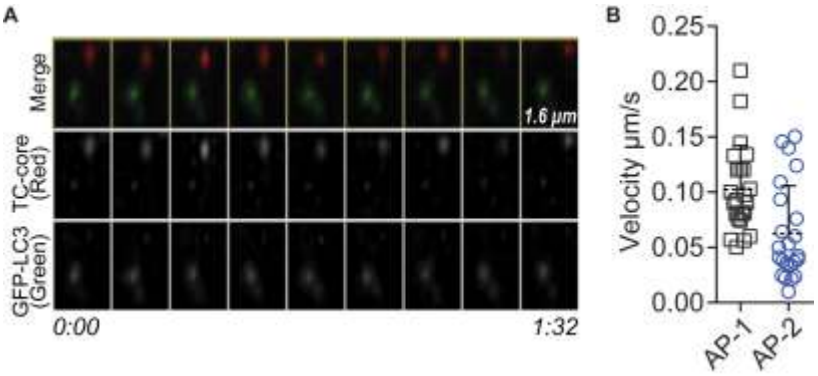
Supplemental Materials:

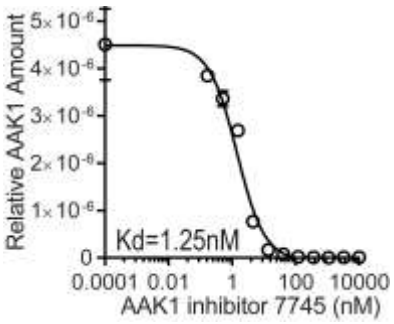
Supplemental Figures 1-7

Supplemental Table 1

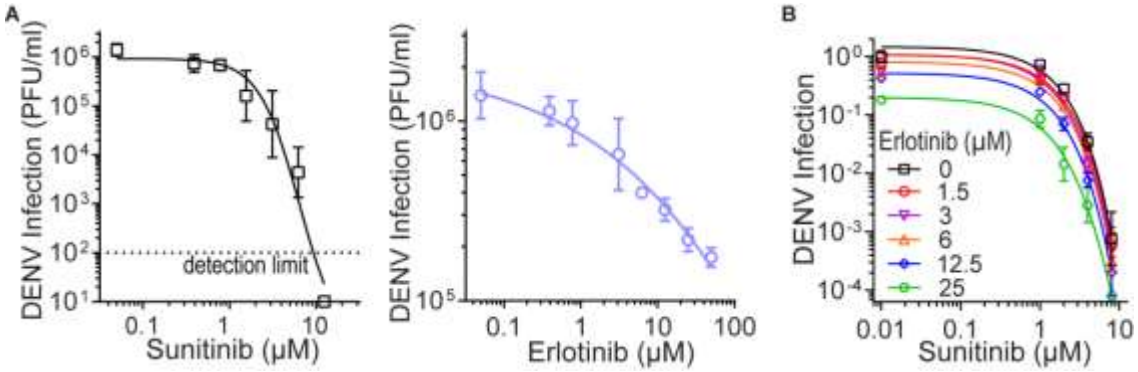
Supplemental Movies 1-10



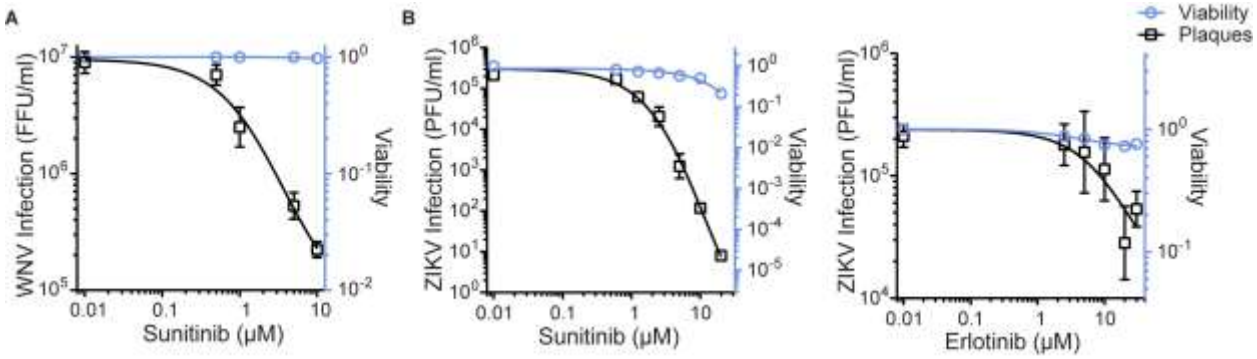
Supplemental figure 1. Co-trafficking of HCV particles with host proteins. (A) Representative montages from live cell fluorescence microscopy of TC-core HCV particles co-trafficking with GFP-LC3. **(B)** Velocity of individual TC-core puncta co-trafficking with AP1 or AP2. Experiments were replicated twice.



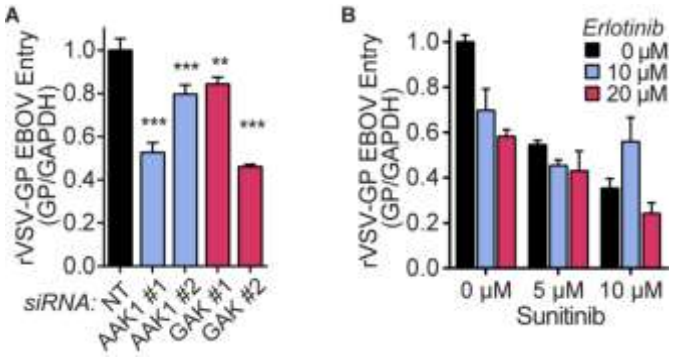
Supplemental figure 2. 7745 Kd. Kd of compound 7745 for AAK1 as measured by a KINOMEscan kinase assay (DiscoverX).



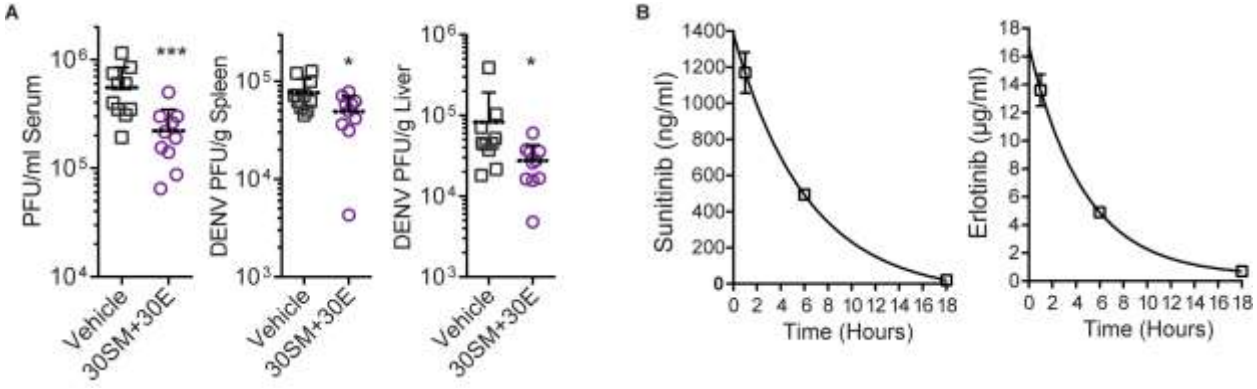
Supplemental figure 3. Dose response of DENV infection to sunitinib and erlotinib. (A) Dose response of overall DENV infection to sunitinib and erlotinib measured by plaque assays at 72 hours post-infection. Assay detection limit is marked with a dotted line. **(B)** Dose response of overall DENV infection to sunitinib/erlotinib combinations measured by luciferase assays at 48 hours post-infection and normalized to DMSO control. All data shown are representative of at least two experiments with 6 biological replicates each. Shown are mean +/- s.d. PFU, plaque forming units.



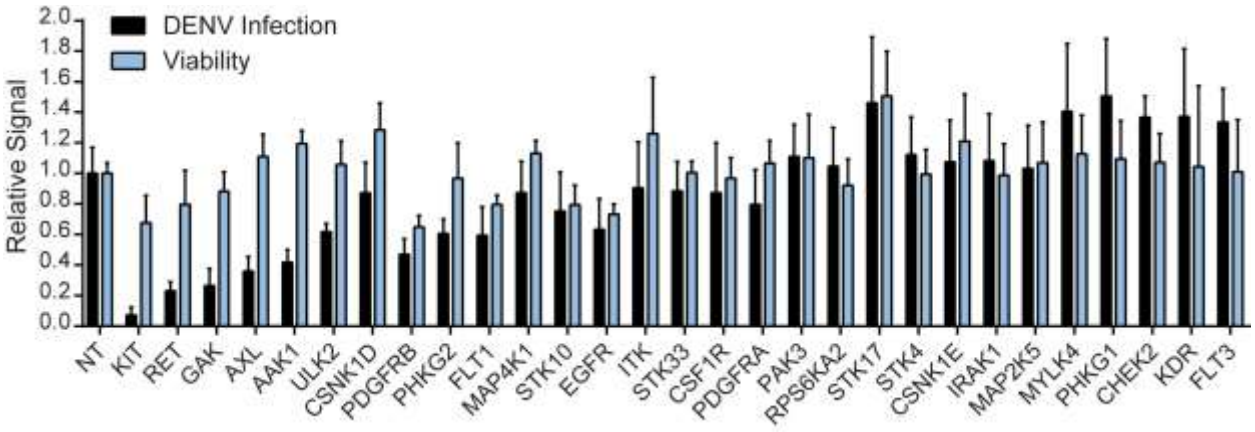
Supplemental figure 4. Activity of sunitinib and erlotinib against additional flaviviruses. (A) Overall infection of murine embryonic fibroblast cells with WNV (black) and relative cell viability (blue) following 24 hour treatment with sunitinib measured by focus formation and MTT assays, respectively. **(B)** Overall infection of Huh7 cells with ZIKV (black) and relative cell viability (blue) following 48 hour treatment with sunitinib and erlotinib measured by plaque and alamarBlue assays, respectively. Shown are representative experiments from at least two conducted with 2 (panel A) and 6 (panel B) biological replicates each.



Supplemental figure 5. Regulation of EBOV entry and overall infection by AAK1, GAK and their pharmacological inhibitors. (A, B) Quantification of rVSV-GP EBOV entry measured in Vero cells at 3 hours post-infection by real-time PCR following knockdown of AAK1 and GAK (**A**) or inhibitor treatment (**B**). Plotted is expression of EBOV GP normalized to GAPDH. Shown are mean +/- s.d. (n=3) relative to NT (A) or DMSO (B) controls (two-tailed unpaired t-test). **p<0.01, ***p<0.001 by 1-way ANOVA followed by Dunnett's multiple comparisons test. Shown are representative experiments from at least two conducted.



Supplemental figure 6. AAK1 and GAK inhibitors are protective in a dengue murine model. (A) Effect of sunitinib (SM) and erlotinib (E) on viral load in serum, spleen and liver on day 3 post-infection of AG-B6 mice measured by plaque assays. Drugs were administered intraperitoneally once daily. Doses are in mg/kg. *p<0.05, ***p<0.001 (nonparametric Mann-Whitney test). Experiments were replicated twice. **(B)** Quantification of drug serum levels in AG-B6 mice by liquid chromatography-tandem mass spectrometry following intraperitoneal administration of a single dose of 30 mg/kg sunitinib and 30 mg/kg erlotinib (n=2). Analysis was performed by Integrated Analytical Solutions (Berkeley, Ca). Shown are representative experiments from at least two conducted.



Supplemental figure 7. siRNA screen testing the involvement of kinases inhibited by sunitinib and erlotinib in DENV infection. Overall DENV infection (black) measured by luciferase assays and relative cell viability (blue) measured by alamarBlue assays at 48 hours post-infection of siRNA-transfected Huh7 cells. Data are expressed relative to NT siRNA. Data are an average of two independent screens with 8 replicates each.

Supplemental Table 1. siRNA library against top 27 kinase targets of sunitinib and erlotinib.

Pool Catalog #	Duplex Catalog #	Gene Symbol	GENE ID	Gene Accession	Sequence
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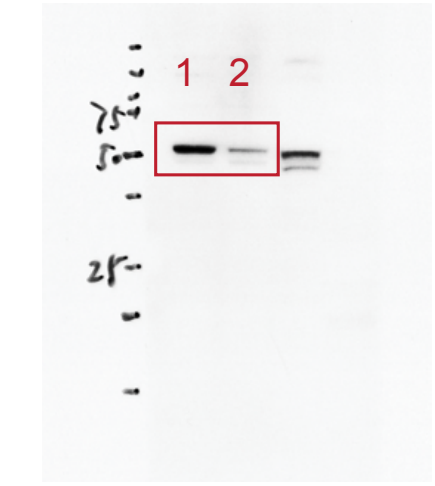
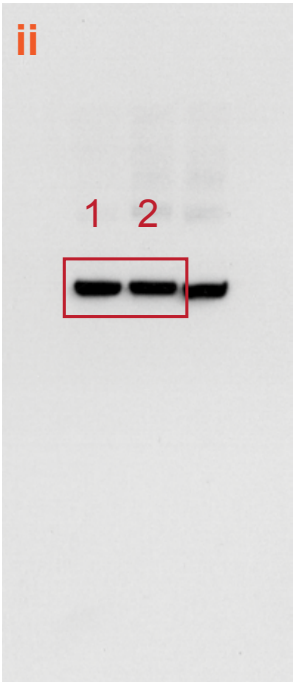
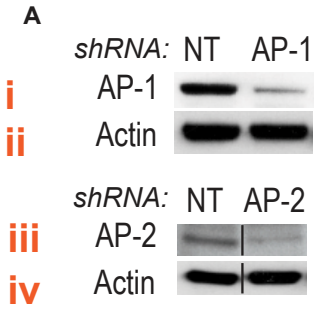
Supplemental Videos

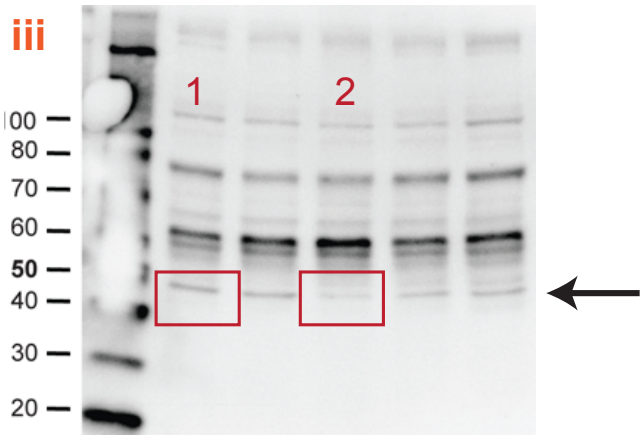
Supplemental Video 1. Co-trafficking of TC-core HCV with AP1. Representative video. TC-core (green), AP1 (red).
Supplemental Video 2. Co-trafficking of TC-core HCV with AP2. Representative video. TC-core (green), AP2 (red).
Supplemental Video 3. Co-trafficking of TC-core HCV with LC3. Representative video. TC-core (red), LC (green).
Supplemental Video 4. Co-trafficking of TC-core Y136A HCV with AP2. Representative video. Mutant TC-core (green), AP2 (red).
Supplemental Video 5. Co-trafficking of TC-core HCV with AP1 upon vehicle treatment. Representative video. TC-core (green), AP1 (red).
Supplemental Video 6. Co-trafficking of TC-core HCV with AP1 upon sunitinib treatment. Representative video. TC-core (green), AP1 (red).
Supplemental Video 7. Co-trafficking of TC-core HCV with AP1 upon sunitinib treatment. Representative video. TC-core (green), AP1 (red).
Supplemental Video 8. Co-trafficking of TC-core HCV with AP2 upon vehicle treatment. Representative video. TC-core (green), AP2 (red).
Supplemental Video 9. Co-trafficking of TC-core HCV with AP2 upon sunitinib treatment. Representative video. TC-core (green), AP2 (red).
Supplemental Video 10. Co-trafficking of TC-core HCV with AP2 upon erlotinib treatment. Representative video. TC-core (green), AP2 (red).

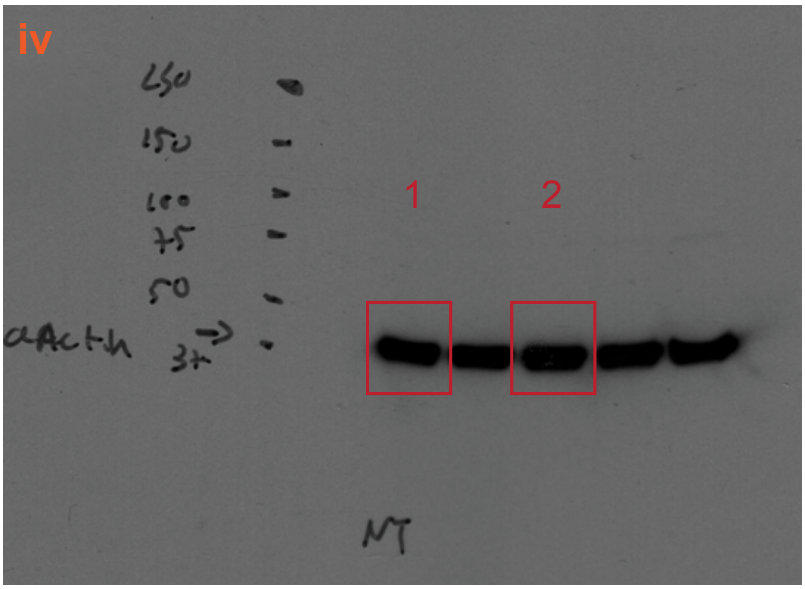
Full uncut gel for Figure 1A











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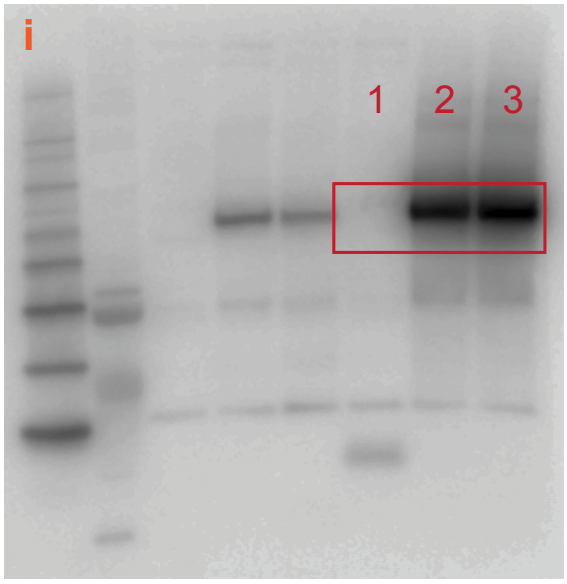

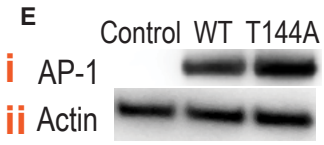

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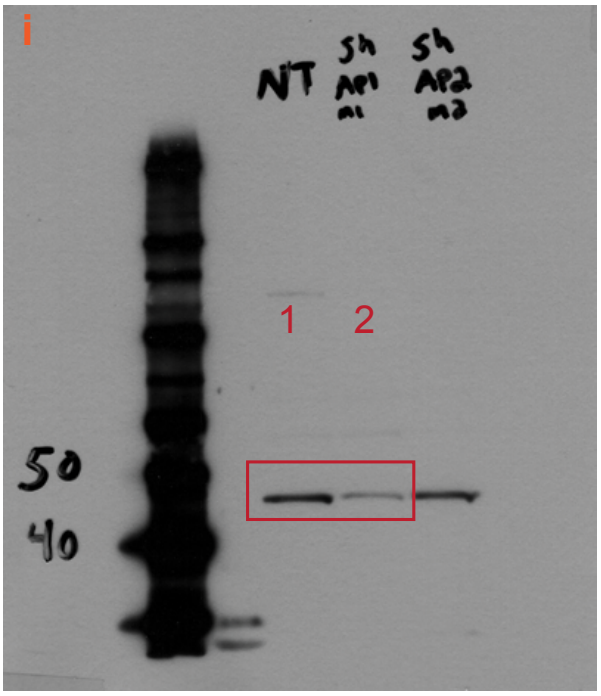
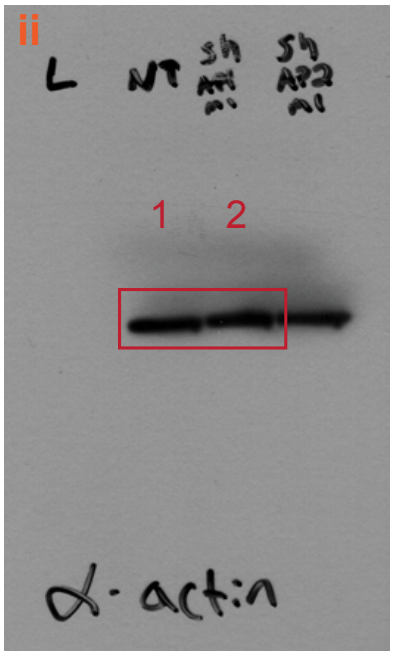
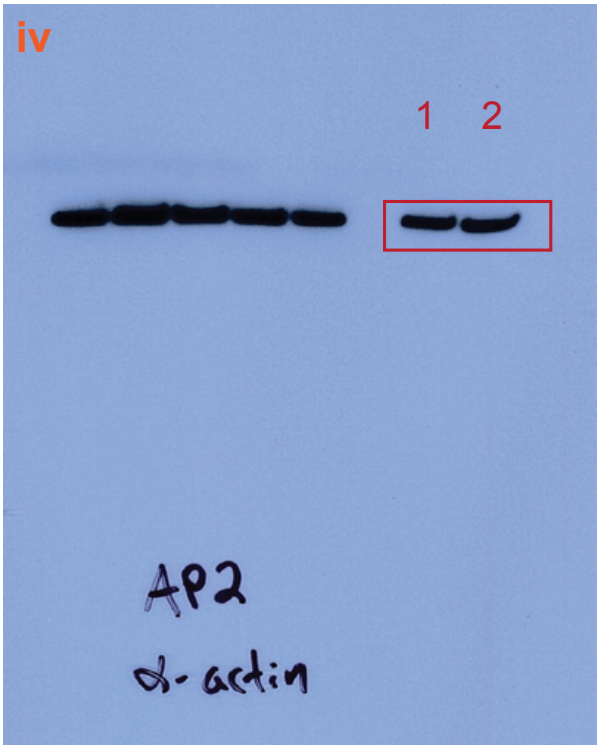
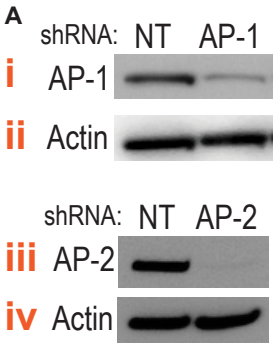
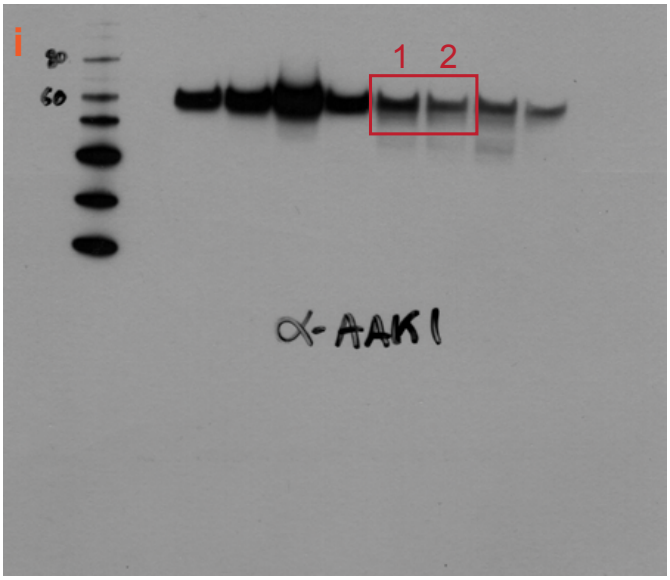


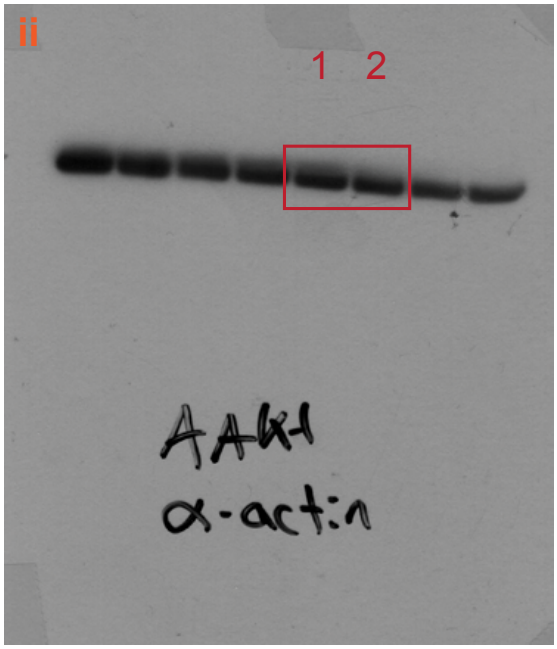


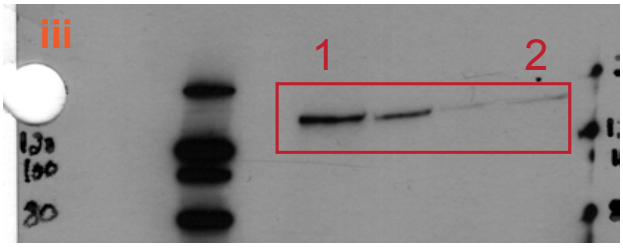


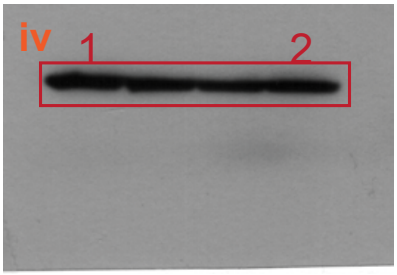


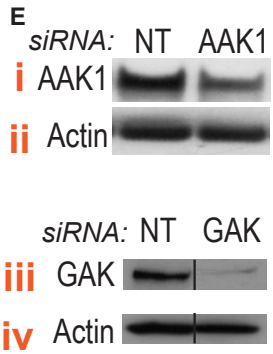
Full uncut gel for Figure 2E



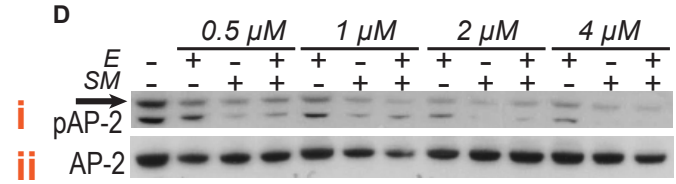


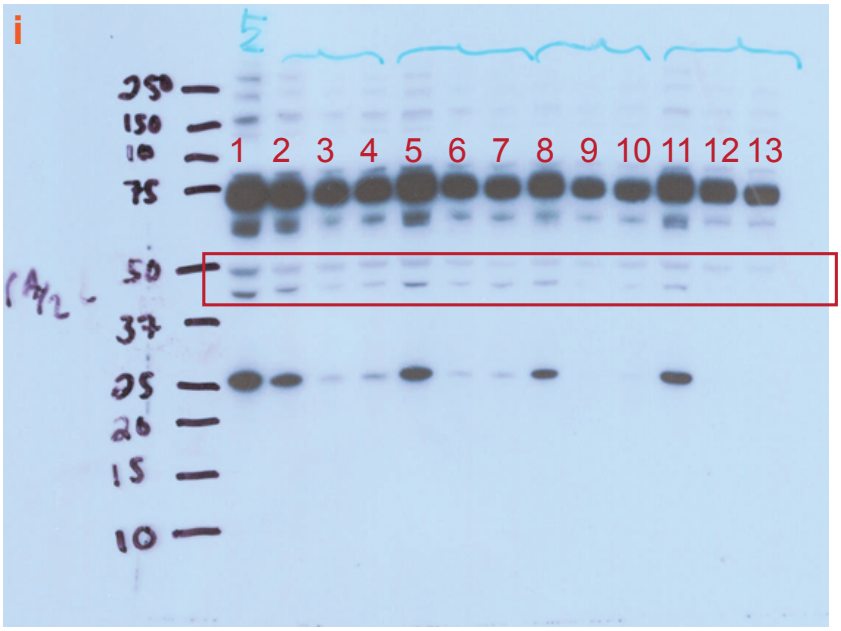


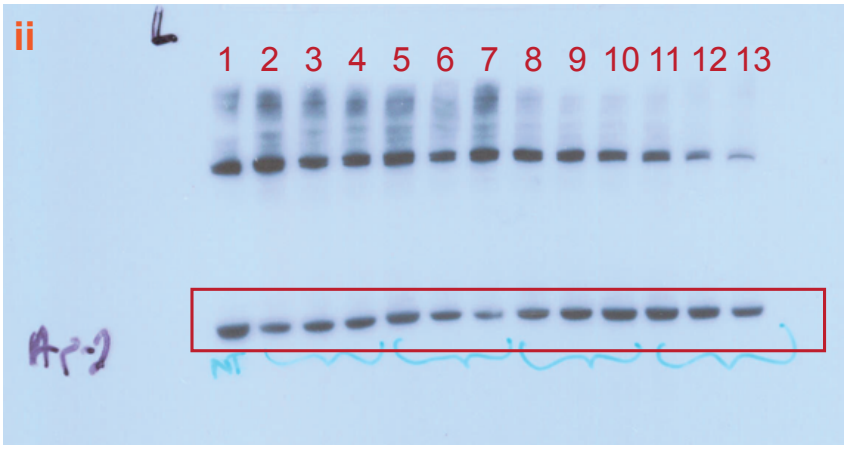




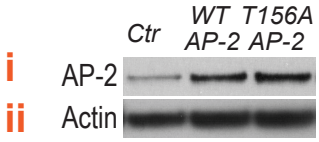
Full uncut gel for Figure 6D

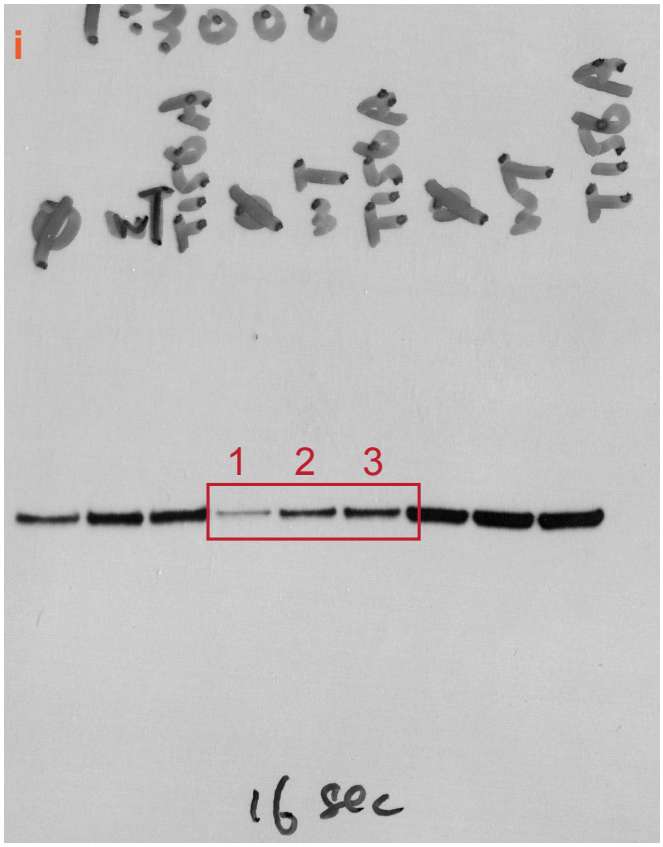


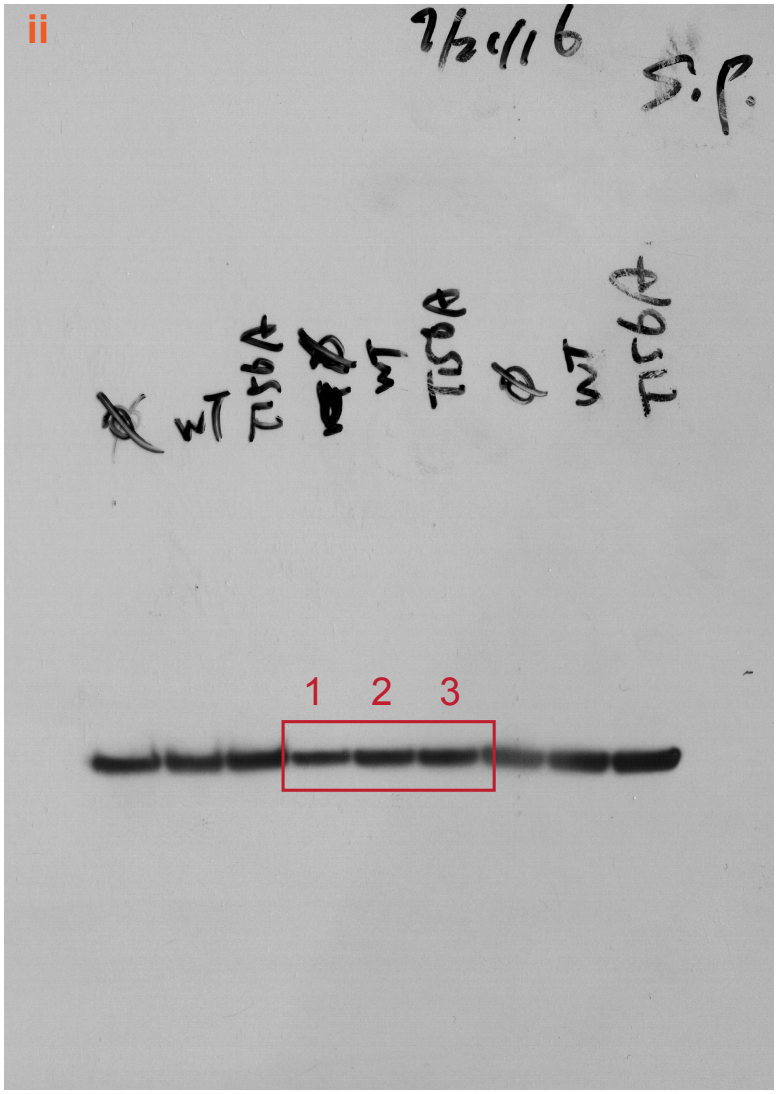




Full uncut gel for Figure 6E







Full uncut gel for Figure 6G