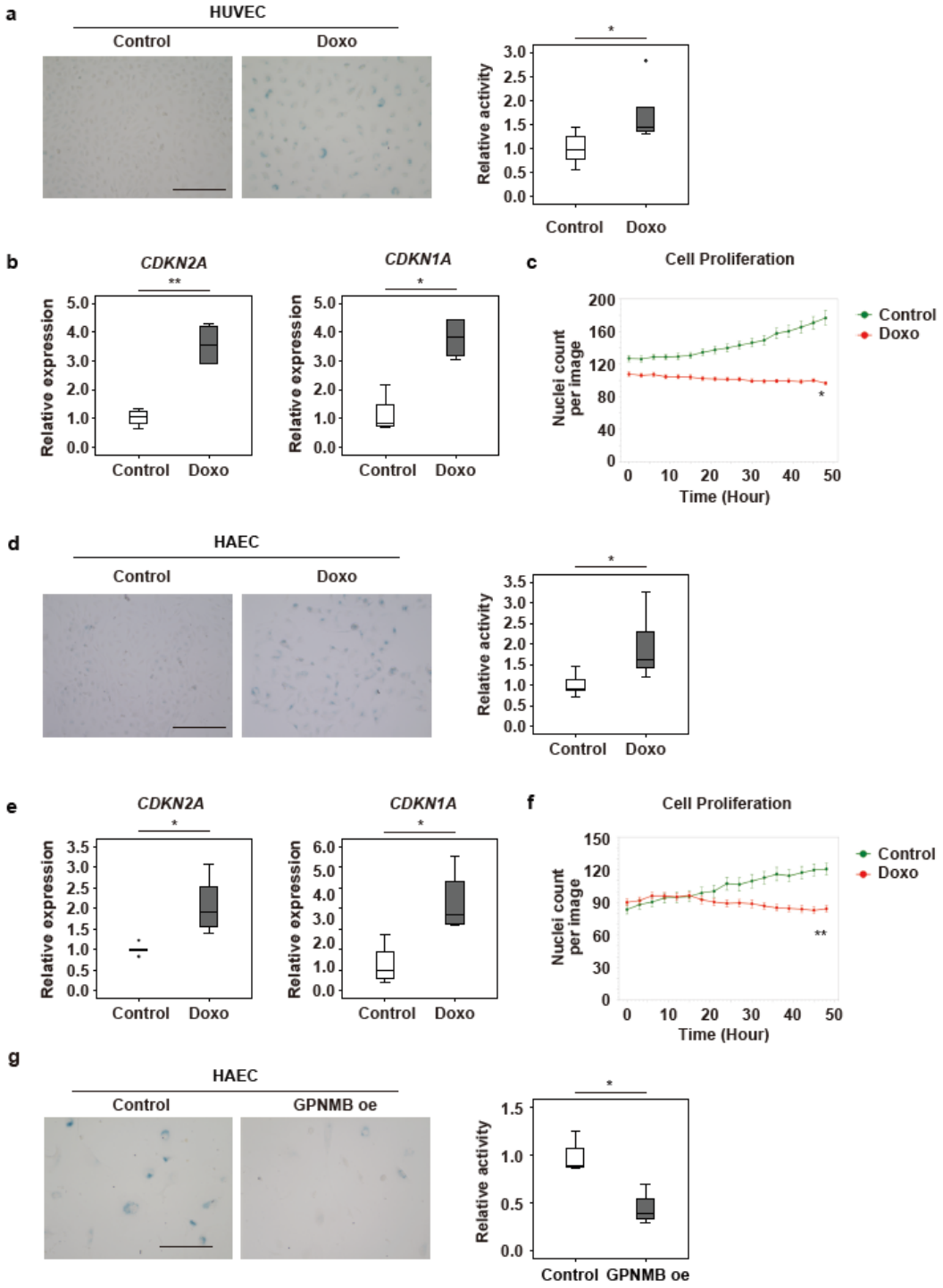
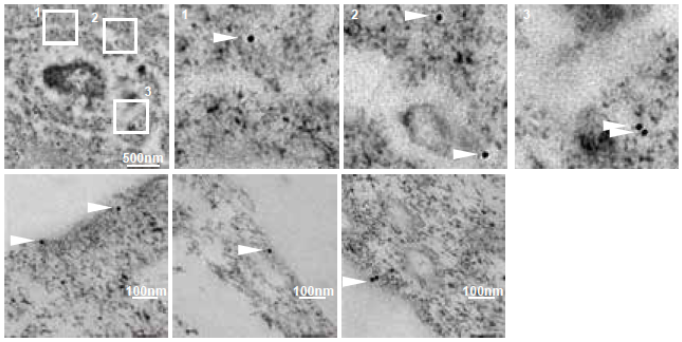
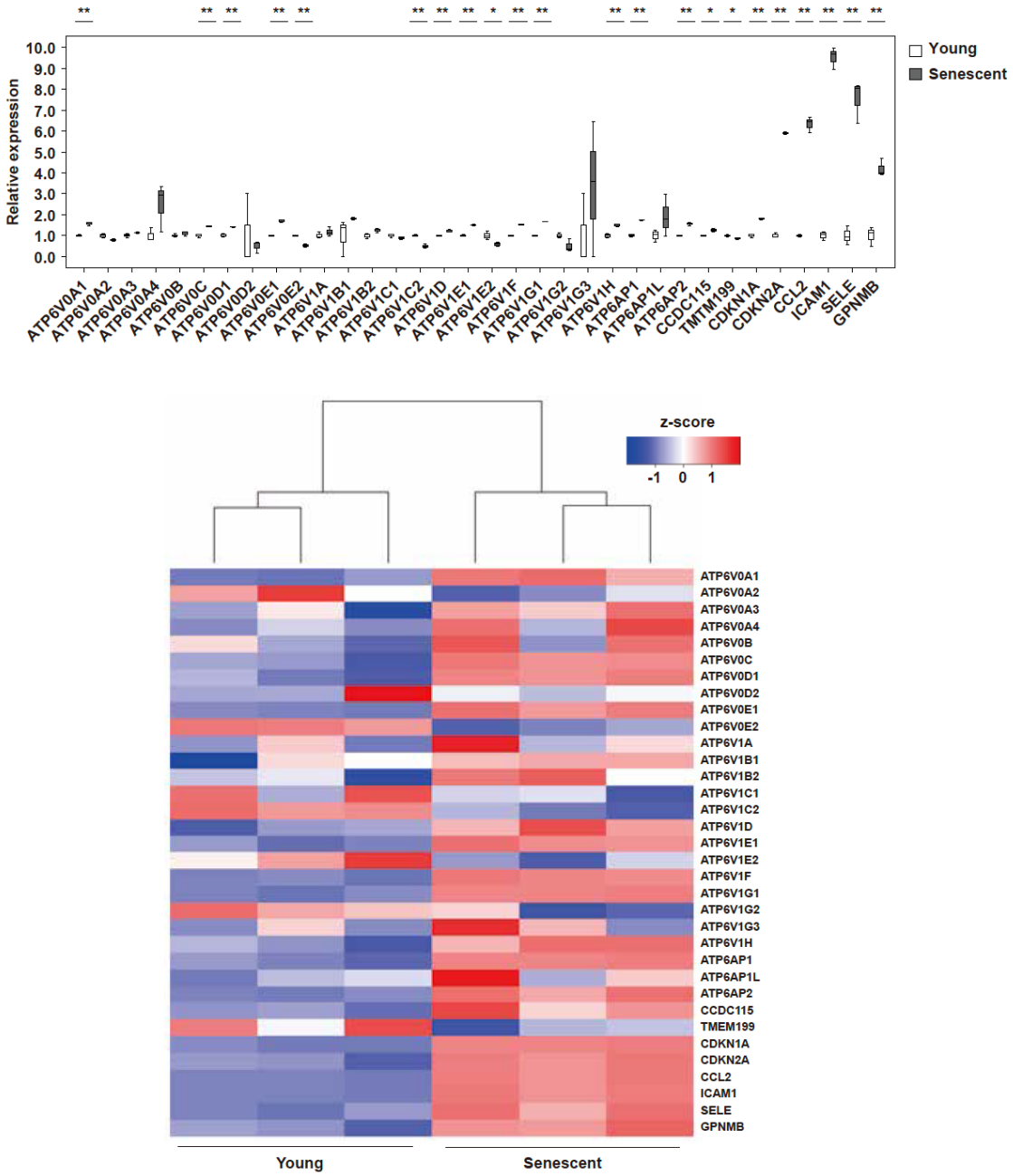


Supplementary Figure 1. Doxorubicin-induced premature senescence.
a-c, HUVECs were treated with 100 nM of doxorubicin (Doxo) for 72 hours twice, followed by the incubation without treatment for 7 days. SA-β-gal activity (**a**, n=6, 6), expression of *CDKN2A* and *CDKN1A* (**b**, n=4, 4), and cell proliferation (**c**, n=6, 6) were examined. **d-f,** Human aortic endothelial cells (HAECs) were treated with 100 nM of doxorubicin as indicated in Supplementary Fig. 1a. SA-β-gal activity (**d**, n=6, 6), expression of *CDKN2A* and *CDKN1A* (**e**, n=5, 5), and cell proliferation (**f**, n=6, 6) were examined. **g,** SA-β-gal assay of HAECs infected with a GPNMB overexpression vector

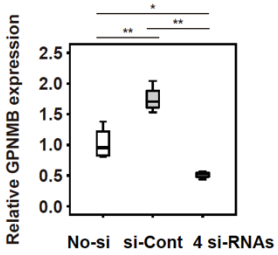
(GPNMB oe) or a control vector (Control) after treatment with doxorubicin as indicated in Supplementary Fig. 1a (n=3, 3). Data were analyzed by the two-tailed Student's t-test (**a, b, d, e, g**) or by repeated measures ANOVA analysis (**c, f**). *P<0.05, **P<0.01. The data are shown as box and whisker plots (**a, b, d, e, g**) or the mean ± SD (**c, f**). Scale bar=200 μ m.



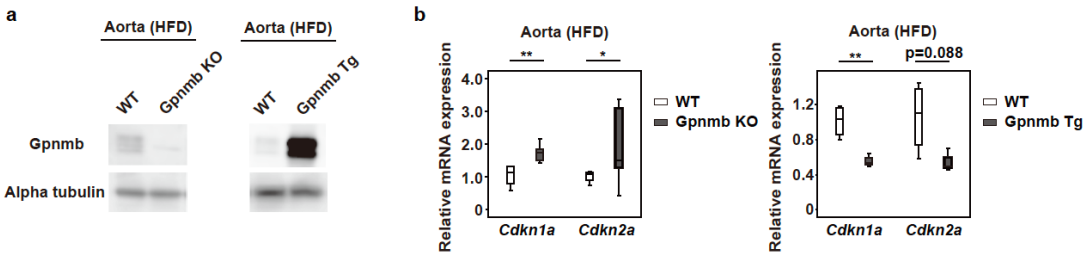
Supplementary Figure 2. Immunoelectron microscopy.
Immunoelectron microscopy labeling mCherry (arrow heads) in HUVECs overexpressing GPNMB-mCherry. GPNMB-mCherry was localized in the lysosomes (upper panels) as well as in the plasma membrane (lower panels).



Supplementary Figure 3. Expression of V-type ATPase components in young and senescent endothelial cells.
Young and senescent HUVECs underwent RNA sequencing analysis. The expression of V-type ATPase components along with senescence markers is shown (n=3, respectively). The data were analyzed by the two-tailed Student's t-test and are presented as box and whisker plots. *P<0.05, **P<0.01.

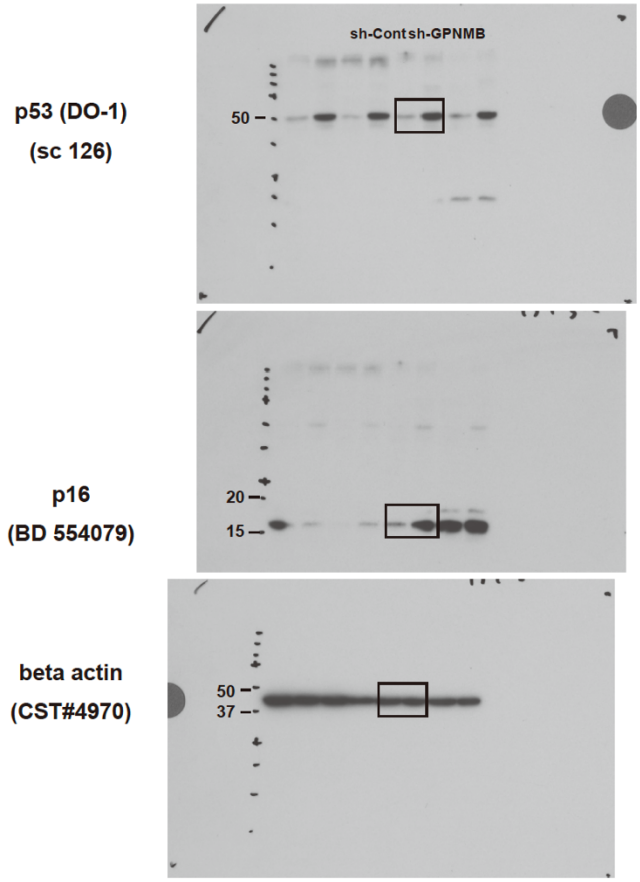


Supplementary Figure 4. Expression of Gpnmb after introduction of siRNAs.
Relative expression of *GPNMB* in replicative senescent HUVECs after introduction of siRNAs for the MITF/TFE transcription factors (4 si-RNAs: si-MITF, si-TFEB, si-TFEC, and si-TFE3), control siRNA (si-Cont), or no siRNA (No-si) (n=4, 4, 3). Data were analyzed by two-way ANOVA analysis followed by Tukey's multiple comparison. *P<0.05, **P<0.01. The data are shown as box and whisker plots.

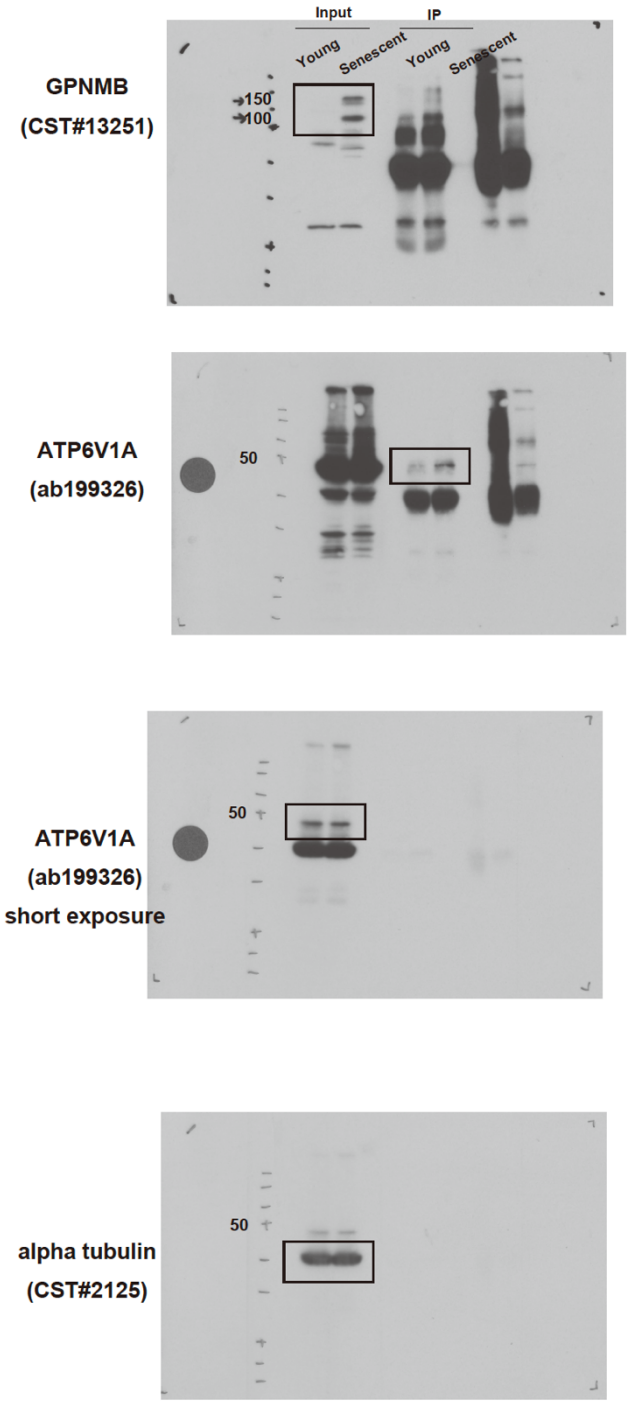


Supplementary Figure 5. Expression of Gpnmb and senescence markers in Gpnmb KO/Tg mice.

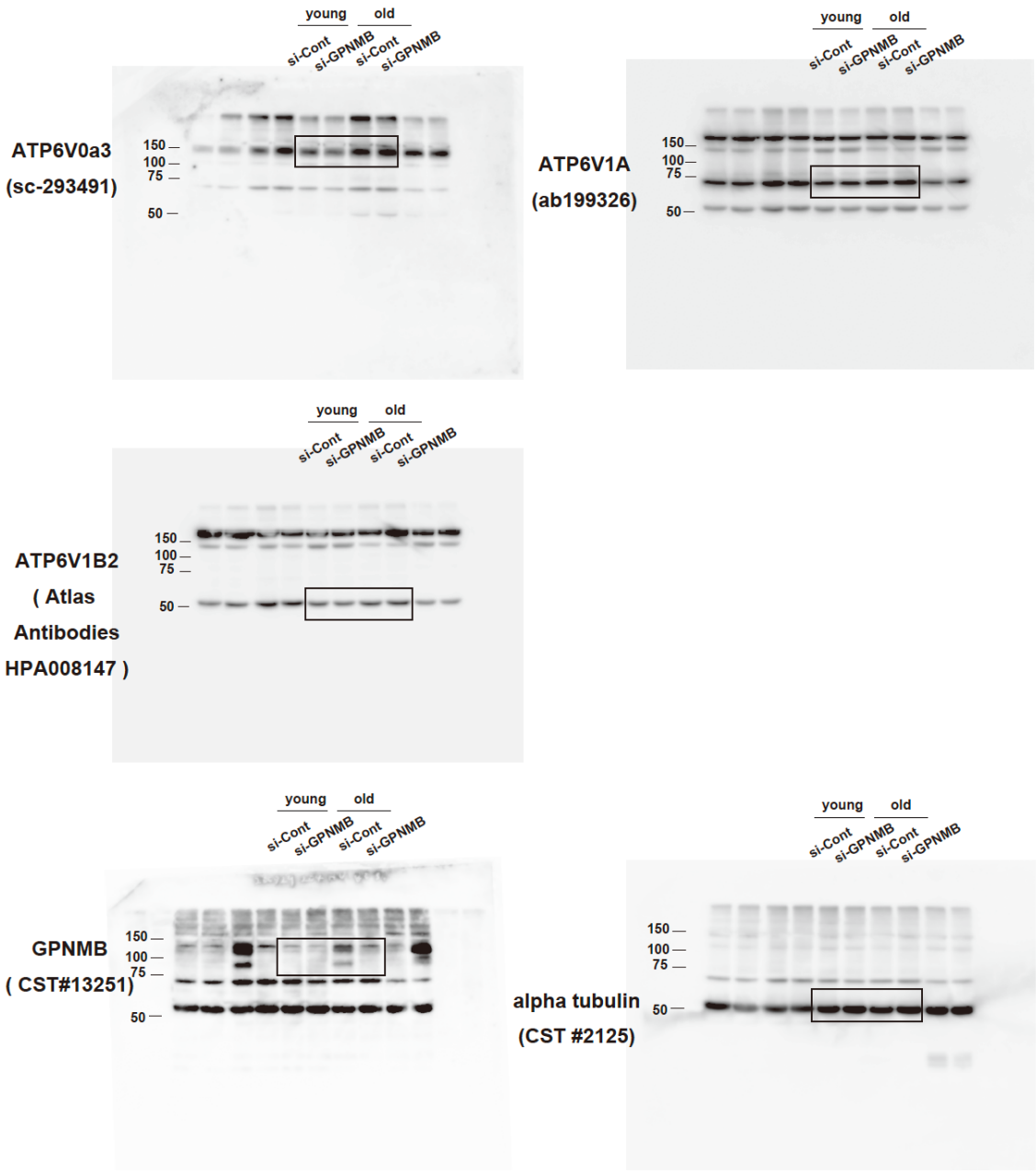
a, Western blot analysis for expression of Gpnmb in the aortas of Gpnmb KO/Tg mice or littermate controls (WT) on the HFD. Original blots are presented in Supplementary Figure 10. **b**, qPCR for relative expression of *Cdkn1a* and *Cdkn2a* in the aortas of Gpnmb KO/Tg mice or littermate controls (WT) on the HFD (n=4 for WT and n=8 for KO, n=4 for WT and n=3 for Tg). The data were analyzed by the two-tailed Student's t-test (**b**). **P<0.01. The data are shown as box and whisker plots (**b**).



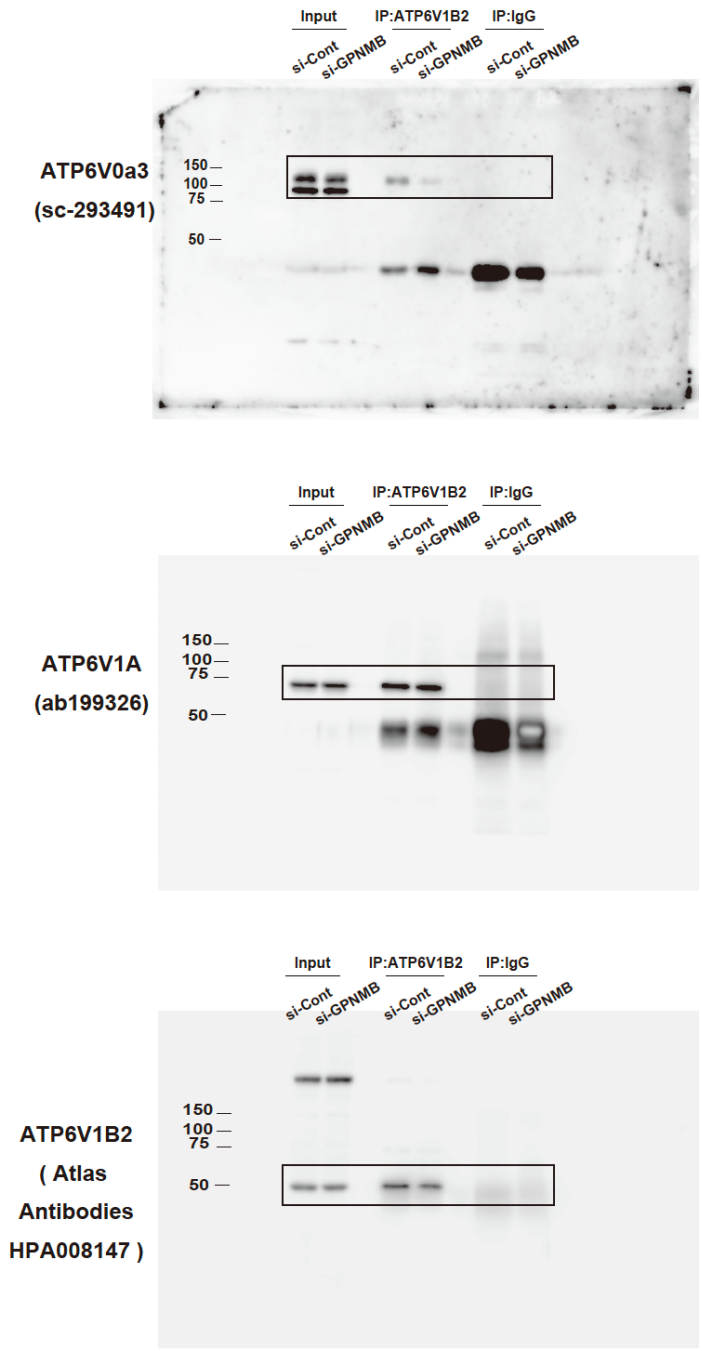
Supplementary Figure 6. Full blots of Figure 1b



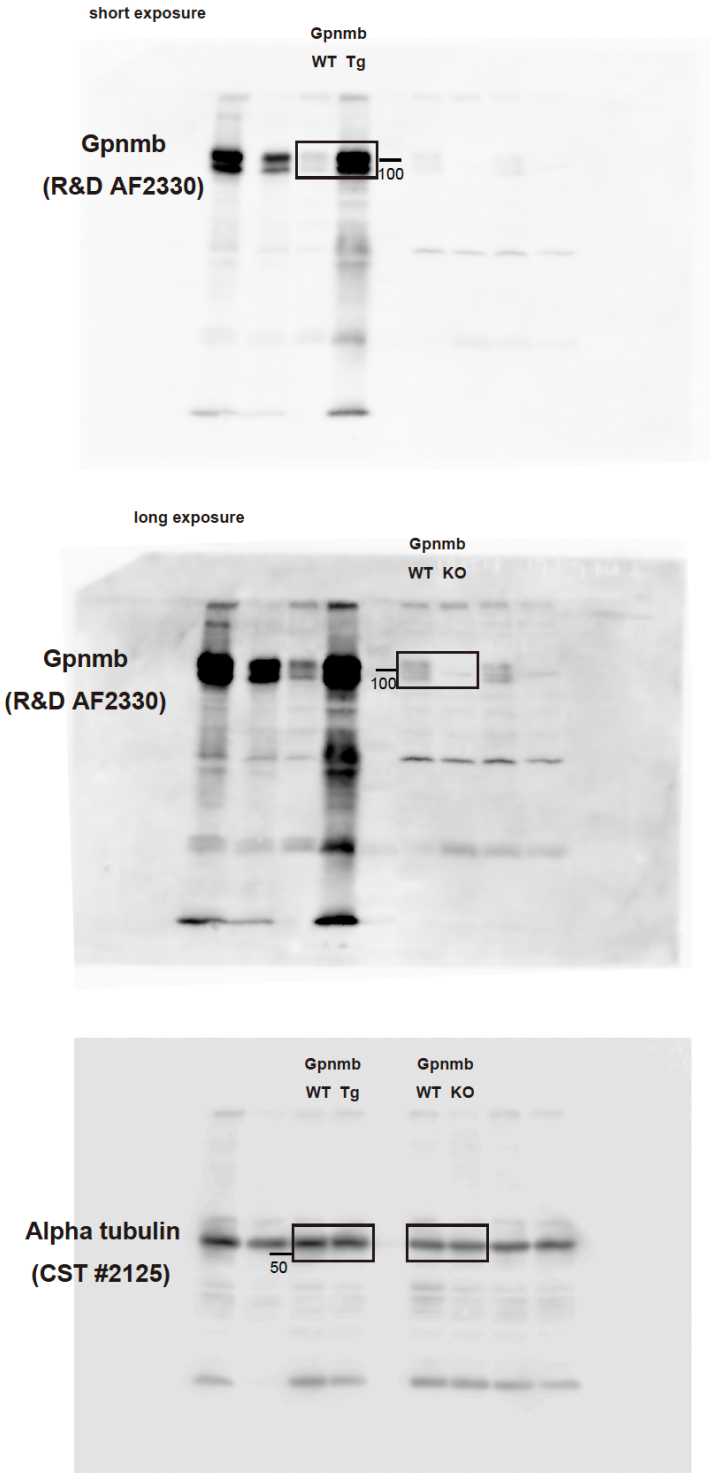
Supplementary Figure 7. Full blots of Figure 3b



Supplementary Figure 8. Full blots of Figure 3c



Supplementary Figure 9. Full blots of Figure 3d



Supplementary Figure 10. Full blots of Supplementary Figure 5a