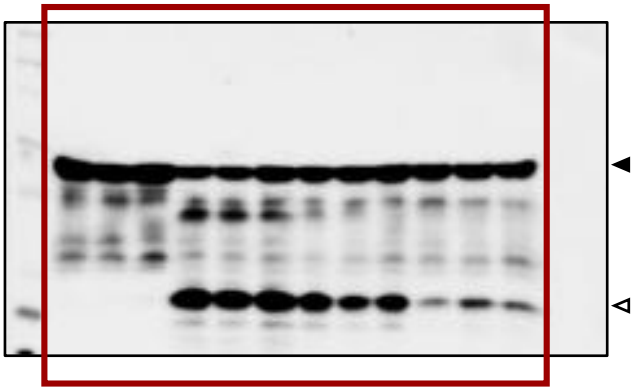

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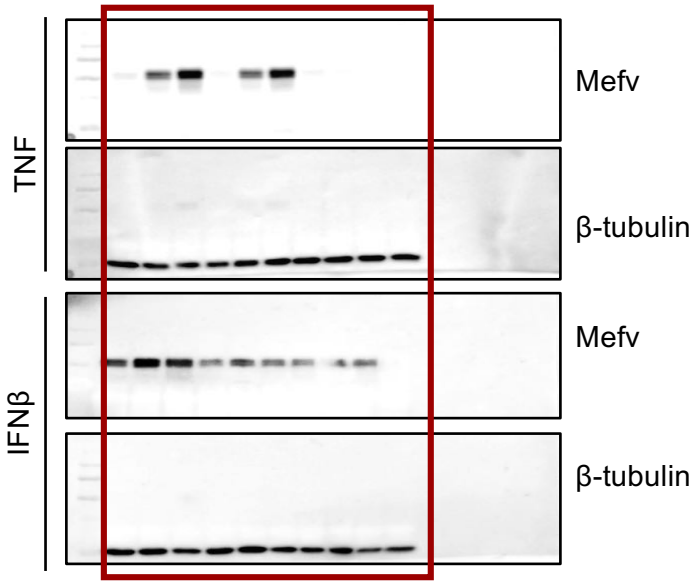

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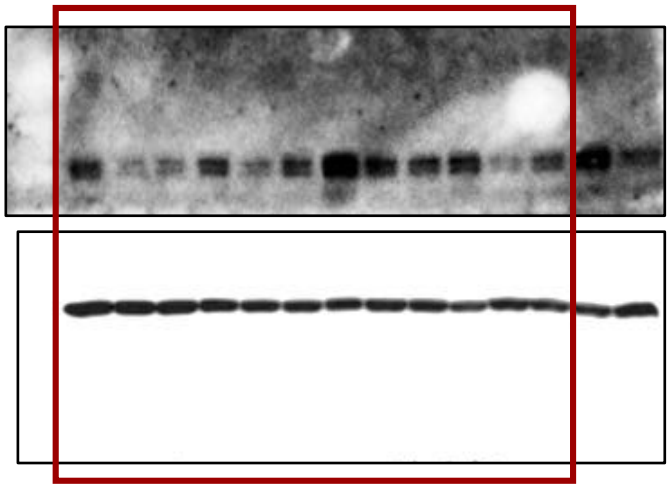

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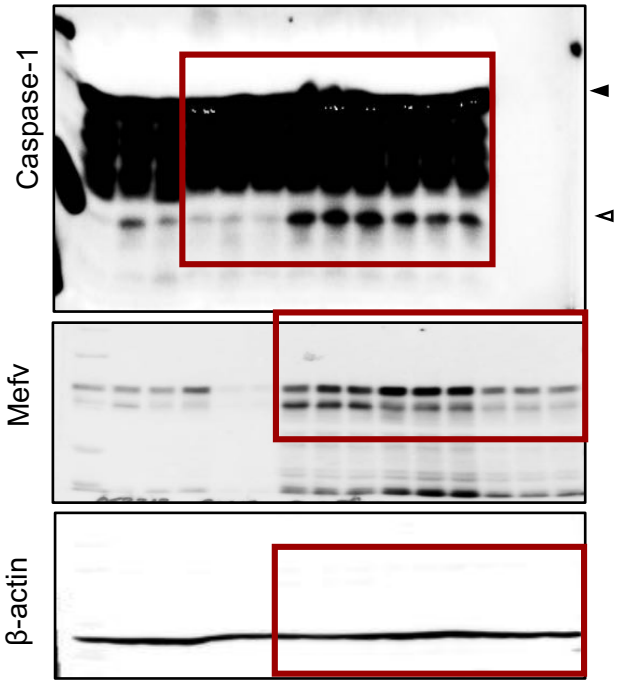

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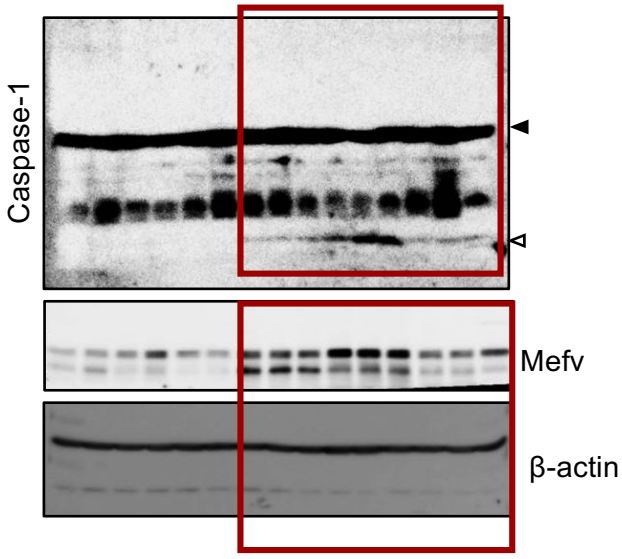

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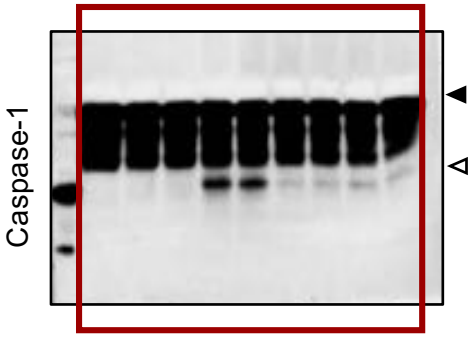

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