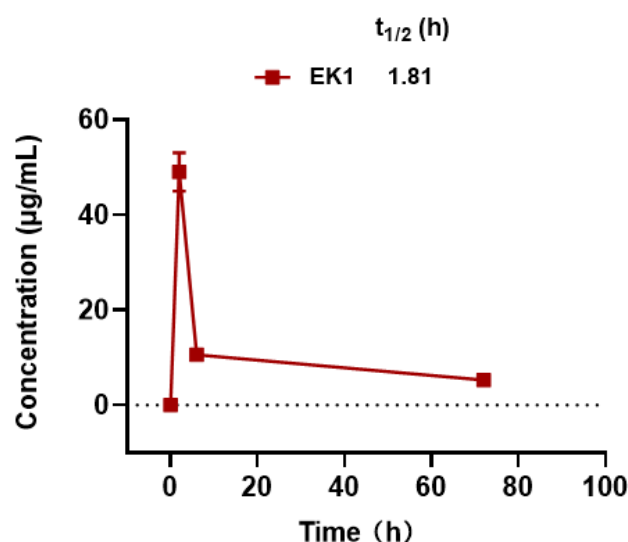


**Figure S2.** Pathology sections of mouse brain tissues of each group 5 days after administration. (a) Pathology sections of mouse brain tissues of each group 5 days after prophylactic administration. (b) Pathology sections of mouse brain tissues of each group 5 days after therapeutic administration. Scale bar, 50  $\mu$ m.

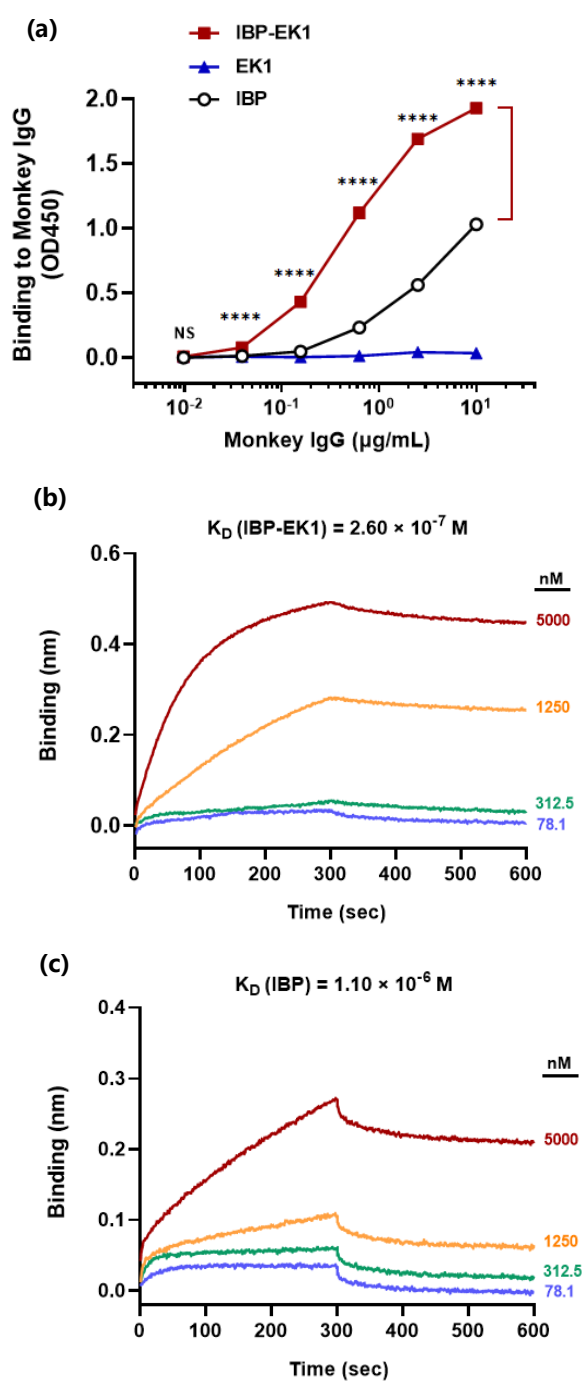
(a)

Identities		Positives	Gaps
200/223 (90%)		210/223 (94%)	0/223 (0%)
5W5L 225	TCPPCPAPELLGGPSVFLFPPKPKD	LMISRTPEVTCVVVDVSQEDPDVKFN	
6D4E 225	.....AA.AS.....A...E....		
5W5L	WYVNGAEVHHAQTKPRETQYNSTYRVVSVLTVTHQDWLNGKEYTCKVSNKAL		
6D4E	...D.V...N.K.....E.....L.....K.....		
5W5L	PAPIQKTISKDKGQPREPQVYTLPPSREELTKNQVSLTCLVKGFYPSDIIVE		
6D4E	.SS.E.....A.....D.....A..		
5W5L	WESSGQPENTYKTTTPVLDSGYSFLYSKLTVDKSRWQQGNVFCFSVMHEAL		
6D4E	...N.....N.....F.....		
5W5L	HNHYTQKSLSVSPGK 447		
6D4E	.....L..... 447		

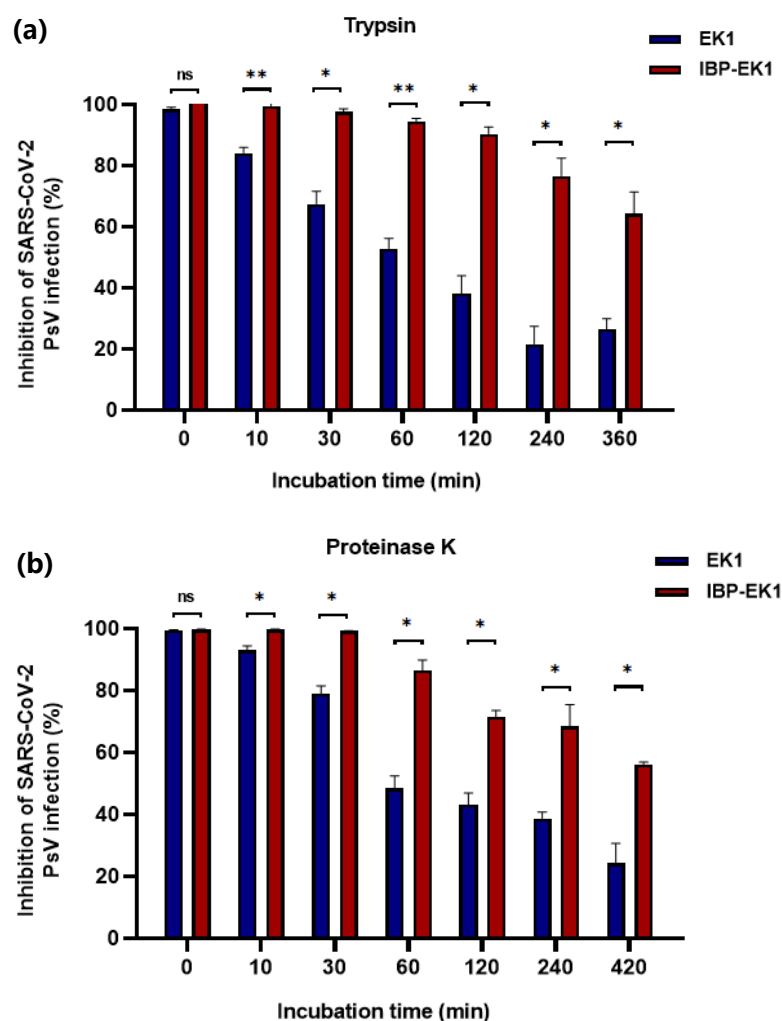
(b)



**Figure S3.** Homology between IgG1 Fc region of homo sapiens and rhesus monkey, and measured EK1 concentrations in sera by HPLC-MS/MS. **(a)** Homology between IgG1 Fc region of homo sapiens and rhesus monkey. Fasta files of IgG1 Fc CH2-CH3 region of human (PDB ID: 5W5L) and rhesus monkey (PDB ID: 6D4E) were exported from PDB, respectively, and aligned by blastp tool. Residues in red boxes are critical residues binding to IBP. **(b)** Measured EK1 concentrations in rhesus monkey sera by the method of HPLC-MS/MS. Sera were diluted 10-fold and then injected into UPLC-Q-TOF-MS for detection.



**Figure S4.** Binding of IBP, EK1 and IBP-EK1 to rhesus monkey IgG, as detected by ELISA (a) and BLI (b-d). NS,  $p > 0.05$ ; \*\*\*\*  $p < 0.0001$ . In the BLI assay, 10  $\mu\text{g/mL}$  IgG were immobilized at the surface of Fc biosensors, and then diluted peptide solutions were loaded. Data were analyzed and globally fit with the ForteBio software. Equilibrium dissociation constants ( $K_D$ ) are reported above the plot.



**Figure S5.** Tolerance of IBP-EK1 to protease digestion. (a) Inhibitory activities against SARS-CoV-2 PsV infection of EK1 and IBP-EK1 samples incubated with 25  $\mu\text{g/mL}$  trypsin for different time. (b) Inhibitory activities against SARS-CoV-2 PsV infection of EK1 and IBP-EK1 samples incubated with 100  $\mu\text{g/mL}$  proteinase K for different time. Unpaired, 2-tailed  $-t$  test was performed. No significance (ns),  $p > 0.05$ ; \*  $p < 0.05$ , \*\*  $p < 0.01$ . A representative example of two independent experiments was shown.

**Table S1.**  $\text{IC}_{50}$  values of S309 and 10933 against PsV infection of sarbecoviruses (mainly SARS-CoV-2 variants). ND, not detected. Each experiment was repeated twice.

Sarbecoviruses	$\text{IC}_{50}$ (ng/mL) against pseudotyped sarbecoviruses on Caco-2 cells	
	S309	10933
SARS-CoV	86	ND
WIV1-CoV	769	ND
SARS-CoV-2 prototype	722	27
B.1.1.7	134	12
B.1.351	90	114
P.1	150	137

B.1.617.2	284	20
BA.1	323	1859
BA.2	482	>10,000
BA.2.12.1	574	>10,000
BA.2.75	640	>10,000
BA.5	706	>100,000
BA.4.6	1340	>100,000
BF.7	1098	>100,000
XBB	1278	>100,000
BQ.1.1	4180	>100,000

**Table S2.** Combination index and dose reduction values of inhibiting SARS-CoV-2 S-mediated cell-cell fusion by IBP-EK1 combination with S309.

% Inhibition for IBP-EK1 in combination with S309 against cell- cell fusion	CI	S309			IBP-EK1		
		Concentration		Dose reduction	Concentration		Dose reduction
		(nM)			(nM)		
		Alone	Mix		Alone	Mix	
10	0.44	0.13	0.03	3.9	25.7	4.8	5.4
20	0.34	0.42	0.07	5.8	65.6	11.0	6.0
30	0.29	0.96	0.13	7.5	122.2	19.1	6.4
40	0.26	1.86	0.20	9.3	203.6	30.0	6.8
50	0.23	3.42	0.30	11.3	325.0	45.5	7.1
60	0.21	6.30	0.46	13.7	519.0	68.9	7.5
70	0.18	12.25	0.72	17.0	864.3	108.4	8.0
80	0.16	27.59	1.25	22.0	1610	188.2	8.6
90	0.14	93.55	2.88	32.5	4105	432.1	9.5

**Table S3.** Prediction of the physicochemical properties of IBP-EK1 and IBP. GRAVY, Grand average of hydropathicity; if the value is negative, the protein/peptide is hydrophilic, otherwise hydrophobic. The ProtParam tool (<https://web.expasy.org/protparam/>) was adopted to predict these properties.

Properties	IBP-EK1	IBP	EK1
Instability index	29.30 (stable)	46.72 (unstable)	22.73 (stable)
GRAVY	-0.206	0.423	-0.433
Aliphatic index	111.43	90.00	119.17

**Table S4.** Rate constants and  $K_D$  values of IBP-EK1 and IBP to human or rhesus monkey IgG.

Constants	human IgG		rhesus monkey IgG	
	IBP-EK1	IBP	IBP-EK1	IBP
$K_{on}$ ( $M s^{-1}$ )	$3.30 \times 10^3$	$2.80 \times 10^3$	$2.04 \times 10^3$	$1.27 \times 10^3$
$K_{off}$ ( $s^{-1}$ )	$7.17 \times 10^{-4}$	$2.87 \times 10^{-3}$	$5.29 \times 10^{-4}$	$1.40 \times 10^{-3}$
$K_D$ (M)	$2.17 \times 10^{-7}$	$1.03 \times 10^{-6}$	$2.60 \times 10^{-7}$	$1.10 \times 10^{-6}$