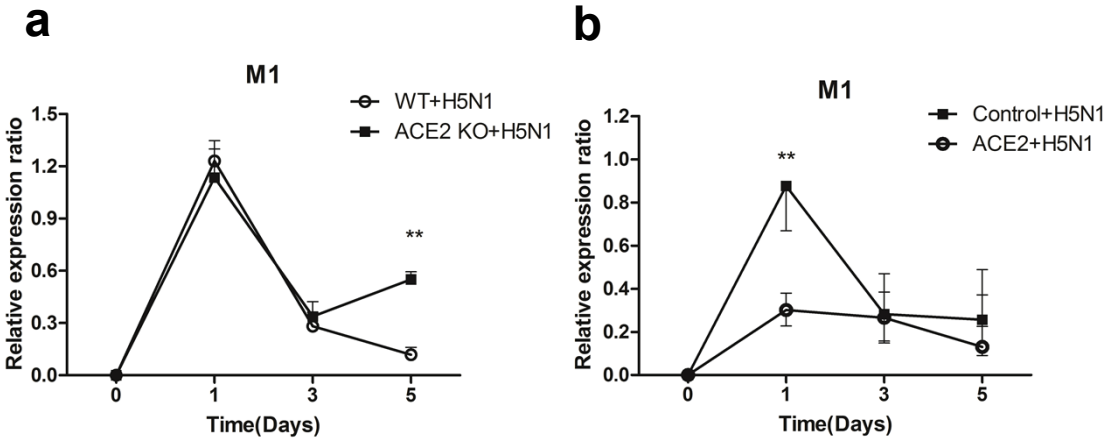
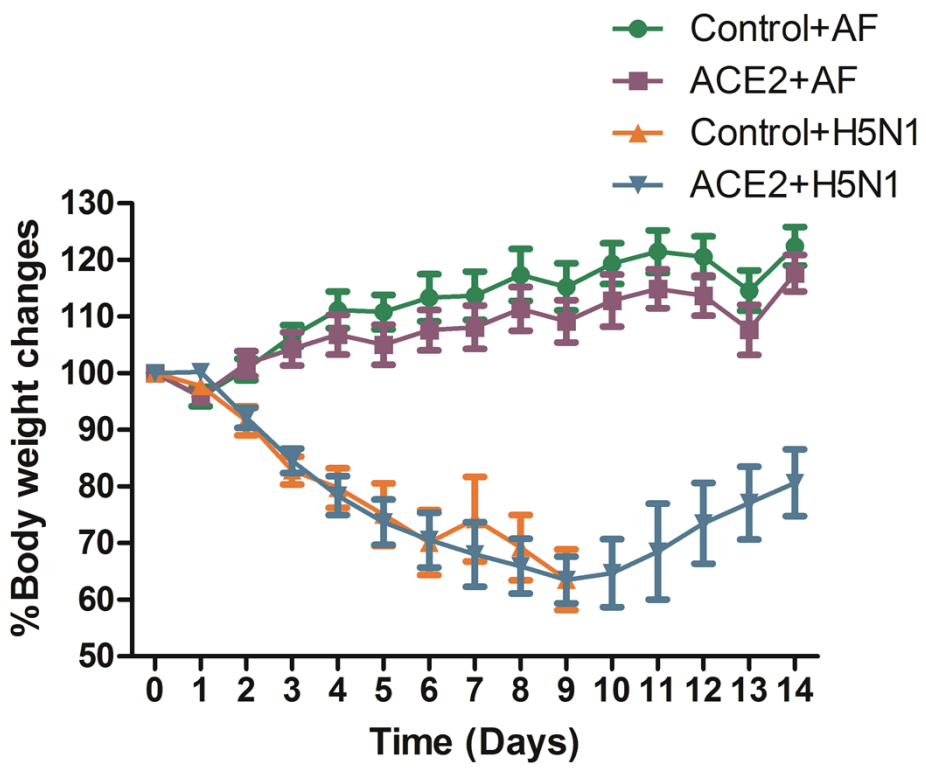
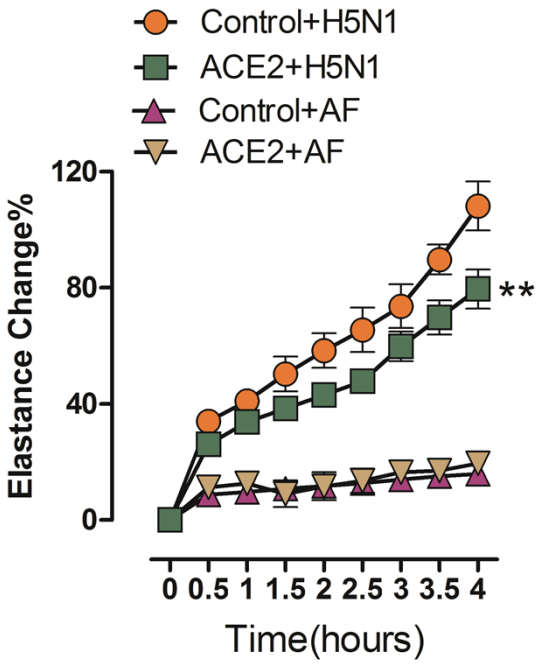


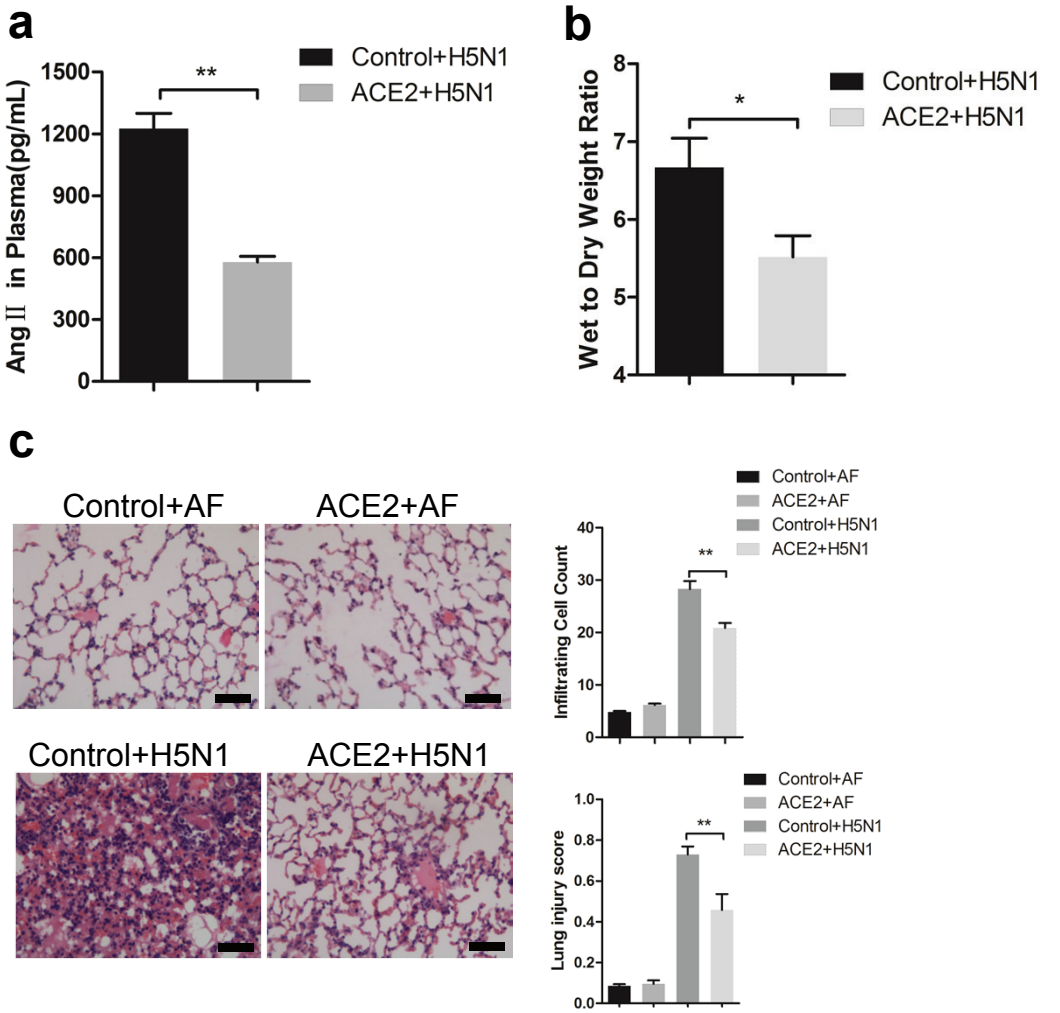
Supplementary Figure 1. Virus replication changes in ACE2 KO and recombinant hACE2-treated mice after H5N1 virus infection. (a)WT and ACE2 KO mice, **(b)** vehicle (BSA) or recombinant hACE2-treated mice were intratracheally instilled with H5N1 virus (10^6 $TCID_{50}$). The relative mRNA levels of H5N1 influenza A matrix 1(M1) expression were determined in the lungs of mice at the indicated time points using Real-Time PCR. Data are shown as mean±s.e.m., n=3-5 mice per time point. ** $p < 0.01$ (two-tailed t-test). Each experiment was repeated at least twice.



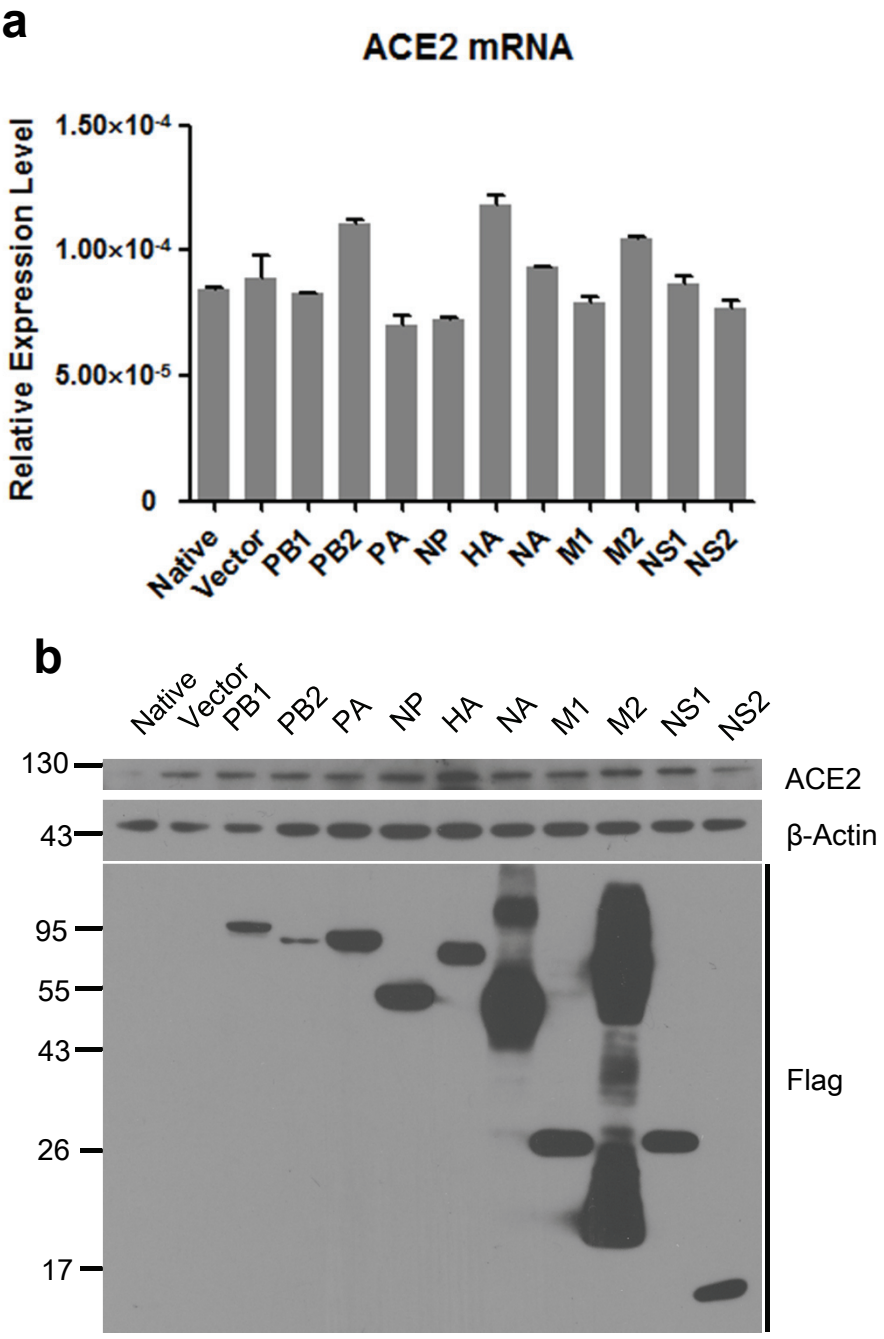
Supplementary Figure 2. Body weight changes in recombinant hACE2 protein-treated mice after H5N1 virus infection. Mice were treated with BSA+AF (control + AF, n = 5), recombinant hACE2 plus AF (n = 5), BSA plus H5N1 (n=21), and rhACE2 plus H5N1 (n=21). Mice were infected intratracheally with H5N1 (10^6 $TCID_{50}$). Body weights were recorded for a 14 day period after H5N1 infection. Data are shown as mean±s.e.m. The experiment was repeated three times.



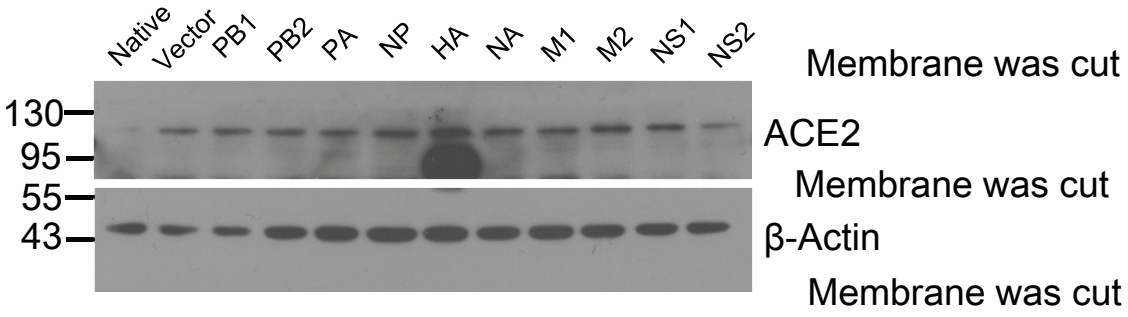
Supplementary Figure 3. Lung elastance changes in recombinant hACE2-treated mice after the intratracheal instillation of inactived H5N1 virus. Percent change in lung elastance following the intratracheal instillation of vehicle control or inactivated H5N1 virus (10 μg/g). The mice were treated with recombinant hACE2 protein (i.p.:0.1 mg/kg) or a vehicle (PBS). Data are shown as mean±s.e.m. n = 4-6 mice per group. ** p <0.01 (ANOVA with Bonferroni post-t-tests). Experiment was repeated twice.



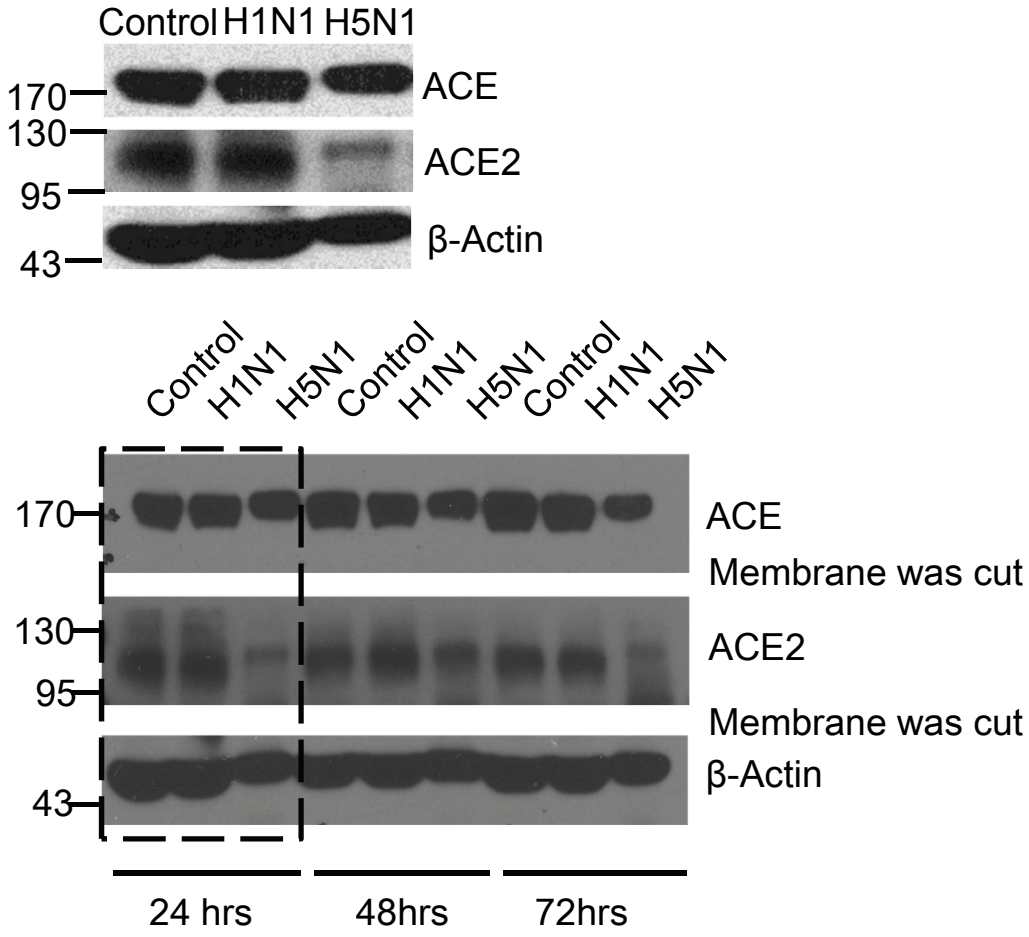
Supplementary Figure 4. Recombinant hACE2 protein shows protection effect in a different administration strategy. BALB/c mice were treated with vehicle (BSA) or recombinant hACE2 protein 1 hr, 1 day and 2 days after the instillation of AF or H5N1virus (10^6 $TCID_{50}$). **(a)** Angiotensin II levels in the serum of mice were determined using radioimmunoassays after 4 days. Data are shown as mean±s.e.m. n = 3-4 mice per time point. ** $p < 0.01$ (two-tailed t-test). **(b)** Wet/dry lung weight ratios were assessed after 4 days, Data are shown as mean±s.e.m. n = 4-5 mice per group. *$p < 0.05$ (two-tailed t-test). **(c)** Representative lung histopathology of mice. Scale bar = 100 μm. The numbers of infiltrating cells per microscopic field (mean ± SEM; top panel) and lung injury scores (mean± SEM; bottom panel) are shown for day 4 after infection in the bar graphs. n = 100 fields analyzed for three mice for each treatment.** $p < 0.01$ (two-tailed t-test). Each experiment was repeated three times.



Supplementary Figure 5. ACE2 expression levels in 293T cells expressing different H5N1 proteins. Ten indicated H5N1 protein-coding plasmids were transfected into 293T cell line. **(a)** Relative ACE2 mRNA (Data are shown as mean±s.e.m.) and **(b)** protein expression level determined after 48 hrs. GAPDH mRNA and β-Actin expression are set as control individually . The experiment was repeated four times.



Supplementary Figure 6 . Scans of Western blot shown in Supplementary Fig 5b. ACE2 expression in 293T cell 48 hours after transfection with indicated H5N1 protein-coding plasmids. β-actin expression is shown as a loading control.



Supplementary Figure 7. Scans of Western blot shown in Figure 2a. ACE2 expression in lung tissue of mice infected with live H5N1 virus, live H1N1, or treated with allantoic fluid (AF) as a control. β-actin expression is shown as a loading control.