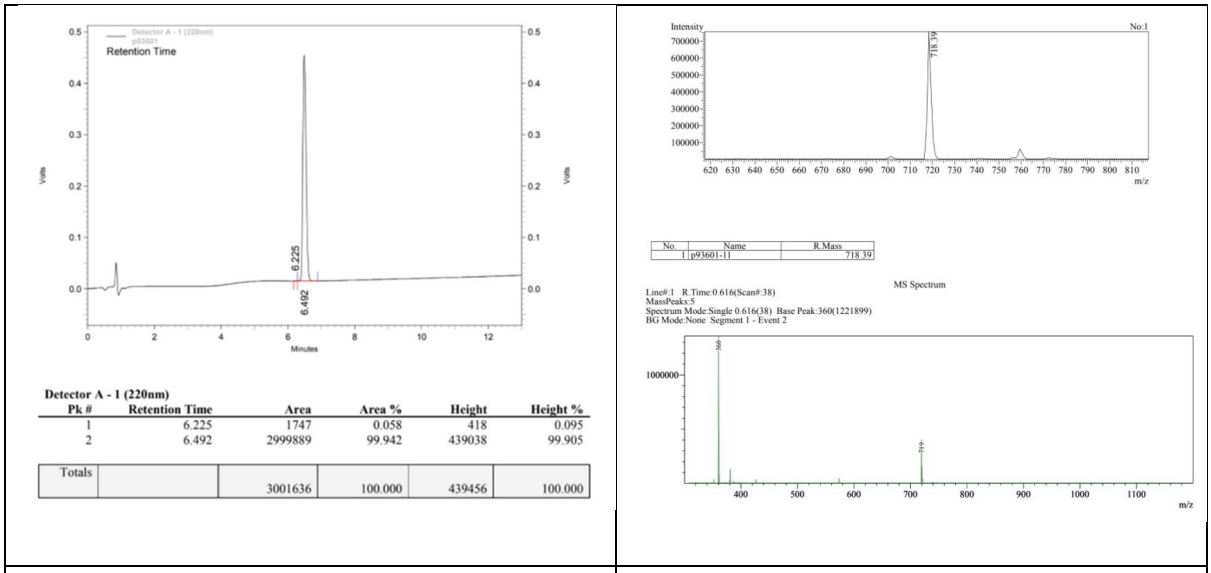
## SUPPLEMENTARY LEGENDS

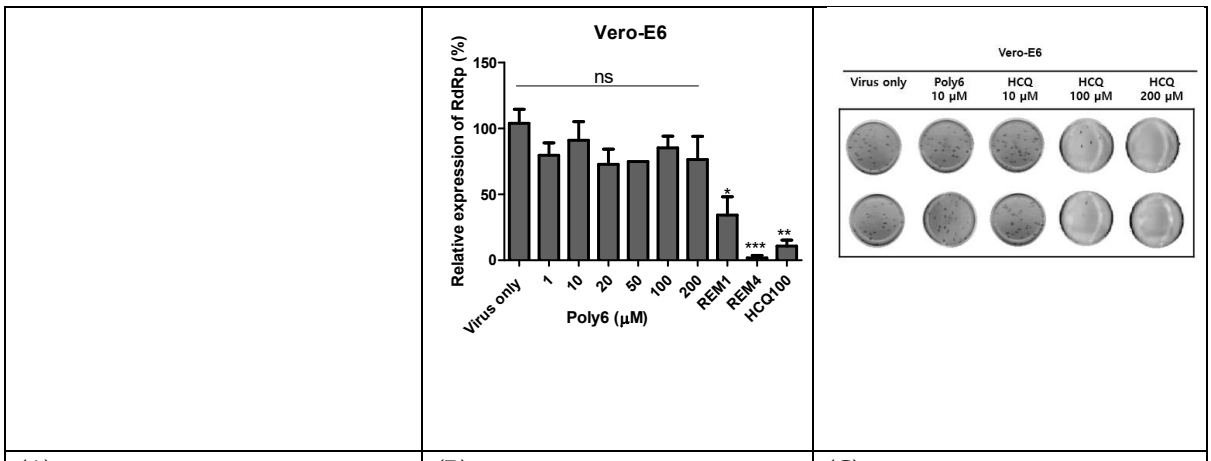
### Figure S1.




| (A) Area % Report | (B) MS Data Report |
|---|---|

The Poly6 (GRLVFQ) peptide was synthesized by the Fmoc (9-fluorenylmethoxycarbonyl)-based solid-phase method. The area percent report and MS data report was performed.

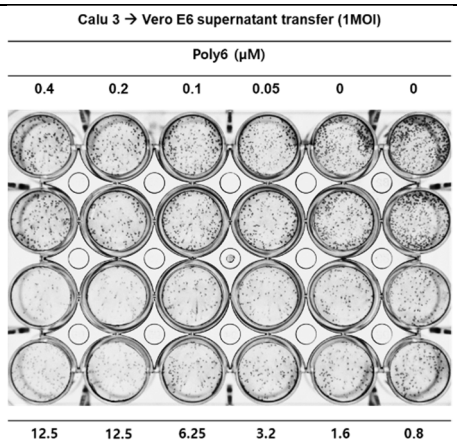
### Figure S2.

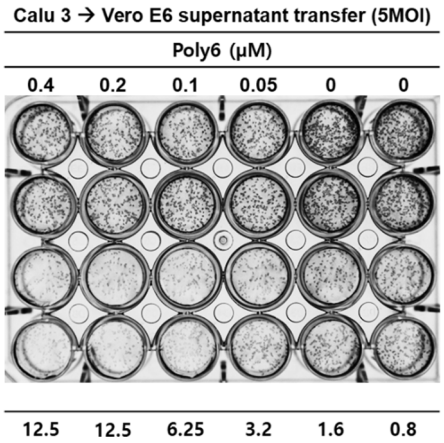


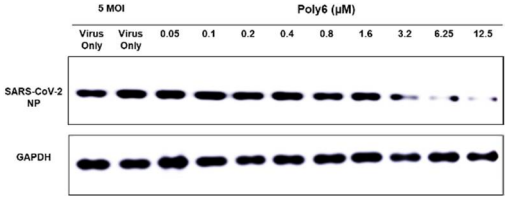

| (A) | (B) | (C) |
|---|---|---|

**Poly6 displayed limited ability to control SARS-CoV-2 in Vero E6 cells (A)** Vero-E6 cell viability subject to different doses of Poly6 treatment was measured by MTS assay. **(B)** SARS-CoV-2 viral load reduction assay in Vero-E6 cells. **(C)** SARS-CoV-2 plaque reduction assay in Vero-E6 cells. (D) Plaque assay of Poly6 on Calu-3 cells (Calu-3→Vero-E6 supernatant transfer). The experiments were performed in triplicate and repeated twice for confirmation. *indicates $p < 0.05$, **indicates $p<0.01$, and ***indicates $p<0.001$. The results are presented as mean values±SD. Abbreviation: RDV, remdesivir.

HCQ, hydroxychloroquine sulfate.

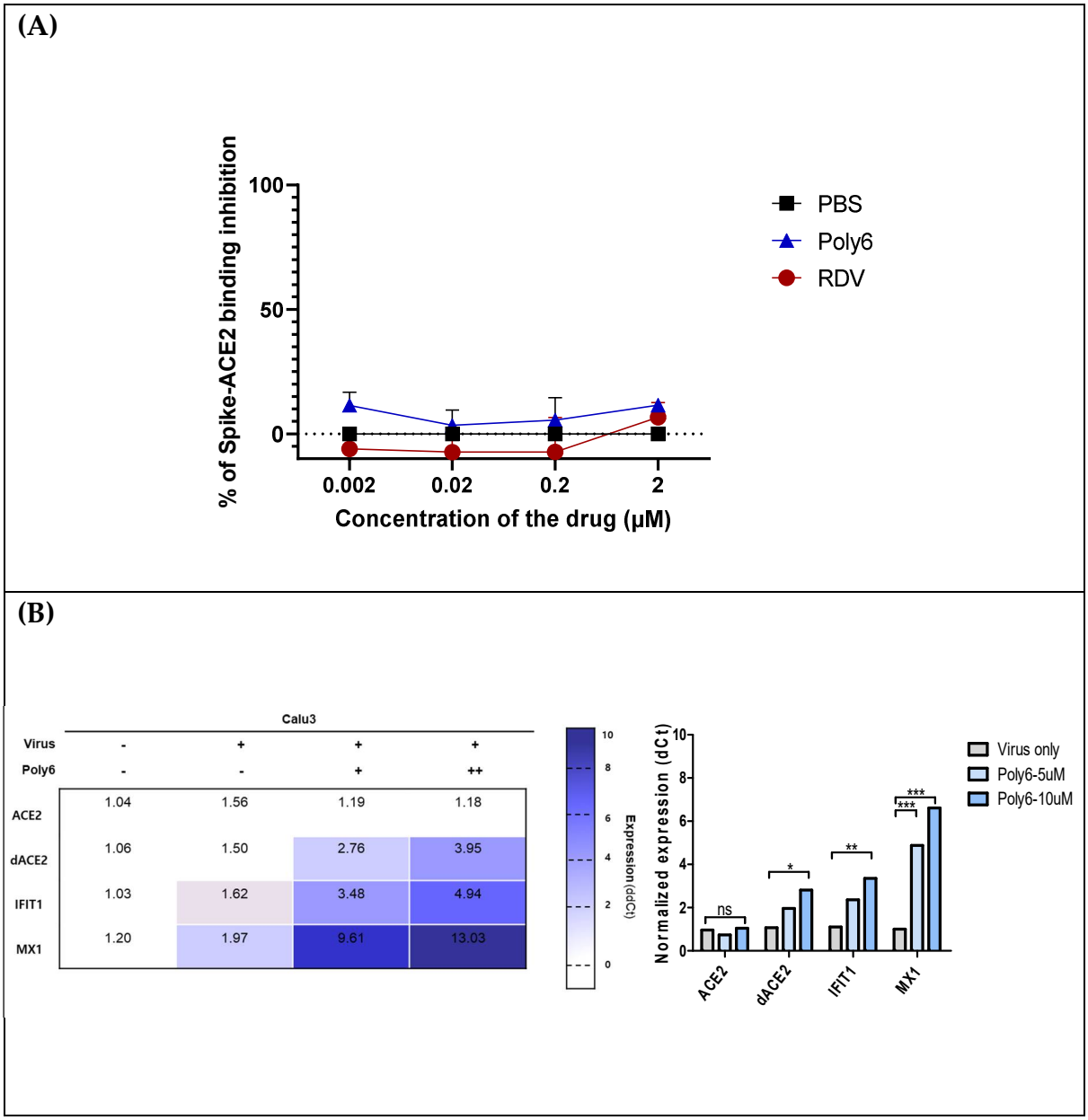



**(D)**

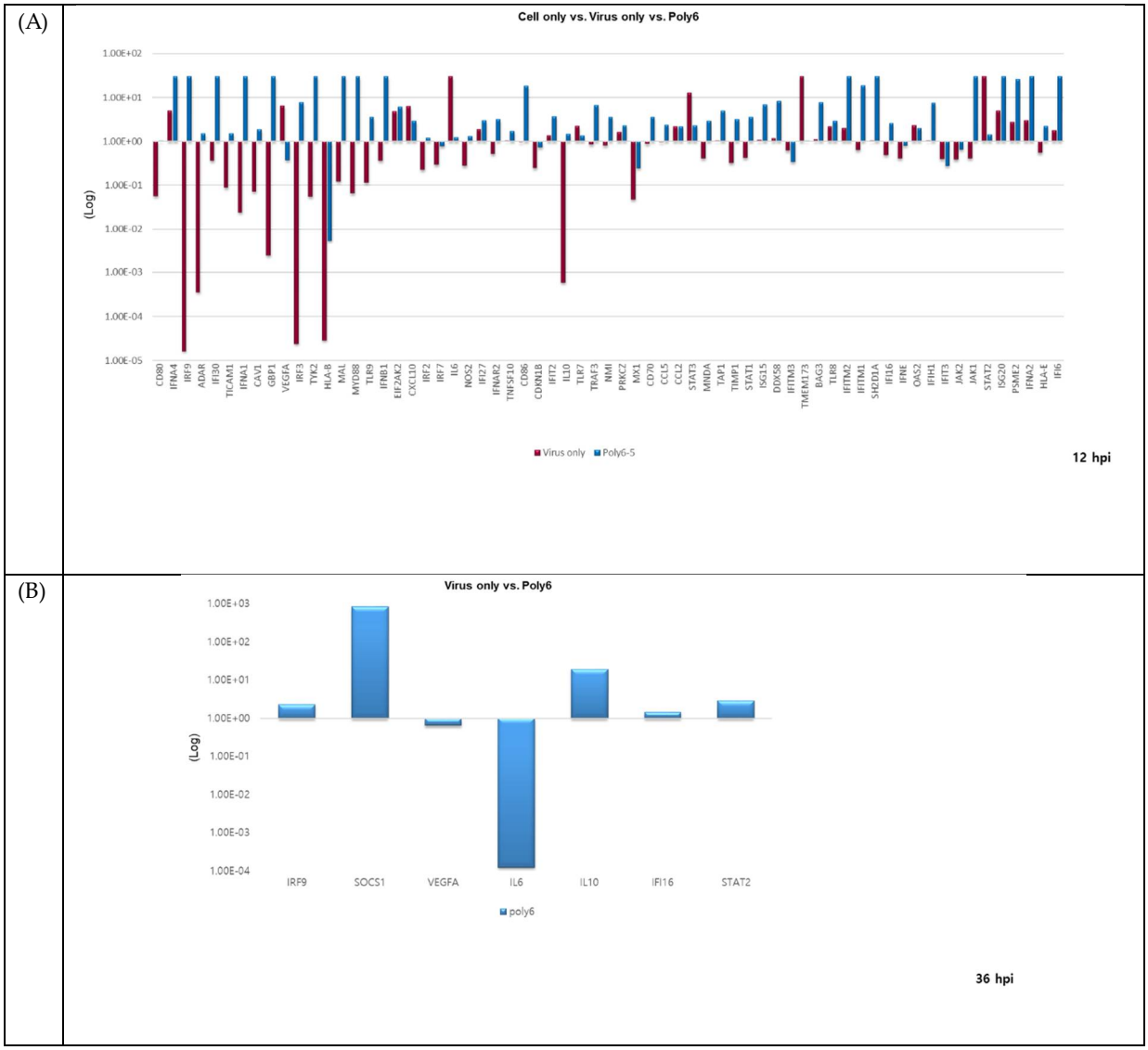
**Figure S3.**




**Poly6 and Remdesivir tested for neutralizing activity with SARS-CoV2 Spike-ACE2 binding assay**

(A) Competitive binding assay by Spike-ACE2 binding assay ELISA. SARS-CoV-2 RBD protein was coated on 96-well plates; recombinant ACE2 and serial dilutions of Poly6 and RDV were added for competitive binding to SARS-CoV-2 RBD. Values are the mean±SD. Experiments were performed in duplicate. (B) The expression of ACE2, dACE2, and positive control ISGs, IFIT1 and MX1 in Calu-3 cells treated with Poly6 following SARS-CoV-2 infection. A heatmap was depicted and the colors represent fold change levels as ddCt normalized by control (bActin). Data represent the mean±SD. *$p < 0.05$, **$p < 0.01$, and ***$p < 0.001$. The experiments were performed in triplicate and repeated twice for confirmation.

**Figure S4**.




**mRNA expression profiles for IFN-I response genes encoding interferons/receptors in SARS-CoV-2 infected Calu-3 cells and following treatment of Poly6. (A)** mRNA expression profiles in SARS-CoV-2 infected cells and treatment of Poly6 (12hpi). Fold changes in Virus only or Poly6-treated group were normalized to Cell only group **(B)** mRNA expression profiles in SARS-CoV-2 infected cells and treatment of Poly6 (36hpi). Fold changes in the Poly6-treated group were normalized to Virus only group. The experiments were repeated twice for confirmation. The experiments were performed in duplicate and repeated twice for confirmation.

## Western blot whole blot data

**Figure S5.**

**SARS-CoV-2 Spike (S1)**

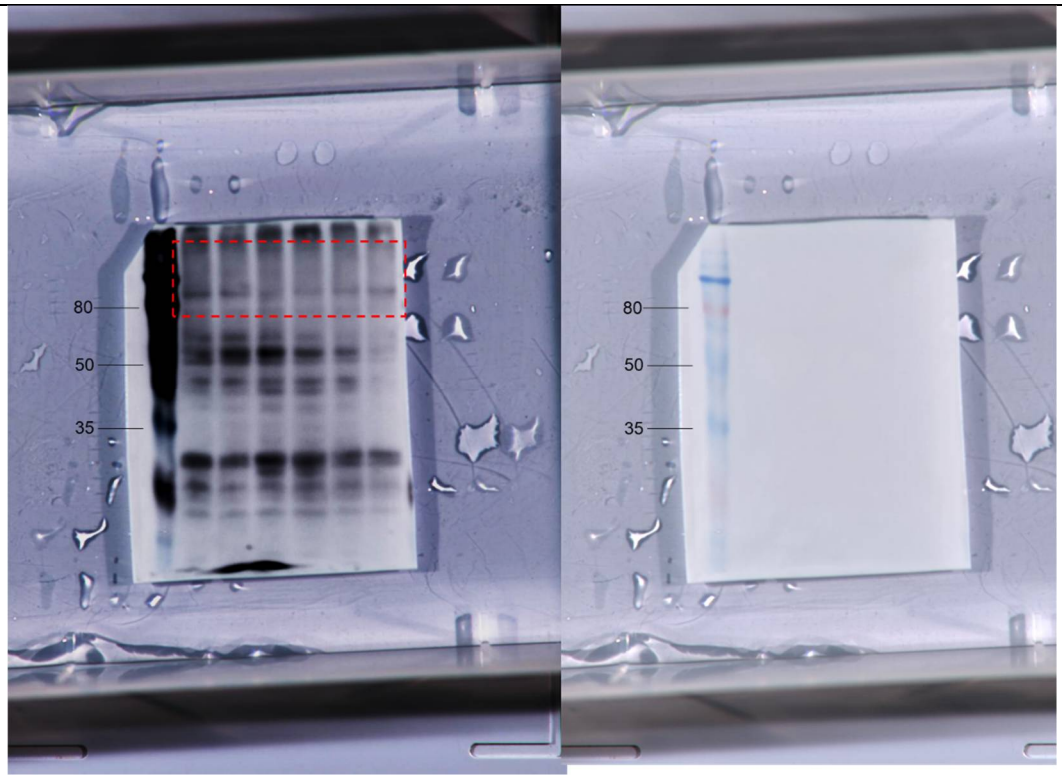
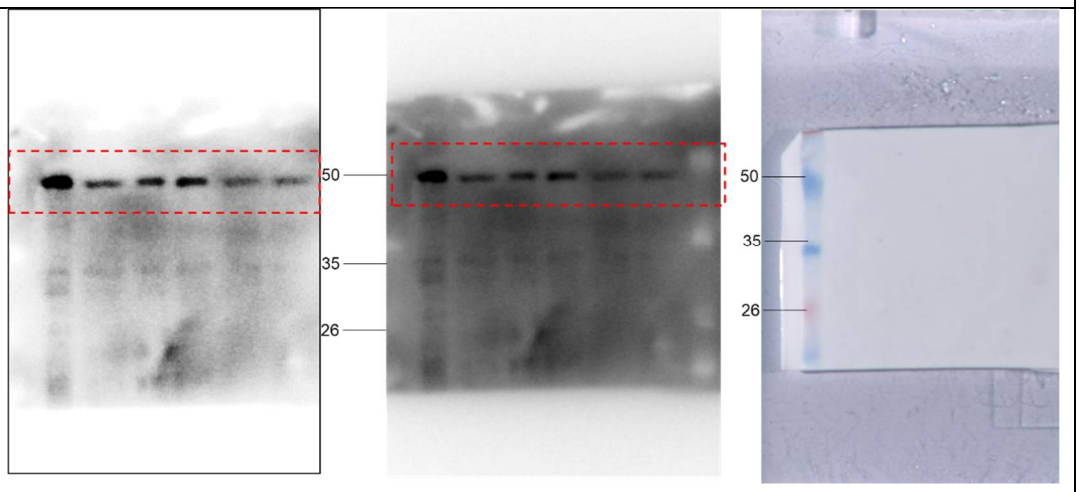
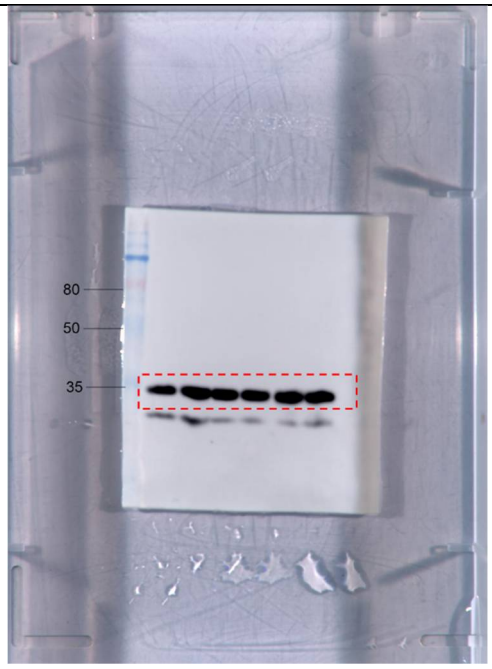
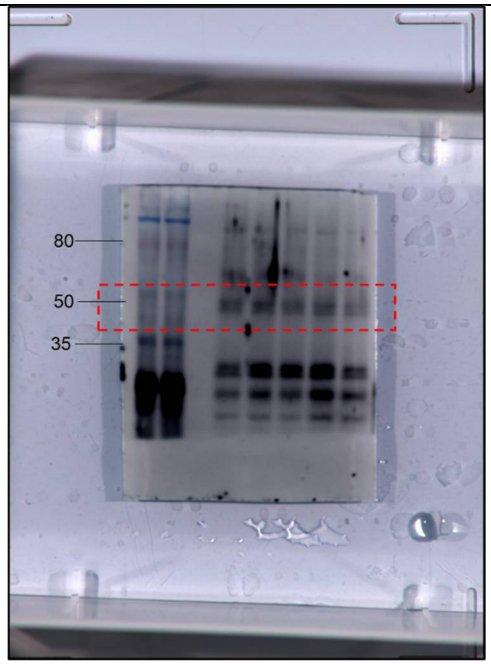



**Figure S6.**

**SARS-CoV-2 NP**



| | |
|---|---|
| **Figure S7.**<br><br>**GAPDH** |  |
| **Figure S8.**<br><br>**IRF3** |  |

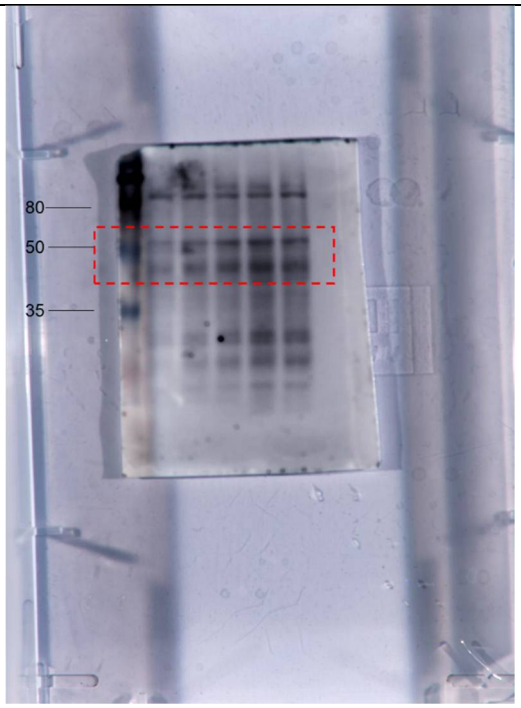
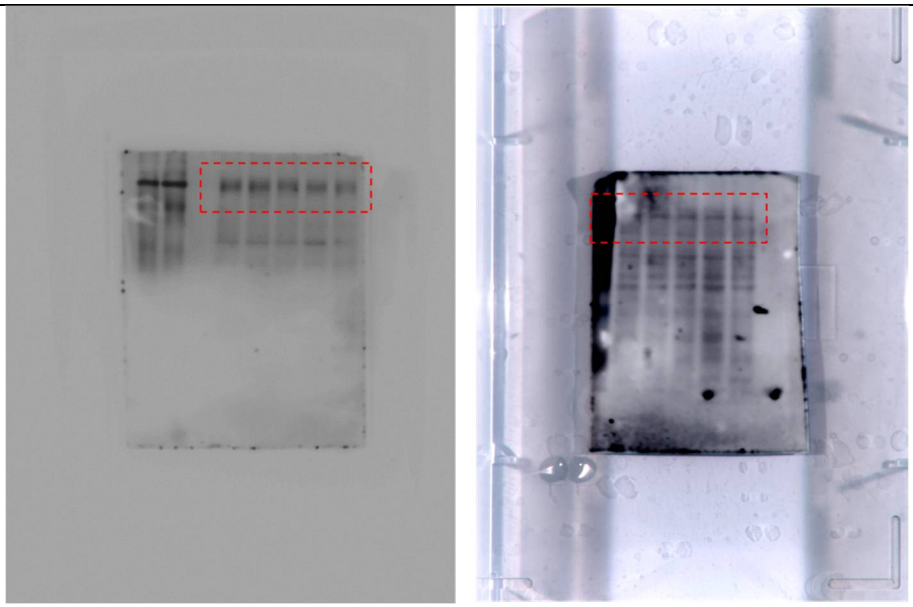
| | |
|---|---|
| **Figure S9.**<br><br>**p-IRF3** |  |
| **Figure S10.**<br><br>**STAT1** |  |

**Figure S11.**

**p-STAT1**

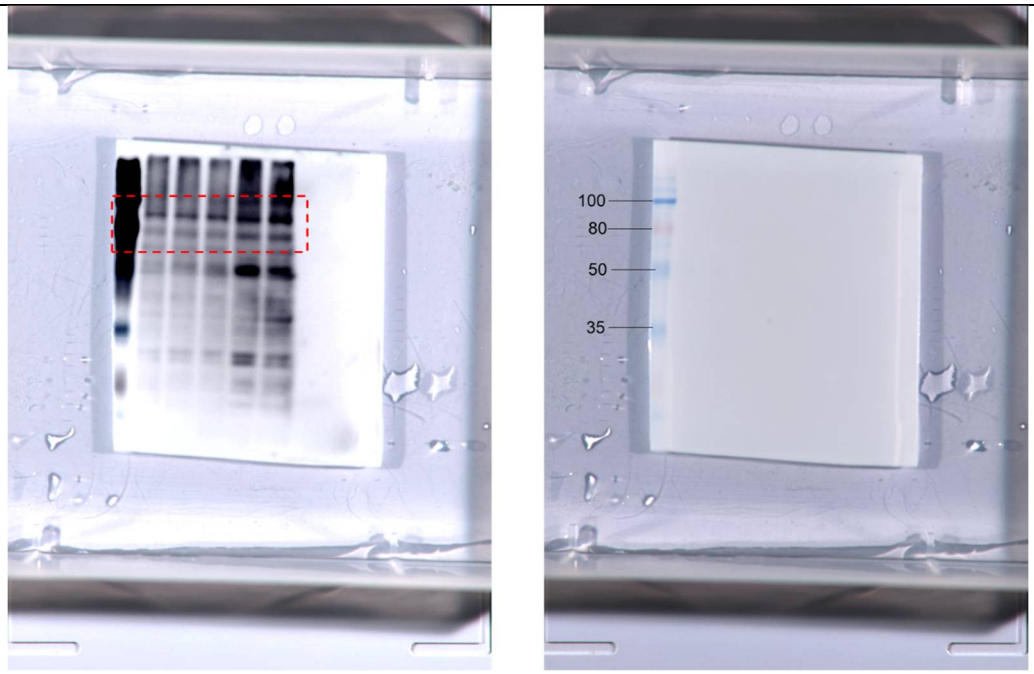



**Figure S12.**

**SARS-CoV-2**

**NP**

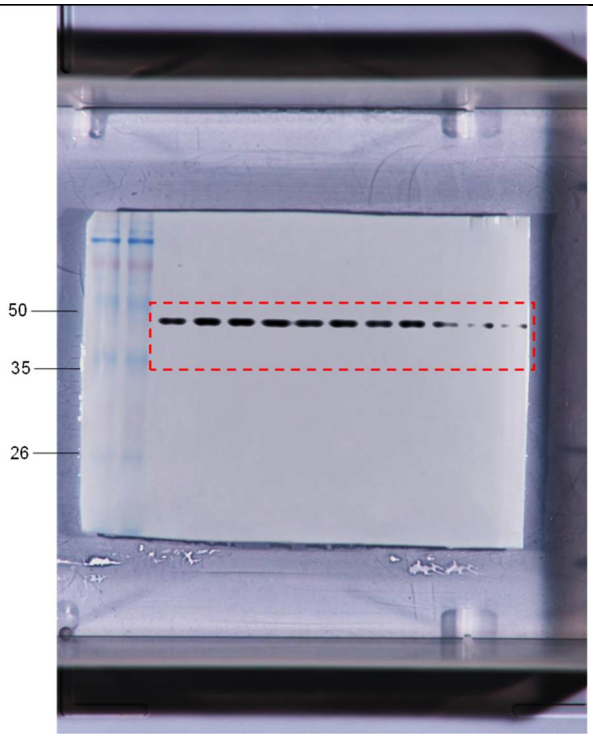
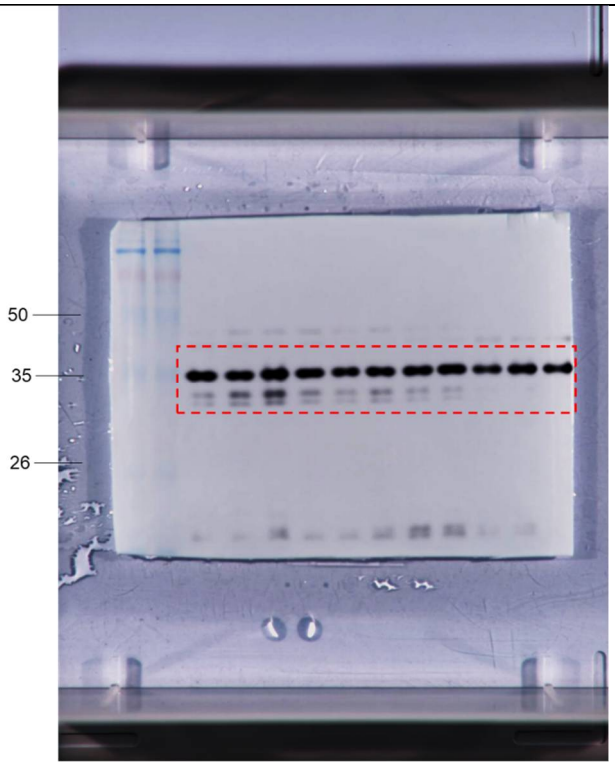


**Figure S13.**

GAPDH