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**Supplementary Data**

**Design of antiviral AGO2-dependent short hairpin RNAs**

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**Supplementary figs and tables**

**Supplementary Figure-S1**

**Figure S1. Transcriptome sequencing analysis of gene expressions in cells transfected with agshEV71-h1 and agshNC.** Human 293T cells were transfected with agshEV71-h1 and agshNC, respectively. At 24 h post transfection, total RNAs were extracted to perform RNA sequencing. Reads align to human genome (GRCh38) were annotated using htseq-count. Genes with counts per million reads (CPM) lower than 5 were excluded. Different expression genes (DEGs) were defined by |log2FC| > 1, P.adj < 0.05. Up-regulated DEGs were showed in red and down-regulated in blue.

**Supplementary Table S1. Feature matrix of siRNA used for model training**

**Supplementary Table S2. Scores of evaluated siRNA sequences targeting differernt viruses**

**Supplementary Table S3. The sequences of agshRNAs**

**Supplementary Table S4. Transcriptomic analysis of 293T cells transfected with agshEV71-h1 and agshNC**

**Supplementary Table S5. Profiles of small RNAs**

**Supplementary Table S6. Primers and probes used in this study**