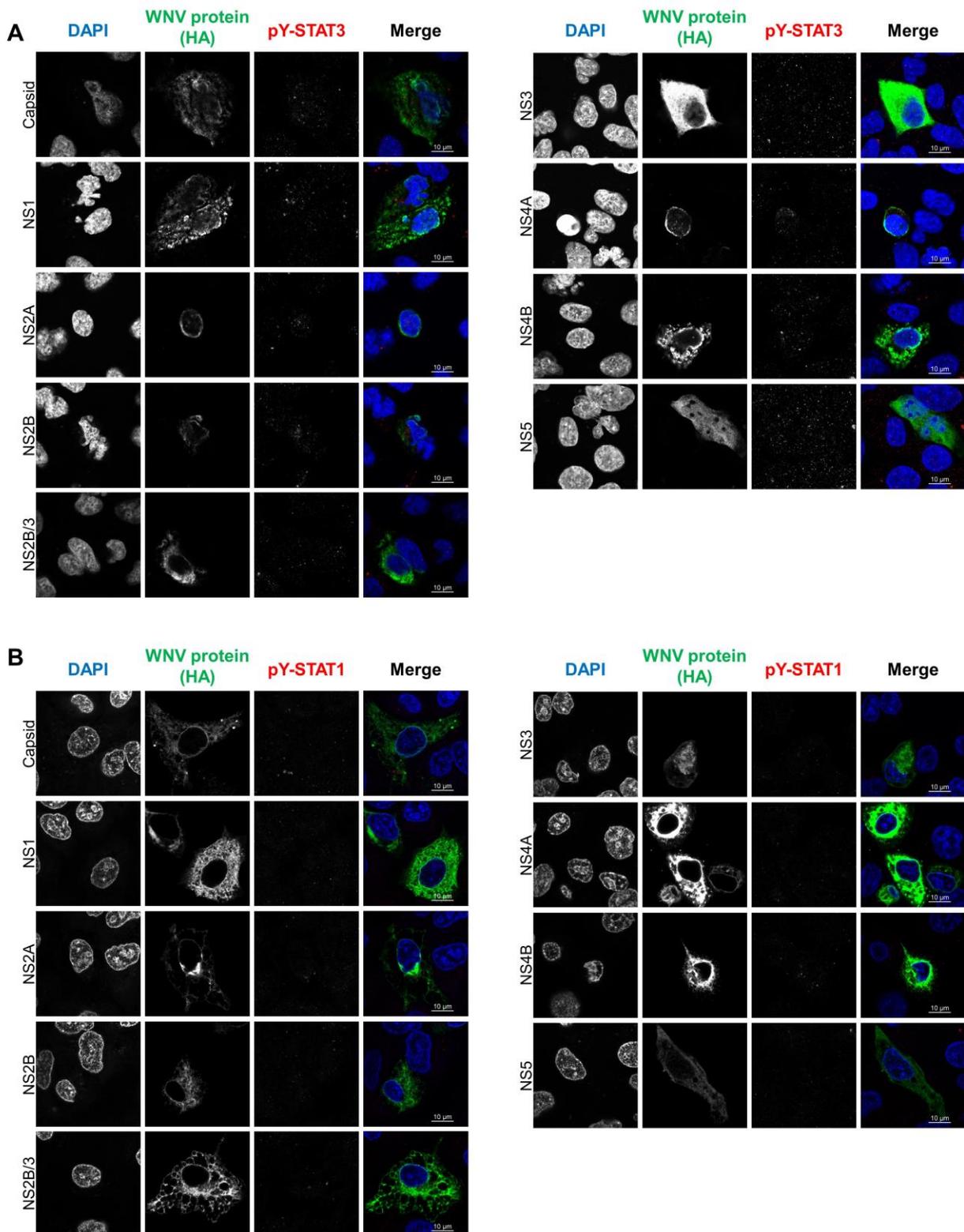


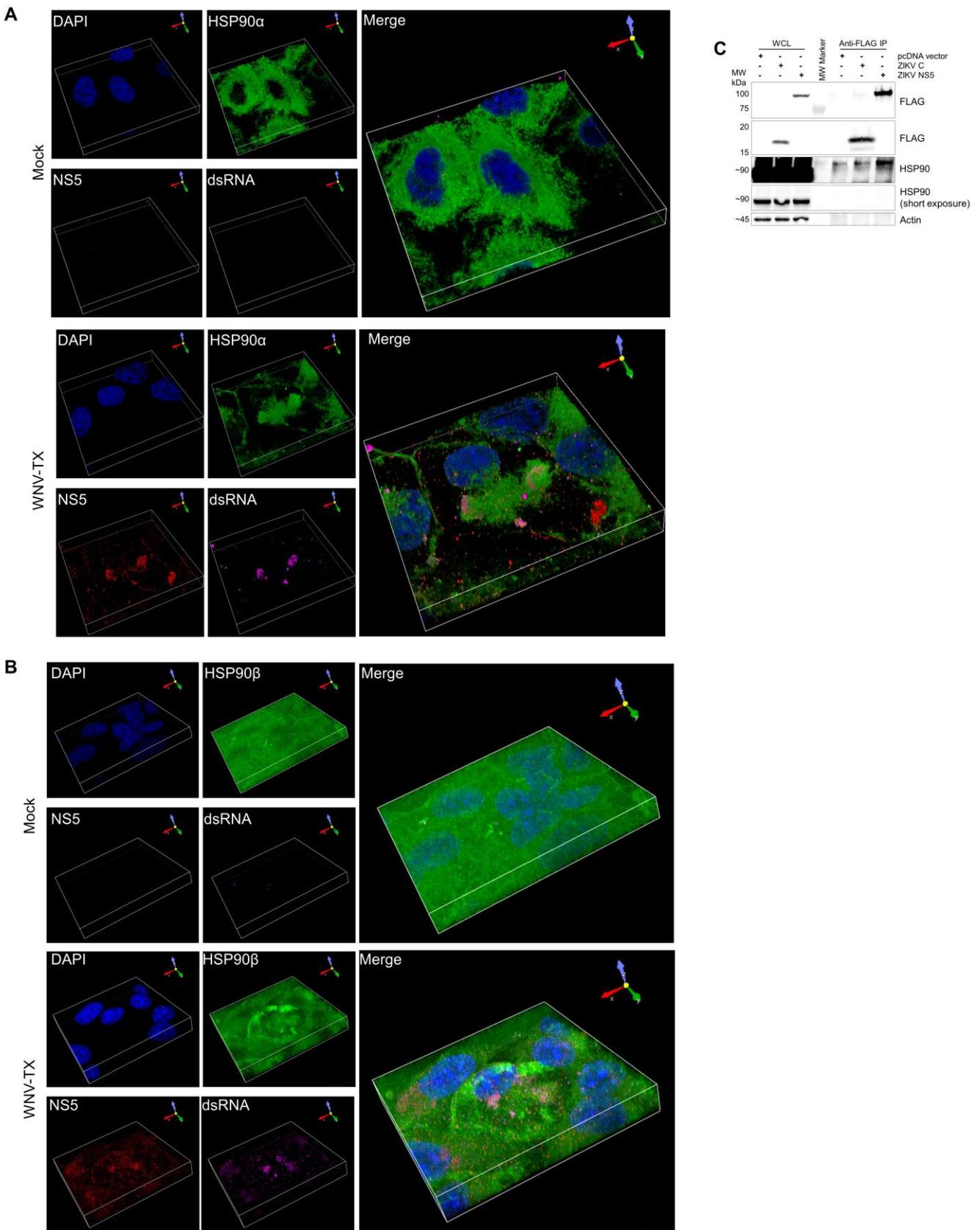
**Figure S1: WNV infection inhibits STAT phosphorylation in response to multiple cytokines.**

(A) WNV infection of A549 cells attenuates the pY-STAT1 response to IFN $\gamma$ . (B) WNV infected MEF cells showed attenuated pY-STAT3 to 30 min murine IL6 treatment. (C) A549 cells infected with MOI = 5 WNV for 24 hrs and subsequently treated with 200 ng/mL IL6 for 30 min. WNV infection prevents the accumulation of pY-STAT3 in response to IL6 (arrow heads). THP-1 cells differentiated into macrophages with PMA and infected with MOI = 30 WNV for 24 hrs were unable to generate a pY-STAT1 response to 30 min treatment with (D) 1,000 IU IFN $\beta$ , or pY-STAT3 response to 30 min treatment with (E) IL10 (arrow heads). (F) Analysis of downstream signaling in response to IL1 $\beta$  in WNV infected A549 cells. WNV infection leads to reduced abundance of I $\kappa$ B $\alpha$ , however the degree of pS-p65 was largely unaffected by 15 min post-treatment. (G) Proximal signaling components of the IL1 $\beta$  response are altered in WNV infected A549 cells. The abundance of TRAF6, IKK $\beta$ , and IKK $\gamma$  all appear reduced by 24 hpi with WNV. (H) Timecourse experiments revealed that JAK1 abundance starts to diminish between 14 and 16 hpi with MOI = 5 WNV, commensurate with increasing viral protein production. All infections were conducted at MOI = 5 unless otherwise stated. All data are representative of 3 independent experiments or are a combination of all 3 experiments (mean  $\pm$  SEM). The red pY-STAT3 channel for microscopy images in panels C and E was enhanced equally across all samples to aid visual clarity post-acquisition.



**Figure S2: Recombinant WNV protein expression does not induce pY-STAT3 or pY-STAT1.**

Expression of recombinant WNV proteins in transfected A549 cells does not by themselves stimulate (A) pY-STAT3 or (B) pY-STAT1. All data are representative of 3 independent experiments. The red pY-STAT3 channel for microscopy images in panel A was enhanced equally across all samples to aid visual clarity post-acquisition.



**Figure S3: HSP90 interacts with NS5 and is localized to sites of viral dsRNA.**

3D rendering reveals discrete co-localization of (A) HSP90 $\alpha$  and (B) HSP90 $\beta$  with WNV NS5 and dsRNA in infected A549 cells (arrow heads). The extent of HSP90 $\alpha/\beta$  perinuclear condensation is also revealed in these 3D renderings. (C) Expression of FLAG-tagged ZIKV C and NS5 in HEK-293T cells followed by anti-FLAG co-IP showed endogenous HSP90 interacts specifically with ZIKV NS5. All infections were conducted at MOI = 5 unless otherwise stated. All data are representative of 3 independent experiments.

